

## Author Response: Estimation of Hemoglobin Levels in the Optic Nerve Head for Glaucoma Management

The authors thank Dr Jonathan Denniss<sup>1</sup> for his interest and comments on our study.

The color of the optic nerve head is related to the hemoglobin distribution.<sup>2</sup> While performing ophthalmoscopic examination of the optic disc, the ophthalmologist's brain usually tries to interpret the cup-to-disc ratio by analyzing the color changes captured by the three types of cones in the human retina, which constitute the sensors of our personal photographic camera. Although the eyes act well as a discriminative tool, they are not so good at quantifying. Our method of analysis allows for papillary hemoglobin levels to be measured individually for differentiation of healthy eyes from those with glaucomatous optic neuropathy. Thus, it has become a complementary tool for standard visual examinations in clinical practice.

Indeed, as commented by Jonathan Denniss, if we could accurately segment papillary structures and separate the ring of neural tissue from the optic cup, we could better interpret any changes in the hemoglobin levels within the neuroretinal rim. Furthermore, we could also evaluate whether these changes exactly match the anatomic features, if they precede atrophy, or if increased perfusion prevents such atrophy. In theory, this would allow for better assessment of rapid changes in well-differentiated papillary regions. Such rapid modifications could be detected even from changes in the sectors represented in Figure 3,<sup>2</sup> but we agree with Jonathan Denniss that greater discriminant ability could be expected if the neuroretinal tissue could be more accurately identified.

Our study was a preliminary phase that did not attempt to address this issue, because it is impossible to segment the two regions from a single two-dimensional photographic image. As suggested by Jonathan Denniss, one could superimpose, for example, the results of scanning laser ophthalmoscopy (Heidelberg Retina Tomograph [HRT]; Heidelberg Engineering GmbH, Heidelberg, Germany) on the fundus photographs, but this instrument distinguishes between the neuroretinal rim and the optic cup based on a fixed reference plane.<sup>3,4</sup> The HRT defines the reference plane at 50  $\mu\text{m}$  posterior to the temporal disc margin, which is an arbitrary selection to separate the rim (above the reference plane) from the cup (below the reference plane). Although this separation is valid from a clinical point of view,<sup>5</sup> in many cases it does not accurately reflect anatomic reality. Spectral-domain optical coherence tomography (SD-OCT) would be a superior system to separate these structures and, except for some technical difficulties, is a possible option. Its increased scanning speed allows SD-OCT to obtain a three-dimensional cube of data, enabling a far more extensive assessment of the optic nerve head. Most SD-OCTs delineate the disc margin as the inner termination of Bruch's membrane.<sup>6-8</sup> The boundary of the neuroretinal rim is determined by algorithms that measure the distance from the termination of Bruch's membrane to the inner limiting membrane within the three-dimensional volume. Thus, the rim area measured by SD-OCT corresponds to the actual anatomy as would be evaluated along the axis of the optic nerve exit, despite the tilt of the optic disc.<sup>9</sup> This technique would lead to a hypothetical best estimation of the neuroretinal rim tissue. Combined analysis supported by SD-OCT, however, would thwart the objective of creating a simple and low-cost method.

Another solution would be to use stereophotographs.<sup>10</sup> Then, it would be possible to apply the Laguna optic nerve head (ONhE) analysis of hemoglobin on a well-defined neuroretinal tissue. Although this approach might achieve the objective suggested by Jonathan Denniss with a single instrument, the subjective nature of this method and the need for experienced evaluators would limit its general applicability.

In summary, the combination of different imaging technologies with the Laguna ONhE analysis may improve the performance of our method. SD-OCT seems to be the most precise instrument to differentiate the structures of the optic nerve head, but it would also be the most expensive and technologically complex option, whereas stereophotographs would be easier to adapt.

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