

## Prithee, Why So Pale?

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Why so pale and wan, fond lover?

Prithee why so pale?

Will, when looking well can't move her,

Looking ill prevail?

Sir John Suckling, *Aglaure* (1638). Song, st. I

In 1851, Helmholtz<sup>1</sup> realized the concept of the ophthalmoscope, first proposed in 1823 by Purkinje, and thus ushered in a new era in ophthalmology. This new instrument enabled ophthalmologists to view the inside of the living eye, and a flurry of descriptions filled volumes of journals and texts for many years to come. Although appealing, it is risky to infer causation or the underlying etiology on the basis of a finding on ophthalmoscopy or other forms of physical examination. Clinicopathologic correlation of ophthalmoscopic findings with histopathologic analyses has greatly expanded our understanding of ocular disease. But after 2 centuries of experience with this approach, there remains the question of why an atrophic optic nerve looks pale. This is important, as optic disc pallor or atrophy is a pathological end point that represents the permanent loss of nerve fibers due to a variety of disorders of the inner retina and optic nerve, many of which have very different etiologies. One hypothesis states that the pallor may be due to glial cell (astrocyte) proliferation in the wake of optic nerve axonal degeneration, regardless of the cause.<sup>2</sup> Others postulate that nerve fibers act as light pipes bringing out to the surface of the optic disc the red from deeper capillaries, and a loss of axons reduces this effect.<sup>3</sup> Finally, optic disc pallor may result directly from involution of the capillaries of the anterior optic nerve, as in the case of ischemic optic neuropathies, or secondarily due to autoregulatory changes that follow neurogenic optic atrophy.

In 1982, Sebag et al studied an experimental animal model of neurogenic optic atrophy, in which blood flow was intact on fluorescein angiography. They used laser Doppler velocimetry (LDV), a methodology akin to measuring the speed of receding stars by their red shift, to demonstrate diminution in capillary blood flow in the anterior optic nerve, and confirmed these LDV measures of reduced optic nerve circulation by intracardiac injection of microspheres.<sup>4</sup> In a subse-

quent study, they found that in patients with optic neuritis (ON) clearly not of vasculogenic origin, a similar diminution of blood flow to the anterior optic nerve was detected by LDV.<sup>5</sup> The LDV technique was then coupled with noninvasive oximetry of the retinal vessels to measure decreased blood flow and oxygen saturation in blood vessels of the inner retina due to retrograde ganglion cell degeneration in cases of neurogenic optic atrophy.<sup>6</sup> What remained to be determined was how these findings compared with those in patients with vasculogenic optic atrophy such as that described in a study in this issue.<sup>7</sup>

Collignon-Robe et al evaluated 30 patients with nonarteritic anterior ischemic optic neuropathy (NAION) and 22 with ON, the former representing vasculogenic optic atrophy and the latter, neurogenic optic atrophy. Subjects were evaluated by measuring anterior optic nerve capillary circulation with LDV, and the findings were compared with those of the clinically unaffected contralateral nerves and 50 controls. There was about a 20% diminution of blood velocity in NAION, and about 10% in ON. In both diseases, the reduction was greatest on the temporal side of the optic disc. This may reflect the greater watershed zone that stretches on the temporal side between the posterior ciliary and choroidal circulations. Although small, these differences were statistically significant. However, the authors concluded that their methodology was not robust enough to enable reliable clinical distinction between NAION and ON.

So why did the present and previous studies<sup>4-7</sup> find that in patients with ON there is a diminution of blood velocity almost as much as in NAION? Possible explanations include (1) the result of optic nerve degeneration is the same regardless of etiology (i.e., ischemia or inflammation leads to retinal ganglion cell axon degeneration, with subsequent diminution in circulation), or (2) the LDV methodology is limited in its discriminatory power, due to either artifact or other confounding factors.

It seems logical that after optic nerve axon degeneration there is far less need for circulation, and this leads to atrophy of the capillary bed in the anterior

optic nerve. The present findings add support for this concept. Optic disc edema did not alter the capillary blood velocities significantly in this study, because the condition was still relatively acute and there was an insufficient period for retinal ganglion cell death and vascular remodeling to have occurred. The lack of significant differences between these 2 groups also supports the atrophy explanation, although NAION is a complex of both mechanical and vasculogenic mechanisms. Arteritic anterior ischemic optic neuropathy is more purely vasculogenic, and for future studies, this will be a better group of patients for comparison with ON. The atrophy explanation also holds that timing impacted on the findings. Early in the disease process, capillaries may have dilated and carried more blood in both conditions, whereas later the vessels may have been of smaller caliber and carried less blood due to the optic atrophy. As the subjects were not studied at the same point of the disease, the 2 sets of changes may have canceled each other out, accounting for the small magnitude of effect detected by Collignon-Robe et al in the present study.

Laser Doppler velocimetry methodology does not actually attempt to measure blood flow, for there are no volumetric measurements. Because resistance may vary, a decrease in velocity can be interpreted as either a drop in capillary flow or quite the opposite. Compensatory capillary dilation from inflammation could increase blood flow but might produce a corresponding decrease in blood velocity. Thus, although the authors did an admirable job studying large numbers

of subjects and employing powerful statistical methods, there remain too many degrees of freedom with the LDV approach to define precisely the circulatory conditions in these 2 optic neuropathies.

Lastly, it is difficult to imagine that a 10% (ON) to 20% (NAION) reduction in blood flow could account for the degree of optic disc pallor observed in these patients clinically. Thus, despite the fact that this study adds to our understanding of the underlying pathophysiology of optic neuropathies and that the LDV techniques employed hold great promise to elucidate further mechanisms of disease in the future, the answer to "Prithee, why so pale?" continues to elude us.

#### References

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