

Surrogates for ocular perfusion pressure are not perfect- authors reply

Vital P. Costa, Douglas Anderson and Alon Harris

Dear Editor

Dr. Khawaja and his colleagues commented on our recent review article (Costa et al. 2013) dealing with ocular perfusion pressure (OPP), and we are grateful for the opportunity to clarify certain points. They have quite correctly commented here, and before in the published letter, they cite (Khawaja et al. 2013) that there are theoretical problems with using the traditional formula for OPP (or more correctly, a surrogate for OPP) derived from brachial artery pressure (BP) and intraocular pressure (IOP), as well as how multivariate analyses are performed.

The hidden assumption when testing the impact of OPP on glaucoma is that an abnormally low OPP due to a high IOP may be equivalent to the same OPP due to a low BP. Of course, that is the hypothesis that many of the studies try to address. Stated differently, investigators are attempting to understand whether BP is relevant to the occurrence, severity or progression of glaucomatous damage, or is everything simply dependent on IOP (Costa et al. 2013).

Should a surrogate OPP be studied at all? It is difficult, if not impossible, to measure true ocular OPP directly, and if the problem is to be studied, it becomes necessary to use an estimate and hope that the estimate is not too bad. Should the surrogate OPP be corrected for IOP? Probably not, as OPP is calculated with IOP (along with BP) as one of the variables, and hence, multivariate analysis is ruined by the non-independence of the variables OPP and IOP, as Dr. Khawaja and colleagues explain in detail in

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their already published letter (Khawaja et al. 2013). The corrected value simply represents BP anyway. However, we still believe that this is an important finding, especially because several researchers tended to assume that the only reason for the positive association between OPP and glaucoma was IOP. When one adjusts for IOP and the association remains significant, it is possible to conclude that not only IOP is affecting the positive association, but BP too also is an important driving factor.

On the other hand, such analysis does not answer the question of whether OPP itself, whether altered by IOP or BP, is in the final common pathway for damage. It may answer whether BP is relevant, but maybe not whether it is as important the IOP considered by itself.

The reviewed studies are not consistent in showing or failing to show a relationship of BP and glaucomatous damage. It does seem that either a very low BP or chronic hypertension, perhaps on treatment with a now-normal BP, each might logically affect the course of glaucoma (Costa et al. 2009). It might be speculated that a sufficiently low BP might indeed result in reduced perfusion. At the same time, long-standing hypertension results in narrowed and stiffened arteries and arterioles, which both increases resistance to flow and impairs the regulatory mechanisms for flow. If so, then the relationship of BP to glaucomatous damage is not linear, because either extreme has an adverse effect. The non-linearity confounds any multivariate analysis that assumes linearity between the independent variables being tested for impact on the dependent variable, glaucomatous damage.

Finally, flow depends not only on perfusion pressure, but also on resistance in the vascular bed. The resistance to flow is not fixed, even under completely normal circumstances. The resistance is modified by regulatory mechanisms over a range of perfusion pressures, so the OPP by itself may not have an effect except at the extremes when the capacity for regulation has been exceeded. It is a complex physiological system to study adequately. The innate capacity for regulation may vary from one person to another, and it may be altered by disease, such as stiffening of the arteries by chronic hypertension

(arteriosclerosis). Therefore, the review did not have a firm conclusion about the place of OPP in the glaucomatous process. Our only conclusion, cautiously stated in the abstract, is summarized in the sentence: ‘We believe that the balance between IOP and BP, influenced by the autoregulatory capacity of the eye, is part of what determines whether an individual will develop optic nerve damage.’

Dr. Khawaja and colleagues have served us well by highlighting what might be lost in our lengthy review, namely, the difficulties in reaching more targeted conclusions from the studies to date, for both mathematical and physiological reasons. We thank them.

References

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Khawaja AP, Crabb DP & Jansonius NM (2013): The Role of Ocular Perfusion Pressure in Glaucoma Cannot Be Studied With Multivariable Regression Analysis Applied to Surrogates. *Invest Ophthalmol Vis Sci* 54: 4619–4620.