damage was associated with a greater number of hours of playing the instruments over their lifetimes; and 2) on studies in which 45% of patients with normal-pressure glaucoma (as compared to 11% with primary open-angle glaucoma) were exposed to conditions causing intrathoracic or intra-abdominal pressure elevation, including playing high resistance wind instruments, weightlifting, chronic asthma and cough, obstruction of the urinary system and constipation (Schuman et al. 2000; Krist et al. 2001).

According to our study (Zhang et al. 2013), Valsalva manoeuvres are associated with a rise in the cerebrospinal fluid pressure (CSFP), at least partially compensating for the rise in IOP with respect to the trans-lamina cribrosa pressure difference (TLCPD). Dr. Wostyn wonders whether not only the absolute pressures but also the pressure changes on both sides of the lamina cribrosa and thus the fluctuations in the TLCPD may play a role in the pathogenesis of glaucomatous optic neuropathy.

The authors fully agree with this notion. Morgan and colleagues demonstrated in a previous study a difference in the phasing of the IOP curve and the phasing of the CSFP curve with respect to the cardiac cycle, with the ICP curve reaching its height earlier than the CSFP curve (Morgan et al. 2012). It was then wondered whether these physiological short-term changes in the TLCPD, potentially even resulting in short-term reversals of the TLCPD and thus in a swinging TLCPD, may physiologically be needed to allow the retrograde axoplasmic flow entering the eye (Jonas et al. 2012). The thoughts by Dr. Wostyn and colleagues, the observations by Morgan and co-workers and the considerations based on Morgan’s finding may show that the dynamics of IOP, ICP and TLCPD, including the physiological time shift between the cardiac cycle-related CSFP curve and IOP curve (‘ocular pulse’), may be of potentially high importance for both the physiological stability and the pathophysiology of the optic nerve.

References

Jonas JB, Yang D & Wang N (2012): Retinal vein pulsation is in phase with intracranial pressure and not intraocular pressure. Invest Ophthalmo Vis Sci 53: 6045.

Krist D, Cursiefen C & Junemann A (2001): Transitory intrathoracic and –abdominal pressure elevation in the history of 64 patients with normal pressure glaucoma. Klin Monatsbl Augenheilkd 218: 209–213.

Morgan WH, Lind CRP, Kain S, Fatehee N, Bula A & Yu DY (2012): Retinal vein pulsation is in phase with intracranial pressure and not intraocular pressure. Invest Ophthalmo Vis Sci 53: 4676–4681.

Schuman JS, Massicotte EC, Connolly S, Hertzmark E, Mukherji B & Kunen MZ (2000): Increased intracranial pressure and visual field defects in high resistance wind instrument players. Ophthalmology 107: 127–133.

Wostyn P, De Groot V, Van Dam D, Aude-naert K & De Deyn P (2013): Intracranial pressure fluctuations: a potential risk factor for glaucoma? Acta Ophthalmol (in press).

Zhang Z, Wang X, Jonas JB et al. (2013): Valsalva manoeuvre, intracranial, cerebrospinal fluid pressure, optic disc topography: Beijing Intracranial and Intraocular Pressure Study. Acta Ophthalmol [Epub ahead of print].

Correspondence:
Junfa Li
Department of Neurobiology
School of Basic Medical Sciences
Capital Medical University
No.10 You An Men Wai Xi Tou Tiao
Beijing 100069, China
Tel: +8610-8395-0061
Fax: +8610-8395-0060
Email: junfal@ccmu.edu.cn

Ningli Wang
Beijing Tongren Eye Center
Beijing Tongren Hospital
Capital Medical University
Beijing Ophthalmology and Visual Sciences
Key Laboratory
No.1 Dongjiacaoqinxing Street
Dongcheng District
Beijing 100730, China
Tel: +8610-8382-9968
Fax: +8610-8382-9930
Email: wningli@vip.163.com

Time to abandon over-simplified surrogates of ocular perfusion pressure in glaucoma research

Anthony P. Khawaja, David P. Crabb and Nomdo M. Janssonius

1 Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge School of Clinical Medicine, Cambridge, UK; 2 Department of Optometry and Visual Science, City University London, London, UK; 3 Department of Ophthalmology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; 4 Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands

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Editor,

The role of ocular perfusion pressure (OPP) in the pathogenesis of glaucoma has attracted a great deal of research interest, as highlighted in a review article recently published in Acta Ophthalmologica (Costa et al. 2013). For the majority of studies in this field, blood pressure (BP) minus intraocular pressure (IOP) has been used as a simple surrogate measure of OPP. The authors of the review article correctly acknowledge that interpretation of these surrogate measures is problematic and that any crude association observed between OPP and glaucoma may be related solely to the IOP component, given the known strength of IOP as a risk factor for glaucoma. However, we strongly disagree with the authors’ conclusion that statistically adjusting for IOP is a satisfactory solution to this problem. We have previously shown that it is quite impossible to untangle the effects of IOP and BP in a model containing OPP results (Khawaja et al. 2013). In short, adjusting for IOP in a model containing OPP will inevitably result in the situation that the coefficients for OPP actually represent the effect of BP only, and not OPP. This has been substantiated theoretically and demonstrated clearly using a simulated dataset; the coefficients for OPP in IOP adjusted regression models were exactly the same as those for BP in IOP adjusted models (Khawaja et al. 2013). Therefore, in studies that have found a significant association between OPP and glaucoma using regression models adjusted for IOP, it is actually a significant association between BP and glaucoma that has been demonstrated, and no conclusions can be drawn regarding perfusion pres-
Dear Editor

Vital P. Costa, 1 Douglas Anderson2 Alon Harris 3

1Department of Ophthalmology, University of Campinas, Campinas, Brazil; 2Department of Ophthalmology, Bascom Palmer Eye Institute, Miami, FL, USA; 3Department of Ophthalmology and Physiology, Indiana University School of Medicine, Indianapolis, IN, USA
doi: 10.1111/aos.12381

Surrogates for ocular perfusion pressure are not perfect- authors reply

Vital P. Costa,1 Douglas Anderson2 Alon Harris3

1Department of Ophthalmology, University of Campinas, Campinas, Brazil; 2Department of Ophthalmology, Bascom Palmer Eye Institute, Miami, FL, USA; 3Department of Ophthalmology and Physiology, Indiana University School of Medicine, Indianapolis, IN, USA
doi: 10.1111/aos.12381

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 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