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Ocular perfusion pressure and glaucoma: clinical trial and epidemiologic findings

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Abstract

Purpose of review—A possible connection between ocular perfusion pressure and open-angle glaucoma (OAG) has been hypothesized. This review summarizes the scientific rationale for the proposed relationship, presents recent data, and outlines potential implications.

Recent findings—Population-based epidemiologic studies found strong relationships between low ocular perfusion pressure and OAG prevalence, as well as OAG incidence. Clinical studies report similar associations between low perfusion pressure and OAG progression. These consistent findings suggest that altered blood flow in the optic disc increases both the risk of OAG development and the progression of established OAG. An underlying factor would be impaired vascular autoregulation, which may lead to poor perfusion in OAG. In contrast, there is conflicting evidence on the possible link of glaucoma to blood pressure/hypertension.

Summary—Current evidence supports the role of vascular factors as part of the multifactorial etiology of OAG. Since ocular perfusion pressure reflects the vascular status at the optic disc, it may be more relevant than systemic blood pressure alone. While the associations of OAG to perfusion pressure are strong, consistent and biologically plausible, they require careful interpretation. The evidence implicating a vascular etiology in OAG is mounting, but the clinical implications for patient management are still uncertain.

Keywords

Open-angle glaucoma; ocular perfusion pressure; glaucoma risk factors; blood pressure

II. INTRODUCTION

The etiology of primary open-angle glaucoma (OAG) remains in doubt, despite extensive research. As discussed in various summary reviews,[1-3] one mechanism of causation would relate to alterations of ocular perfusion pressure, leading to glaucomatous damage of the optic nerve.

This report aims to:

- **a.** provide a summary overview of the scientific rationale for the proposed relationship between OAG and ocular perfusion pressure;
- **b.** review recent epidemiologic and clinical trial evidence on the potential links of glaucoma to blood pressure and perfusion pressure; and,

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c. outline the possible implications of these findings.

III. TEXT OF REVIEW

BACKGROUND AND DEFINITIONS

The normal functioning of tissues depends on the maintenance of an adequate perfusion, with sufficient blood flow. A key element is the presence of an ample perfusion pressure to meet tissue needs, a process that requires a balance between arterial and venous blood pressure (BP).

How is perfusion pressure defined for the eye? Ocular perfusion pressure is expressed as the difference between the arterial BP and the intraocular pressure (IOP), which is considered a substitute for the venous pressure. Because BP can be measured in several ways, it is necessary to distinguish among systolic, diastolic and mean perfusion pressures. The latter pressure equals 2/3 the mean arterial pressure minus IOP (arterial pressure: diastolic BP + 1/3 (systolic BP – diastolic BP).

Alterations of ocular perfusion could cause ischemia and poor irrigation of tissues in the optic nerve, thus having deleterious effects. These effects could be especially relevant for the causation of OAG, an optic neuropathy of unknown origin, which presents with a distinctive pattern of nerve changes and visual field loss. One possible etiologic explanation for OAG pathogenesis concerns the ‘vascular hypothesis’, based on the premise that abnormal perfusion of the optic disc would be a major cause of glaucomatous damage.

VASCULAR DYSREGULATION AND OAG

A low ocular perfusion pressure could be due to a relatively low BP or a relatively high IOP. Neither of these variables, alone, has been implicated conclusively as the sole cause of low perfusion in glaucoma. As discussed in a later section, there is no clear relationship between BP levels and OAG damage.[4-6] In fact, studies relating BP to OAG report positive, negative or no associations, casting doubts on the relevance of BP by itself as a glaucoma risk factor. The independent role of IOP alone is also in doubt. As is well known, while many OAG patients have elevated IOP, glaucoma can occur at any IOP level; furthermore, elevated IOP or ‘ocular hypertension’ is usually sustained without damage.[7] The underlying cause of abnormal perfusion in glaucoma, therefore, is likely to be a disruption of the normal mechanisms that regulate perfusion pressure.

The maintenance of ocular perfusion pressure depends on a complex regulation process that balances BP and IOP to ensure adequate irrigation of ocular tissues. Abnormal perfusion occurs when this process is altered due to vascular dysregulation, which has been proposed as an underlying cause for glaucoma damage.[2,3,8]

Vascular dysregulation has been described and discussed in recent reviews, along with the scientific rationale and evidence for potential associations with OAG.[1-3] Dysregulation could lead, not only to chronically low perfusion, but to unstable perfusion with wide fluctuations. These fluctuations would be particularly marked at night, with nocturnal dips in perfusion pressure.

Although the role of vascular factors has been proposed for many years, newly available technology has expanded the scope of relevant evaluations. For example, using recent measurements of retinal blood flow rate, the retinal vascular autoregulation response was related to changes in ocular perfusion pressure.[9] The broad range of hemodynamic responses in OAG patients, *versus* controls, suggested dysregulation of the retinal vasculature, or no autoregulation in some patients.

If vascular status affects the glaucomatous process, a low ocular perfusion pressure could be a potential *'risk factor'* for new OAG in susceptible individuals. Additionally, it could be a *'progression factor'*, that is, lead to a worsening of established disease in OAG patients.

OCULAR PERFUSION PRESSURE AS A 'RISK FACTOR' FOR NEW GLAUCOMA DAMAGE

A low ocular perfusion pressure has been associated with OAG in a number of population-based epidemiologic studies. The relationship was found initially in prevalence or cross-sectional studies, with consistent results across ancestries.[10-13] Thus, a low diastolic perfusion pressure, under 50−55 mmHg, was associated with OAG prevalence in epidemiologic studies conducted in the United States, Europe, and the Caribbean **(Table 1).**

A recent publication from the Rotterdam Eye Study has augmented the prevalence data on perfusion pressure [14] **(Table 1).** The results are not directly comparable to those of previous population studies, as the Rotterdam analyses were limited to persons receiving medications to treat systemic hypertension, rather than including all participants. Also, only a minority of the cases had definite OAG with visual field defects and over three-fourths had probable OAG. Of the 404 treated hypertensives with low (under 50mmHg) diastolic ocular perfusion pressure, 14 had 'high tension' OAG (median IOP over 21 mmHg or IOP-lowering treatment) and 6 had 'normal tension' OAG. Among the 'high tension' group, there was a significant odds ratio of 4.68 (95% confidence interval (CI): 1.29, 17.01) for low diastolic perfusion pressure, which is consistent with previous results, but the odds ratio was 0.25 (95% CI: 0.10, 0.63) in the 'normal tension' group. Interpretation of these results must consider the previous caveats, the cross-sectional study design and small sample sizes involved.

Associations based on prevalence data are subject to a number of biases, and do not indicate risk, hence raising questions on the interpretation of their results. More valid data originate from longitudinal or incidence studies, which follow a population over time and thus truly measure risk and risk factors, i.e., those related to the disease onset or incidence. For OAG, these data were first provided by the incidence phase of the Barbados Eye Studies, a set of investigations based on individuals of mainly African descent (n=4,631 at baseline). The cohort was followed over time, with high participation of 85% and 81% at the 4-year and 9-year examinations, respectively. After 4-years of follow-up, a low ocular perfusion pressure at baseline was associated with a 3-fold increased risk of developing OAG.[15]

Recently, the 9-year follow-up data from the Barbados studies affirmed these findings.[6] Persons with low ocular perfusion pressure at baseline had a significantly increased risk of OAG development, as compared to those with higher pressures **(Table 2).** The relative risks (RR) ranged from 2.0 to 2.6 for systolic, diastolic and mean perfusion pressures (**Table 2**). These longitudinal results thus support the role of low ocular perfusion pressure as a risk factor for incident OAG.

OCULAR PERFUSION PRESSURE AS A 'PROGRESSION FACTOR' FOR ESTABLISHED GLAUCOMA

If low perfusion pressure and ocular blood flow are implicated in glaucoma damage, these conditions could also affect the progression of established OAG. Although not all studies are consistent, vascular factors have been implicated in the clinical course of glaucoma patients. [16,17] Furthermore, circadian fluctuation of the mean ocular perfusion pressure was consistently related to disease severity in normal tension OAG. [18]

Long-term progression data (up to 11 years) were provided recently by the Early Manifest Glaucoma Trial, a randomized clinical trial evaluating the role of immediate treatment, as compared to no initial treatment, on glaucoma progression.[5,19] The new results indicate that

patients with low systolic perfusion pressure at baseline progressed faster than their counterparts. When considering all patients (n=255), the Hazard Ratio (HR) was 1.42 and statistically significant, suggesting almost a 1.5-times increased hazard of progression in these patients.[5] **(Table 3).** Similar non-significant trends were observed for diastolic and mean perfusion pressures.

The study also evaluated factors for progression separately for patients with higher vs, lower IOP at baseline, as defined by a median split. A significant HR of 1.55 for low ocular perfusion pressure was observed in patients with higher baseline IOP **(Table 3).** This finding parallels the results of some prevalence studies, where the association was observed only in patients with 'high tension' glaucoma **(Table 1**). Another progression factor was the history of cardiovascular disease, significant in patients with IOP over the median value. Taken together, these results are consistent with a hypothesized effect of vascular factors on progression.

IS BLOOD PRESSURE RELATED TO GLAUCOMA?

Many studies have reported a positive, statistically significant relationship between blood pressure (BP) and IOP, which is consistent across studies and stronger for systolic than for diastolic BP.[4] Additionally, BP often explains a larger proportion of the variation in IOP than other known variables, although the percent explained is relatively small, about 5%. For systolic BP, estimates from cross-sectional studies suggest that each 10 mmHg higher BP is associated with a 0.23−0.32 mmHg higher IOP.[4,10,12] Similar estimates, of 0.21 and 0.22mmHg higher IOP, have been derived from longitudinal data in the Beaver Dam and Barbados studies.[20,21] Results for diastolic BP are less consistent.[4]

A relationship between BP and IOP has been well established, but a parallel relationship between BP and OAG has not. The link between systemic hypertension and OAG also remains in doubt, with some recent reviews suggesting a more prominent role for hypotension instead. [4,22]

Epidemiologic studies of prevalence provide mixed findings. In fact, some of the reported positive 'associations' between OAG and BP are based on non-statistically significant results; other studies have found weak or no relationships with high BP or low BP.[4] These disparate results could be influenced by the OAG definition of specific studies. If elevated IOP is included in this definition, a positive association between OAG and BP/hypertension is difficult to interpret, because IOP is related to BP. The recent analyses of the Rotterdam prevalence data found no statistically significant associations with high BP or hypertension, confirming their previous findings.[14]

Similarly, cohort studies showed no positive links between OAG incidence and BP. The 9-year follow-up from the Barbados studies revealed a weak negative association with systolic BP (RR= 0.91 (95% CI: 0.84, 1.00) per 10 mmHg); the RR for persons with systemic hypertension at baseline was 0.8 and non-statistically significant, overall and in all age groups. [6] These findings suggest a marginal 'protective' role for high BP/hypertension. Given the inconsistencies in the epidemiologic literature, BP cannot be considered as an established risk factor for OAG. [7]

The role of BP or hypertension in the progression of established OAG is also unclear. In the long-term follow-up of the Early Manifest Glaucoma Trial, patients with higher systolic BP at baseline had significantly lower hazards for progression (HRs of 0.44 to 0.69 (p= 0.04−0.10), again in the negative or 'protective' direction.[5] No significant relationship was detected with systemic hypertension, where the HR was 0.8. The recent data thus provide little support for high BP/ hypertension as important factors affecting glaucoma prevalence, incidence, or progression.

SYSTEMIC ANTIHYPERTENSIVE TREATMENT AND GLAUCOMA

Since antihypertensive treatment would tend to decrease ocular perfusion pressure, it could have a potential effect on glaucoma, as suggested in some studies.[23] As mentioned previously, the associations of perfusion pressure to OAG prevalence in the Rotterdam study were seen only in persons using systemic antihypertensive therapy (**Table 1**). Also, the population-based Thessaloniki Eye Study found increased disc cupping and decreased rim areas in persons without OAG, but with diastolic BP <90mmHg and using systemic antihypertensives. [24] A plausible explanation is that marked lowering of the BP in susceptible individuals may lead to optic disc changes, a possibility that has clinical implications.

Specific antihypertensive agents could have varying effects on OAG. Recent incidence data from the Rotterdam Eye Study revealed an increased risk of OAG in users of calcium channel antagonists after 6.5 years of follow-up (RR=1.9 (95% CI: 1.1, 3.3)).[25] These agents decrease BP without affecting IOP, thus reducing ocular perfusion pressure, which could explain the findings. The results suggest caution when using calcium channel antagonists in glaucoma patients. On the other hand, the same study found a non-significant trend toward a reduced risk in persons using beta-blockers.[25]

IMPLICATIONS

The recent results from epidemiologic studies and clinical trials, as reviewed, suggest that vascular factors are related to both the risk and the progression of glaucoma. The strongest and most consistent evidence supports an association with low ocular perfusion pressure; this association is biologically plausible and underpinned by a creditable scientific hypothesis. The interpretation of this finding, however, is not straightforward.

Ocular perfusion pressure is a complex variable that may be affected by one or more of its components, that is, low BP, high IOP, treatment to lower BP or IOP, or a combination thereof. Analyses of perfusion pressure need to consider all these factors and control for pertinent variables.

Another consideration concerns the wide variation in BP and IOP, as both fluctuate over time according to internal and external influences; OAG relationships at various BP and IOP levels should be considered. Also, the level of BP and IOP vary across populations and perfusion pressure-OAG relationships could vary accordingly. For example, since the African-origin population of the Barbados studies has a higher mean IOP than others, individuals with high BP/hypertension could be ‘protected’ from developing glaucoma damage, a mechanism that may be less applicable to other populations. Furthermore, brachial BP may not reflect BP at the optic disc. Careful interpretation of associations is thus needed.

Despite these caveats, ocular perfusion pressure seems more pertinent to glaucoma than BP alone. If we accept its relevance to OAG risk or progression, the clinical implications for patient management should be considered, particularly for those with low perfusion values. One practical issue concerns the adoption of a careful protocol to obtain accurate measurements of BP and history of hypertension treatment, which are not always implemented in patients presenting for eye care. Additionally, by virtue of the relationship between BP and IOP, patients with elevated IOP would have an increased frequency of systemic hypertension. Since antihypertensive medications could substantially affect ocular perfusion pressure, clinicians caring for ocular hypertensive or glaucoma patients may face difficult decisions regarding the use of BP-lowering treatment in these patients,

IV. CONCLUSIONS

- A positive association exists between BP and IOP, but a similar link between BP and OAG is not established.
- Recent epidemiologic studies and clinical trials found that low ocular perfusion pressure was significantly related to OAG, confirming previous findings. Such results require careful interpretation and replication in future studies.
- OAG is a multifactorial disease that develops from the interaction of genetic and non-genetic factors. Perfusion pressure and vascular factors are likely involved in this interaction,
- While the importance of these factors remains to be determined, there is mounting evidence for their role on OAG development and/or progression.

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REFERENCES

1 **. Flammer J, Mozaffarieh M. What is the present pathogenetic concept of glaucomatous optic neuropathy? Surv Ophthalmol 2007;52(Suppl 2):S162–173. [PubMed: 17998042]The paper reviews the potential mechanisms leading to glaucomatous optic neuropathy. It discusses the various factors that could be involved in the glaucoma process and proposes a pathogenetic concept that integrates these factors. Results are based on an extensive 1996−2007 literature review.

2 **. Grieshaber MC, Mozaffarieh M, Flammer J. What is the link between vascular dysregulation and glaucoma? Surv Ophthalmol 2007;52(Suppl 2):S144–154. [PubMed: 17998040]Based on a literature search from 1996 to 2007, this article reviews the relevant evidence on the topic described in its title. It provides a comprehensive discussion of the regulation of ocular blood flow and issues related to vascular dysregulation, as well as relationships with glaucoma.

3 *. Nicolela MT. Clinical clues of vascular dysregulation and its association with glaucoma. Can J Ophthalmol 2008;43:337–341. [PubMed: 18493274]In addition to providing an overview on the literature relating vascular dysregulation and glaucoma, this paper focuses on clinical issues, such as the identification of glaucoma patients with alterations of autoregulatory mechanisms.

4 **. Deokule S, Weinreb RN. Relationships among systemic blood pressure, intraocular pressure, and open-angle glaucoma. Can J Ophthalmol 2008;43:302–307. [PubMed: 18493272]This comprehensive review summarizes the literature on the possible associations of glaucoma to blood pressure and intraocular pressure. It provides pertinent data on the consistent evidence relating blood pressure and intraocular pressure, as well as on the inconstant relationship of blood pressure, antihypertensive treatment and glaucoma.

5 **. Leske MC, Heijl A, Hyman L, et al. Predictors of long-term progression in the early manifest glaucoma trial. Ophthalmology 2007;114:1965–1972. [PubMed: 17628686]The paper provides new data on factors related to the progression of established glaucoma in a cohort of clinical trial patients. In addition to previous findings, e.g., intraocular pressure and age, the analyses of the long-term data identified various vascular factors related to progression, such as low perfusion pressure, low blood pressure, and cardiovascular disease.

6 **. Leske MC, Wu SY, Hennis A, et al. Risk Factors for Incident Open-Angle Glaucoma: The Barbados Eye Studies. Ophthalmology 2008;115:85–93. [PubMed: 17629563]This is the first article to provide population-based data on risk factors for the incidence of open-angle-glaucoma after a long follow-up period. Low perfusion pressures at baseline were important predictors of glaucoma risk, while systemic hypertension played no role.

7 *. Leske MC. Open-angle glaucoma -- an epidemiologic overview. Ophthalmic Epidemiol 2007;14:166–172. [PubMed: 17896292]In this summary overview, the current information on

open-angle glaucoma is discussed. In particular, the paper focuses on the main risk factors for glaucoma.

8 *. Flammer J, Mozaffarieh M. Autoregulation, a balancing act between supply and demand. Can J Ophthalmol 2008;43:317–321. [PubMed: 18493273]Issues regarding autoregulation are covered in detail, including a discussion of recent data.

9. Feke GT, Pasquale LR. Retinal blood flow response to posture change in glaucoma patients compared with healthy subjects. Ophthalmology 2008;115:246–252. [PubMed: 17689612]

10. Tielsch JM, Katz J, Sommer A, et al. Hypertension, perfusion pressure, and primary open-angle glaucoma. A population-based assessment. Arch Ophthalmol 1995;113:216–221. [PubMed: 7864755]

11. Leske MC, Connell AM, Wu SY, et al. Risk factors for open-angle glaucoma. The Barbados Eye Study. Arch Ophthalmol 1995;113:918–924. [PubMed: 7605285]

12. Bonomi L, Marchini G, Marraffa M, et al. Vascular risk factors for primary open angle glaucoma: the Egna-Neumarkt Study. Ophthalmology 2000;107:1287–1293. [PubMed: 10889099]

13. Quigley HA, West SK, Rodriguez J, et al. The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. Arch Ophthalmol 2001;119:1819–1826. [PubMed: 11735794]

14 **. Hulsman CA, Vingerling JR, Hofman A, et al. Blood pressure, arterial stiffness, and open-angle glaucoma: the Rotterdam study. Arch Ophthalmol 2007;125:805–812. [PubMed: 17562992]The paper reports new analyses of the glaucoma prevalence data from the population-based Rotterdam study. It found no relationship between glaucoma and hypertension, but found associations with perfusion pressure among persons receiving treatment for systemic hypertension.

15. Leske MC, Wu SY, Nemesure B, et al. Incident open-angle glaucoma and blood pressure. Arch Ophthalmol 2002;120:954–959. [PubMed: 12096967]

16. Fuchsjager-Mayrl G, Wally B, Georgopoulos M, et al. Ocular blood flow and systemic blood pressure in patients with primary open-angle glaucoma and ocular hypertension. Invest Ophthalmol Vis Sci 2004;45:834–839. [PubMed: 14985298]

17. Zeitz O, Galambos P, Wagenfeld L, et al. Glaucoma progression is associated with decreased blood flow velocities in the short posterior ciliary artery. Br J Ophthalmol 2006;90:1245–1248. [PubMed: 16825276]

18. Choi J, Kim KH, Jeong J, Cho HS, Lee CH, Kook MS. Circadian fluctuation of mean ocular perfusion pressure is a consistent risk factor for normal-tension glaucoma. Invest Ophthalmol Vis Sci 2007;48:104–111. [PubMed: 17197523]

19. Leske MC, Heijl A, Hyman L, Bengtsson B, Komaroff E. Factors for progression and glaucoma treatment: The Early Manifest Glaucoma Trial. Curr Opin Ophthalmol 2004;15:102–106. [PubMed: 15021220]

20. Klein BE, Klein R, Knudtson MD. Intraocular pressure and systemic blood pressure: longitudinal perspective: the Beaver Dam Eye Study. Br J Ophthalmol 2005;89:284–287. [PubMed: 15722304]

21. Wu SY, Leske MC. Associations with intraocular pressure in the Barbados Eye Study. Arch Ophthalmol 1997;115:1572–1576. [PubMed: 9400792]

22. Pache M, Flammer J. A sick eye in a sick body? Systemic findings in patients with primary open-angle glaucoma. Surv Ophthalmol 2006;51:179–212. [PubMed: 16644363]

23. Punjabi OS, Stamper RL, Bostrom AG, Lin SC. Does treated systemic hypertension affect progression of optic nerve damage in glaucoma suspects? Curr Eye Res 2007;32:153–160. [PubMed: 17364748]

24. Topouzis F, Coleman AL, Harris A, Jonescu-Cuypers C, Yu F, Mavroudis L, Anastasopoulos E, Pappas T, Koskosas A, Wilson MR. Association of blood pressure status with the optic disk structure in non-glaucoma subjects: the Thessaloniki Eye Study. Am J Ophthalmol 2006;142:60–67. [PubMed: 16815251]

25 *. Muskens RP, de Voogd S, Wolfs RC, et al. Systemic antihypertensive medication and incident open-angle glaucoma. Ophthalmology 2007;114:2221–2226. [PubMed: 17568677]Recent analyses of the Rotterdam study, based on incidence data, found positive associations between calcium channel antagonists and glaucoma. Beta-blockers were not statistically significant factors.