REVIEW ARTICLE

Intraocular pressure variations: Causes and clinical significance

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ABSTRACT • RÉSUMÉ

Reduction of intraocular pressure (IOP) is the only known effective treatment for glaucoma. However, IOP is a highly variable and dynamic parameter, undergoing virtually constant changes from numerous factors, including body position and circadian rhythms. Despite this variability, evidence for the efficacy of IOP reduction in glaucoma is based on studies designed to assess mean IOP and not IOP variations. Post hoc analysis of data from major clinical trials has suggested that IOP variations may be an independent risk factor for the development of glaucoma or glaucomatous progression, at least in some patients, but the evidence is incomplete and further studies are required. In the interim, judicious selection of existing therapies can help to minimize IOP variations. In general, therapies that improve outflow instead of suppressing aqueous humor production result in more stable IOP. However, new technology to allow better monitoring of IOP, ideally in a continuous 24-hour manner, is required to fully understand the role of IOP variations in glaucoma.

La réduction de la pression intraoculaire (PIO) est le seul traitement efficace du glaucome actuellement connu. Toutefois, la PIO est un paramètre grandement variable et dynamique, présentant des changements quasi-constants en raison de nombreux facteurs, y compris la position du corps et les rythmes circadiens. Malgré cette variabilité, l'évidence de l'efficacité de la réduction de la PIO dans le traitement du glaucome est basée sur les études d'évaluation de la moyenne de la PIO, et non pas la variabilité de la PIO. L'analyse post-hoc des données des principaux essais cliniques a suggéré que les variations de la PIO pouvaient être un facteur indépendant de risque de développement du glaucome ou de la progression glaucomateuse, au moins chez certains patients, mais l'évidence courante est incomplète et d'autres études sont requises. Entretemps, le choix judicieux des thérapies existantes peut aider à minimiser les variations de la PIO. En général, les thérapies visant à augmenter l'écoulement d'humeur aqueuse plutôt que d'en supprimer sa formation, mènent à des PIO plus stables. Cependant, la nouvelle technologie permettant de mieux suivre la PIO, idéalement de façon constante à travers 24 heures, est requise pour comprendre entièrement le rôle des variations de la PIO dans le glaucome.

Intraocular pressure (IOP) has long been known to be variable, with Sidler-Huguenin first reporting diurnal variations in 1898.[1] However, the clinical significance of IOP variations has been much less clear. IOP variation has been suggested as an independent risk factor for glaucoma. However, the evidence in the literature is inconclusive, and the nature of IOP variations is incompletely understood.

One of the difficulties in understanding the clinical significance of IOP variations is that the definition of this parameter is sometimes unclear. Three categories of IOP variations can be defined to help guide discussions concerning clinical significance. First, *circadian IOP variations* can be used to describe the normal circadian pattern that individuals experience through a 24-hour period. Second, *short-term IOP fluctuations* can be used to describe IOP changes within a 24-hour period. Third, *long-term variations* can be used to describe the variations that occur in IOP measured over multiple office visits.

This review discusses the patterns of IOP fluctuations (as measured under laboratory conditions and in clinical studies) and the potential role of those fluctuations in glaucoma pathogenesis. It also discusses clinical strategies that can minimize IOP variations using existing therapeutic options.

Intraocular Pressure Variations in Animals

The intermittent nature of clinical IOP monitoring, involving a single measurement every few months, does not enable the true nature of IOP variability to be detected. To overcome this deficiency, McLaren et al.[2] used implantable pressure sensors in rabbits to allow continuous telemetric monitoring of IOP. They found that IOP undergoes virtually constant short-term fluctuations, with changes occurring because of systemic pulse pressure, eye position, lid position, breathing patterns, physical activity, and application of external tonometers, among other factors. Rabbits also showed a circadian rhythm in IOP, with pressure on average higher in the nocturnal period compared with the diurnal period. More recent work from Downs et al.[3] found similar rapid IOP fluctuations in nonhuman primates. However, their studies did not find any clear circadian pattern. The clinical significance of short-term fluctuations, which can last a few seconds or less, is unknown. Although a single short-term fluctuation is likely of negligible significance, the cumulative effect of constant fluctuations could potentially contribute to glaucoma pathogenesis.[4]

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Presented in part at the Glaucoma Management Review Course, 53rd Annual Walter Wright Day, Toronto, Ont., December 6-7, 2013

Originally received Jun. 25, 2014. Accepted Jul. 21, 2014

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Can J Ophthalmol 2014;49:484–488
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http://dx.doi.org/10.1016/j.jcjo.2014.07.008

Table 1—Sources of short-term intraocular pressure fluctuations

Blinks[5,6]	Tight neck ties[7]
Eye movements[5]	Caffeine[8]
Accommodation[9]	Wind instruments[10]
Head position[11]	Water drinking[12,13]
Body position[11,14]	Blood pressure[15]

Common Sources of Intraocular Pressure Variation in Humans

Short-term Intraocular Pressure Fluctuations

Short-term IOP fluctuations in humans can occur for a wide variety of reasons, a few of which are listed in Table 1. In addition to intrinsic fluctuations, measurements of IOP can vary because of numerous sources of error related to measurement technique as well as patient factors.

One source of short-term fluctuations that is of particular interest is the change that occurs with body position. IOP has long been known to vary with body position, increasing from the sitting to supine position. However, measurement sequence can affect the magnitude of the change in IOP. IOP in other body positions is incompletely understood. A recent study from our laboratory compared IOP in 6 head and body positions using a randomized sequence of measurements in healthy participants.[11] We found that in the sitting position, neck flexion and extension both resulted in an increase in IOP compared with having the neck in a neutral position. In all recumbent positions, including supine and right and left lateral decubitus positions, IOP was higher than that found in a position of sitting with the neck in a neutral position. Also, lateral decubitus positions resulted in a higher IOP in the dependent eye compared with the nondependent eye, a result confirmed by other investigators.[16–19] These results suggest that IOP measured while the patient is sitting with the neck in a neutral position (the typical position for a slit lamp examination) is the lowest of any body position, highlighting the need to better understand the role of positional IOP changes in glaucoma pathogenesis.

Circadian Intraocular Pressure Fluctuations

It can be difficult to separate random IOP fluctuations from the normal circadian pattern in an individual patient using routine clinical measurements. However, by using a sleep laboratory and IOP measurements every 2 hours throughout a 24-hour period, Liu et al.[20] have found that IOP is highest in the nocturnal period when measured in the physiologic positions (sitting while awake, supine while asleep). This pattern persists for both healthy participants and patients with glaucoma. The nocturnal elevation in IOP, combined with the drop in systemic blood pressure that normally occurs during sleep, may result in compromise of optic nerve head perfusion in susceptible individuals. In support of this concept, Graham and Drance[21] have found that patients with glaucoma with exaggerated nocturnal declines in blood pressure had significantly greater disease progression rates. Also, Sung et al.[22] found that circadian variation in ocular perfusion pressure was the most consistent prognostic factor for progression in patients with normal tension glaucoma.

Clinical Significance of Intraocular Pressure Variations

Evidence for the clinical significance of IOP variations in glaucoma pathogenesis is limited by difficulty in measuring IOP. Current clinical practice involves a brief measurement of IOP for a few seconds every few months while a patient with glaucoma is in the clinic. What happens during the intervening period is largely unknown for most patients. Despite this limitation, existing studies suggest the possibility that IOP variations may be an independent risk factor for glaucoma, at least in certain patient populations.

Short-term Intraocular Pressure Fluctuations

Bergea et al.[23] investigated the effect of IOP fluctuations, defined as the mean of the daily IOP range obtained during diurnal curves obtained every 2 months for 2 years, on visual field progression in patients with exfoliation and primary open-angle glaucoma (POAG). They found that both mean IOP and IOP fluctuations were correlated with visual field progression in exfoliation glaucoma. However, neither factor was associated with progression in patients with POAG, who tended to have lower IOP. Asrani et al.[24] also investigated short-term fluctuations in patients with open-angle glaucoma by using home self-tonometry to measure IOP 5 times a day for 5 days. They found that, in patients with IOP in the normal range as measured in the clinic, IOP fluctuation was a significant independent risk factor for progression.

Long-term Intraocular Pressure Variations

Evidence for the clinical significance of long-term IOP fluctuations in glaucoma typically comes from ad hoc secondary data analyses of large clinical trial databases. The results from these analyses are intriguing but not yet conclusive.

Nouri-Mahdavi et al.[25] performed a post hoc analysis of the data from the Advanced Glaucoma Intervention Study (AGIS). They defined IOP variation as the SD of IOP at all visits after the initial surgery in the study protocol. IOP fluctuation was found to be a significant risk factor for visual field progression. However, one of the issues with this study was that it included data after therapy was modified owing to visual field progression or IOP greater than the predetermined target of 18 mm Hg. This may have contributed to the IOP variations in patients who were progressing. In a subsequent study using the AGIS cohort, Caprioli and Coleman[26] addressed this issue by limiting the follow-up to the period before visual field

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