IOP: Quantity and Quality

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IOP reduction has been firmly established as effective treatment for glaucoma, as proven in a number of well conducted, prospective, randomized clinical trials. (1,2,3,4,5,6) Here we consider an aspect of the "quality" of IOP: its variation. There is accumulating evidence that, at least in some patients, IOP variation is a separate and important risk factor for glaucomatous damage. IOP variation over time may be divided into diurnal fluctuation that occurs on a daily basis, short-term IOP fluctuation that occurs over days to weeks, and long-term IOP fluctuation that occurs over months to years. In practice, IOP variation is usually quantified as inter-visit IOP variation with IOP measurements being made sequentially during office hours over a long period of time. While this inter-visit IOP variation primarily serves as a surrogate for long term IOP fluctuation, it likely contains some component of diurnal and short-term fluctuation.

In a study of predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study, Nouri-Mahdavi and co-workers found that IOP variation was a significant and independent predictor of worsening, despite the inclusion of mean IOP and the number of glaucoma interventions as independent covariates in the regression models. (7) The study was limited since it was not designed specifically to evaluate IOP variation as a risk factor. A subsequent analysis reported by Caprioli and Coleman sought to more rigorously evaluate this potential relationship. (8) In this post-hoc analysis of the AGIS data, only eyes that had one procedure were included, and only IOP measurements up until the time of visual field progression were included. There was only a weak correlation between magnitude of IOP variation and mean IOP ($r^2 = 0.03$). IOP variation was confirmed as an independent risk factor for visual field progression in a multivariate model, with an odds ratio of 1.39 (95% confidence interval = 1.09, 1.79; p=0.009). A subgroup analysis stratified patients by mean IOP: two groups were evaluated, one with low mean IOP and one with high mean IOP. In those with low mean IOP (mean IOP = 10.8 mmHg), long-term IOP variation was as a significant and independent predictor of visual field progression, while IOP variation in the high mean IOP group (mean IOP = 20.6 mmHg) was not a significant predictor of visual field progression. The authors concluded that IOP variation was important at low mean IOPs (eg, 10-12 mmHg), and that IOP variation was not an important predictor at higher mean IOPs (eg, $>$16mmHg). They concluded that when IOP was high, mean IOP was the overriding risk factor for visual field loss.

Lee and co-workers also found a significant association between long-term IOP variation and glaucoma progression. (9) In a review of charts from several practices across the United States, they found that after controlling for age, mean IOP, visual field stage, and other covariates, each unit increase in IOP SD resulted in an approximately 5 times higher risk in glaucoma. They concluded that IOP variability is an important predictor of glaucoma progression. Hong et al reported that in patients with low IOP after combined glaucoma and cataract surgery, with mean IOPs of approximately 11 mmHg in both groups, the group with the larger IOP variation had significantly worse visual field outcomes than those with lower IOP variations. (10) CIGTS recently confirmed an earlier report that pressure variation was an important, independent risk factor for glaucomatous progression. (11) They found that three IOP measures (range, peak, and standard deviation) were significantly associated with substantial worsening of the visual field defect and that the effects were similar in both surgical and medical groups. More specifically, it was reported that a greater range of IOP ($p < 0.001$), higher peak

IOP ($p = 0.003$), and a larger standard deviation of IOP ($p = 0.006$) were all significantly associated with worse visual field outcomes in the 3 to 9 year follow-up. Predictors of higher range, peak, and SD of IOP were black race, higher baseline IOP, and clinical center. The authors concluded that the results supported the consideration of aggressive treatment when either high peak IOPs or a large variation in IOP is observed. Other well-done studies have found no relationship between IOP variation and progressive glaucomatous damage. In 2007, results from the EMGT showed that there was a high correlation between mean pressure and IOP variation, and that IOP variation was not a separate predictor of visual field progression. (12) Two studies of persons with ocular hypertension also concluded that there was little or no relationship between IOP variation as an independent factor for the prediction of the development of glaucomatous optic disc change or visual field loss. (13,14)

To summarize these apparently disparate findings, IOP variation was not a significant risk factor in EMGT, and in two separate studies in ocular hypertensives. These studies have in common generally higher IOPs and an earlier stage of glaucoma (or no glaucoma at all), and modest or no treatment regimens. Surgery was not used in any of these studies to treat patients and EMGT patients were randomized to ALT and betaxolol or no treatment. IOP variation was a significant risk factor in AGIS, CIGTS, and in studies reported by Hong et al and Lee et al. These studies have in common low IOPs (often after surgery), and moderately advanced disease. In AGIS, when patients were stratified by mean IOP, only those patients with low IOPs showed the detrimental effects of IOP variation. While on initial observation these data may appear to be contradictory, they are in fact complementary. Not all primary open-angle glaucoma patients are the same: existing data would suggest that the effects of IOP variation depend on the characteristics of the patient, the baseline IOP, their stage of damage, the type of glaucoma, and other as yet unknown factors.

Why might IOP variation be damaging? Pathologic changes in medicine are often related to lack of a steady state. Long-term, uncompensated loading and unloading of stresses may break down homeostatic mechanisms at the level of the optic nerve head and lead to additional neuronal, glial and structural damage, particularly in already damaged or vulnerable tissues. Alternatively, irregular and uncompensated excursions of IOP into levels that are damaging may cause progression. A short consideration of optic nerve stresses and strains may be helpful here. The biomechanics of the supporting optic nerve structures of the lamina cribrosa are probably important. With IOP elevation, there is less laminar deformation in an eye with a compliant versus a stiff sclera. Data suggests that eyes exposed to IOP strain undergo remodeling of the lamina cribrosa. (15) The lamina remodels quickly and dramatically in response to IOP. Excavation of the optic nerve may result from laminar failure and progressive remodeling of the connective tissue. For instance, when monkey eyes are exposed to IOP strains, the following events take place: the lamina cribrosa becomes deformed, there is thickening of the laminar lamellae, there are micro-architectural changes and remodeling, and connective tissue volume increases. (16) The remodeled lamellae may be weaker, and the remodeling phase is probably irreversible. There is generally a mechanical failure, which can also result in perfusion changes that contribute to damage. Marked variations in IOP which are uncompensated by protective, homeostatic mechanisms may lead to additional mechanical and vascular failure.

The lack of a steady state contributing to damage is also evident in systemic hypertension where variation of blood pressure is an independent risk factor for end organ damage. The importance of blood pressure variability as a risk factor for vascular events has become increasingly recognized, and has been shown in both animal models and in humans. (17) It is well known that an increase in blood pressure variability is characteristic of hypertensive patients, and that large BP variability aggravates hypertensive damage and is in independent risk factor for untoward vascular events, especially in elderly patients. (18) The reduction of blood pressure variability has become a new strategy for the treatment of systemic hypertension. (19)

A new approach to prevent glaucomatous damage, termed IOP modulation, should be considered. Robust IOP reduction for most patients with progressive primary open-angle glaucoma and a sufficient longevity would be indicated for most patients. We should include the goal of reducing IOP variation, particularly in patients who get worse at low IOP. IOP modulation may maximize treatment by lowering both the mean IOP and IOP variation. The medical modulation of IOP may be enhanced by the use of long acting agents, either topically or through drug delivery systems. Surgical modulation of IOP would also appear to be beneficial in a subset of patients. Varma and colleagues have recently evaluated the use of inter-visit intraocular pressure (IOP) range, as a measure of IOP variation clinical trials in glaucoma. The authors suggested that the impact of reducing high IOP range (variation) on progressive glaucomatous damage deserves further investigation in prospective studies. This approach was the topic of a recent editorial. (20)

Practitioners should consider whether patients who are progressing at low mean IOP may benefit from having their IOP variation reduced. Single elevated measures of IOP noted on a patient visit may not just be an anomaly or related to patient compliance but may in fact identify patients who are at high risk for developing progressive glaucomatous damage and thus should be monitored more carefully and treated more aggressively.

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