Diurnal Perfusion Pressure in Glaucoma Patients

Evaluating this parameter may be useful to the management of the disease.

BY VITAL P. COSTA, MD, AND ALON HARRIS, PHD, MS

Glaucoma is a multifactorial disease characterized by a loss of retinal ganglion cells that leads to typical damage of the optic nerve and visual field. Although IOP is considered the main risk factor for the development of glaucoma and the only parameter subject to treatment, there is sufficient evidence to suggest that glaucoma continues to progress despite lowering patients' IOP to targeted levels.[1-3] All of the major randomized clinical trials have demonstrated that achieving IOP control is not 100% effective in halting the progression of glaucoma.[4-7]

Vascular risk factors are associated with the prevalence and progression of glaucoma.[8] Evaluating patients' diurnal perfusion pressure therefore may provide valuable information to assist clinicians' management of the disease.

PERFUSION PRESSURE AND GLAUCOMA

The utility of several instruments developed to measure blood flow in various ocular beds is limited. Each technology only assesses a small portion of the ocular vasculature. Abnormal ocular blood flow in glaucoma has been documented in the optic nerve, choroid, retina, and retrobulbar circulation. At present, because no single blood-flow device can assess all of the relevant vascular beds, a comprehensive analysis using several modalities is needed to fully evaluate a patient's ocular blood flow.[9] Moreover, due to the complexity of the various datasets and the analysis necessary to interpret these outcomes, it is essentially only possible for scientists who are highly trained in imaging and who have a background in vascular physiology to complete a comprehensive examination of ocular blood flow.

Although clinicians cannot currently visualize ocular blood flow directly, they can easily measure glaucoma patients' blood pressure and IOP to calculate their ocular perfusion pressure and quantify the vascular changes. *Perfusion pressure* is defined as the difference between arterial and venous pressure. In the eye, venous pressure is equal to or slightly higher than IOP. *Ocular perfusion pressure* can therefore be defined as the difference between arterial blood pressure and IOP. It is calculated by taking two thirds of the mean arterial pressure and subtracting the IOP. Ocular perfusion pressure can be further broken down into diastolic perfusion pressure (diastolic blood pressure minus IOP) and systolic perfusion pressure (systolic blood pressure minus IOP).[10] Hence, ocular perfusion pressure can be decreased by raising the IOP or reducing blood pressure.

> "Low diastolic perfusion pressure and large fluctuations in IOP may be strong prognostic factors for glaucomatous progression."

Systemic hypotension has been repeatedly associated with glaucoma.[11-16] In addition, research has demonstrated that decreases in blood pressure secondary to major events such as hemorrhages can lead to glaucomatous optic neuropathy.[17] Patients who experience large fluctuations in blood pressure at night may have a higher risk of glaucomatous progression compared with individuals whose blood pressure fluctuates within normal limits.[18,19]

Population-based studies have identified low perfusion pressure as a risk factor for the development of glaucoma. The Baltimore Eye Survey indicated that individuals with diastolic perfusion pressures lower than 30 mm Hg had a sixfold higher risk of developing the disease than individuals with diastolic perfusion pressures greater than

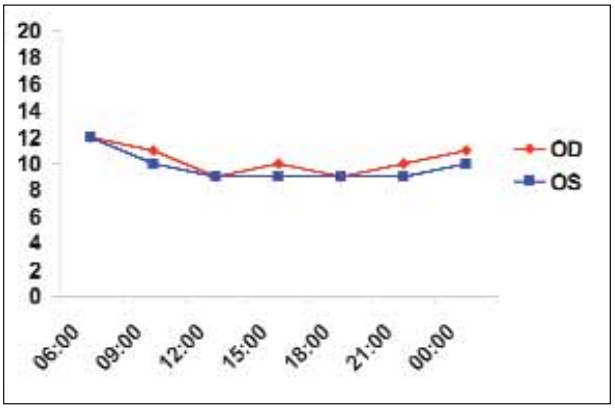

Figure 1. In this 24-hour measurement of a patient with progressive glaucoma despite normal IOPs, the pressure fluctuates between 9 and 12 mm Hg in both eyes.

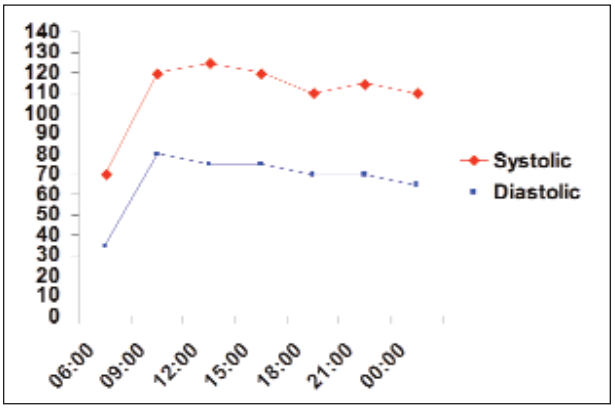

Figure 2. The same patient's diastolic blood pressure dropped at 6:00 AM.

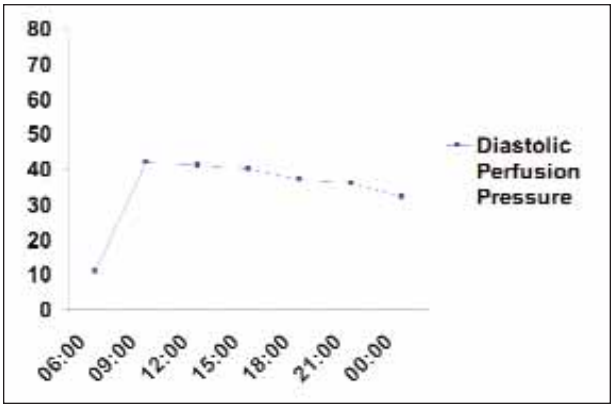

Figure 3. This patient's diastolic perfusion pressure is below the 30-mm Hg value, a cutoff suggested by Tielsch et al to increase the risk of glaucoma sixfold. [20]

50 mm Hg.[20]

The Barbados, Egna-Neumarkt, and Proyecto VER population-based studies also found an increased prevalence of glaucoma in patients with consistently low diastolic perfusion pressures. In the Barbados study, the subjects with the lowest 20% of diastolic perfusion pressures were 3.3 times more likely to develop glaucoma.[21] Similarly, the Egna-Neumarkt study reported a 4.5% increase in the prevalence of the disease in patients with diastolic perfusion pressures of less than 50 mm Hg compared with those whose diastolic perfusion pressures were 65 mm Hg.[11] These findings were born out by the prevalence of glaucoma in the population investigated by the Proyecto Ver study. Patients who presented with a diastolic perfusion pressure of 45 mm Hg had a three times greater risk of developing glaucoma than those with measurements of 65 mm Hg. Although these population-based studies examined individuals from different geographic locations and various ethnic origins,[22] they all found that low diastolic perfusion pressure is an important risk factor for the prevalence of glaucoma. Recently published data from the Early Manifest Glaucoma Trial established lower systolic perfusion and blood pressures as new predictors of disease progression.[23]

DIURNAL FLUCTUATIONS IN IOP AND GLAUCOMATOUS PROGRESSION

Diurnal fluctuations in IOP are an important risk factor for glaucomatous progression. Asrani et al studied 105 eyes of 64 patients with primary open-angle glaucoma and measured their IOPs over a period of 5 days.[24] The relative risk of disease progression within 5 years was six times higher for patients who had a diurnal IOP range of 5.4 mm Hg than for those with a diurnal IOP range of 3.1 mm Hg. In another study, investigators in Sweden evaluated the effects of fluctuations in IOP among patients with pseudoexfoliative glaucoma.[25] Over a period of 2 years, all of the patients' conditions worsened at the same rate despite different mean IOP levels. When the researchers stratified the eyes by the degree of variation in IOP, those with the greatest fluctuation were associated with the fastest rate of visual deterioration.

Oliver et al compared the IOPs of patients blinded by glaucoma with those of patients who maintained their vision despite the disease.[26] The investigators studied the two groups for several decades. Although the mean IOPs were identical, the fluctuation in IOP was significantly greater in the blind individuals. More recently, investigators for the Advanced Glaucoma Intervention Study evaluated patients to analyze their risk factors for visual field progression.[27] A large fluctuation in IOP (standard deviation of the IOP at all visits after the initial surgery) increased the odds of visual field progression by 30% (for each 1-mm Hg increase in the fluctuation of IOP).

GLAUCOMA: BEYOND IOP

By Douglas L. Mackenzie, MD, and Malik Y. Kahook, MD

IOP has long been the only known risk factor for glaucoma that can be modified by medical or surgical intervention. In recent years, researchers have explored other factors such as ocular blood flow and vascular autoregulation/dysregulation for potential diagnostic and/or therapeutic interventions. The utility of these factors is at best experimental and is perhaps more aptly described as hypothetical.

In their article, Vital Costa, MD, and Alon Harris, PhD, eloquently describe the possible utility of measurements of diurnal ocular perfusion pressure in the care of glaucoma patients. The eye, like other organs, uses vascular autoregulation to maintain its equilibrium under different metabolic demands throughout the day. Theoretically, vascular dysregulation in glaucomatous optic neuropathy would leave the optic nerve more susceptible to fluctuations in ocular perfusion pressure that might lead to oxidative stress, injured tissue, and—ultimately, when severe—apoptosis.

Many studies have illustrated the potential importance of ocular perfusion pressure, including both the Baltimore Eye Survey[1] and the Barbados Eye Study.[2] Inconsistencies, however, illustrate the inherent limitation of using an indirect measurement, such as ocular perfusion pressure, to predict what might be happening at the level of ocular tissue. In the Barbados Eye Study, for example, investigators noted that higher IOP might be the culprit in defining glaucomatous optic neuropathy rather than the blood pressure/IOP relationship.[3] In addition, many patients with normal ocular perfusion pressures develop glaucoma while others with low ocular perfusion pressures never do.

As Costa and Harris state, establishing a firm link between vascular dysregulation and glaucomatous optic neuropathy would require measuring the blood supply to the optic nerve, choroid, and retina. Blood flow to each of these areas is controlled by and through different regulatory mechanisms—for example, the endothelial cells (the retina and optic nerve) and hormones and the autonomic nervous system (the choroid and optic nerve). Direct measurements of ocular blood flow may not be subject to the limitations of indirect measurements of ocular perfusion pressure. The former may also be more useful in the diagnosis and treatment of glaucoma. For those reasons, devices that measure blood flow at all levels of the optic nerve as well as choroidal and retinal blood flow are key to expanding clinicians' understanding of ocular blood flow's role in glaucomatous pathology. Unfortunately, the results obtained with current technology are poorly reproducible, and the devices are too expensive, unreliable, and cumbersome for everyday use.

Costa and Harris correctly state that prospective studies are needed to elucidate the importance of calculations of ocular perfusion pressure and how these data may fit into clinical care regimens. Subgroup studies of patients categorized as normal or having ocular hypertension, primary open-angle glaucoma, or normal-tension glaucoma are also required and will likely have widely varying results. In addition, the current instrumentation used to measure ocular blood flow must be validated and improved if they are to be of practical use. Physicians must also recognize the limitations of ocular perfusion pressure and the need for truly direct measurements of ocular blood flow to potentially define an individual's risk of disease, glaucomatous progression, and/or response to treatment.

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POSSIBLE BENEFITS OF 24-HOUR EVALUATION

Based on the literature summarized in this article thus far, low diastolic perfusion pressure and large fluctuations in IOP may be strong prognostic factors for glaucomatous progression. The authors suggest that clinicians investigate patients' ocular perfusion pressure, and they hypothesize that measuring perfusion pressure throughout a 24-hour period may allow physicians to be more comprehensive when determining patients' risk for glaucomatous progression. Interestingly, recent work by Choi et al identified lower mean circadian ocular perfusion pressure as the most consistent clinical risk factor for the severity of glaucomatous damage in eyes

with normal-tension glaucoma.[28]

Some patients may benefit from an assessment of their 24-hour perfusion pressures. Those in whom glaucoma progresses despite apparently normal IOPs may experience nocturnal dips in their perfusion pressures, sometimes induced by antihypertensive medications (Figures 1 and 2). Investigators for the Thessaloniki Eye Study published data in 2006 on the relationship between blood pressure and the structure of the optic disc in subjects without glaucoma. In these individuals, a diastolic blood pressure lower than 90 mm Hg resulting from antihypertensive treatment was associated with increased cupping and a decreased rim area of the optic disc. These findings may suggest that blood pressure could be a contributing factor to damage to the optic nerve and changes in the optic disc.[29] Measuring uncontrolled elevations in IOP and undesirable reductions in blood pressure during a 24-hour period may identify a cause for changes in the optic disc. In the first case, patients would require a further reduction in IOP. When patients' blood pressure is low and they are using antihypertensive therapy, as illustrated in Figures 1 and 2, modifications in their medical regimens may be warranted after consultation with an internist. Clinicians may use a cutoff value of 30 mm Hg, as suggested by the Baltimore Eye Survey,[3] as an indicator of low diastolic perfusion pressure (Figure 3). ❑

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