THE EFFECT OF TRABECULECTOMY ON OCULAR HEOMODYNAMICS*

BY Louis B. Cantor, MD

ABSTRACT

Purpose: To evaluate the effects of chronic reduction of intraocular pressure (IOP) on ocular hemodynamics.

Methods: Multisite, prospective evaluation of patients requiring trabeculectomy for treatment of glaucoma. Patients were recruited from the glaucoma service of 2 university hospitals. Patients were evaluated prior to surgery and at 3, 6, and 12 months after trabeculectomy. Color Doppler imaging was used to measure blood flow in the ophthalmic artery, central retinal artery, and short posterior ciliary arteries. Heidelberg retinal flowmetry was used to evaluate perfusion in the peripapillary and optic disc capillary beds. IOP was measured at baseline and at each study visit.

Results: There were highly significant reductions in IOP from presurgical baseline measures. At 3 months, mean IOP reduction was 17.1 mm Hg (62.3%; \( P < .001 \)). At the 6- and 12-month evaluations, the mean IOP reductions were 15.7 mm Hg (57.3%) and 15.5 mm Hg (56.5%), respectively, \( P < .001 \). Despite the significant reduction in IOP, there were no significant differences in any ocular blood flow parameters before and after trabeculectomy.

Conclusions: The findings of this study suggest that chronic reduction of IOP does not alter ocular blood flow and that IOP may be an independent risk factor for progression of glaucoma. These findings also suggest that the eye has the ability to autoregulate to chronically increased IOP over time and that additional studies evaluating the long-term effects of IOP changes are needed to further define this relationship.

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PURPOSE

For more than a century, elevated intraocular pressure (IOP) has been associated with increased visual field loss in patients with open angle glaucoma, and current treatment strategies place primary importance on lowering IOP to decrease the rate of optic nerve damage. The etiology of the optic neuropathy has been proposed to involve, at least in part, inadequate blood flow to the optic nerve head. However, the relationship between IOP and ocular blood flow has yet to be fully defined. Previous studies examining this relationship have used patients with artificially elevated pressure and have found that acutely increasing IOP results in a significant decrease in ocular blood flow. Few data are available as to whether decreasing naturally elevated IOP improves ocular hemodynamics. Furthermore, studies evaluating blood flow parameters before and after filtration surgery have usually included patients receiving topical glaucoma medications at the time of the preoperative assessment, confounding comparisons with postoperative hemodynamic measurements. This investigation evaluates the ocular hemodynamics of naturally elevated IOP in patients with primary open angle glaucoma, as well as the effects of glaucoma filtration surgery, and the lowering of IOP, on ocular hemodynamics.

HYPOTHESIS

Glaucoma filtration surgery that effectively lowers IOP has no significant long-term effect on ocular hemodynamic parameters; there is no significant difference in ocular hemodynamic parameters measured before and after trabeculectomy.

INTRODUCTION

Several risk factors have been associated with the development of glucomatous optic neuropathy, including elevated IOP, advancing age, diabetes mellitus, African heritage, vascular disease, genetic predisposition, and many others. The causes of glaucoma are still largely unknown, and the contribution of vascular factors to the progression of glaucomatous damage has become an active area of investigation in the last decade. Research identifying higher prevalence of compromised autoregulation, circulatory disorders, and vascular risk factors in glaucoma patients has suggested that impaired ocular blood flow might cause glaucomatous damage, yet damage to the optic nerve head by increased IOP alone has been documented. The role of vascular factors, with or without elevated IOP, is still not clearly understood.

The application of ultrasound technology to the study of vascular tissue in the eye has resulted in a greater understanding of ocular hemodynamics, and color
Doppler imaging (CDI) has become an important tool. CDI is an ultrasonic imaging modality that provides a display of blood flow velocity imposed over a conventional gray-scale B-mode ultrasound image. The principle of Doppler ultrasound is well known. Determination of the blood flow velocity is derived from the ultrasound frequency shift when it is reflected from moving blood cells. The measured velocities are assumed to correlate with blood flow. In ophthalmology, CDI can be used to measure the blood velocity in the ophthalmic artery, the central retinal artery, and posterior ciliary arteries. However, the instrument provides inadequate resolution to allow for the measurement of the diameter of the orbital vessels, and hence a direct extrapolation from blood velocities to blood flow is not possible.

The reliability and reproducibility of CDI were evaluated by Quaranta and associates. In this study the investigators evaluated the intra-observer reliability of CDI for the measurement of ophthalmic artery blood flow in 35 patients. The results suggest that CDI is a reliable tool for the quantitative assessment of blood flow in the ophthalmic artery with a measurement variance of 5.6% for peak systolic velocity, 11.4% for the end diastolic velocity, and 6.2% for the mean envelope velocity. The test/retest reproducibility of CDI for the other orbital vessels were assessed by Harris and associates. Coefficients of reliability were 12%, 25%, and 19% for peak systolic velocity, 6%, 11% and 25% for end diastolic velocity and 4%, 11%, and 38% for the resistive index for the ophthalmic artery, central retinal artery, and short posterior ciliary artery respectively. The CDI measures were highly reproducible for the ophthalmic artery, reasonably reproducible for the central retinal artery, and most variable for the short posterior ciliary artery.

Laser Doppler velocimetry is based on the fact that the frequency of laser light scattered by a moving object, such as an erythrocyte, is shifted by an amount proportional to the velocity of the object. This technique has been further modified to use multiple scattering angles to obtain hemodynamic measurements in the capillary bed of the optic nerve head. This technique, called confocal scanning laser Doppler flowmetry, generates a localized perfusion map of the imaged area with a high resolution. The Heidelberg retina flowmeter (HRF) is an instrument combining the principles of both laser flowmetry and confocal scanning laser Doppler techniques. With use of a scanning laser beam, this method enables high-definition topography of perfused vessels of the optic nerve and retina with simultaneous evaluation of blood flow parameters.

Joos and coworkers evaluated the reproducibility of this technology measuring the velocity, blood volume, and blood flow in the optic nerve head during multiple sessions with a non-confocal system. After 3 months of operator experience, the standard deviation of the intrasession variation was 18% of the velocity mean value and 24% of the flow mean value. The findings suggest that laser Doppler flowmetry, after sufficient operator training, is sufficiently precise to measure human optic nerve head microvascular hemodynamics.

Another study specifically evaluating factors affecting HRF measurements of the retinal and optic nerve head blood flow was conducted by Kagemann and colleagues. In this study the angle of incidence between laser beam and fundus and the camera distance from the eye were evaluated for their possible effect on the measurement of blood velocity, volume, and flow. Both intersession and intrasession variability ratings were calculated, and the images were examined using a pixel-by-pixel histogram of blood flow. Although the ocular hemodynamic measures were unaffected by the angle of incidence between the fundus and the laser beam, the flow measurements showed increasing variability as the camera distance from the eye increased. The coefficient of variation for intersession measures was 7%, but the 4-week intrasession coefficient of variance averaged 30%. In contrast, intersession variability was decreased by using flow histograms of the image with an average value of 16% for total flow and 17% for flow in the pixel of median flow.

Although CDI and HRF are optimally used to measure different ocular hemodynamic parameters, there is a high degree of correlation between the outcome measures. Bohdanecka and associates used both CDI and HRF technology to determine the relationship between blood flow velocities in retrobulbar vessels and blood flow at the optic nerve in glaucoma patients. Correlations between HRF recordings in the optic nerve head and CDI measurements in the ophthalmic artery, the central retinal artery, and the posterior ciliary arteries in the same patients were evaluated. All 3 HRF parameters correlated with CDI measurements obtained from the retrobulbar vessels, with the most significant correlations being between the HRF volume and the end diastolic velocity (EDV) in the ophthalmic and the medial posterior ciliary arteries, and the peak systolic velocity (PSV) in the lateral ciliary artery. The investigators also concluded that glaucoma patients with altered blood flow in retrobulbar vessels are likely to show an alteration in optic nerve blood flow as measured with the HRF.

Doppler ultrasound was utilized in a separate study conducted by Rojanapongpun and associates that evaluated the velocity of ophthalmic artery blood flow in patients with chronic open-angle glaucoma and normal-tension glaucoma (NTG), compared with normal controls. The researchers reported that peak flow velocity, mean velocity, and diastolic velocity were all reduced in the patients with either NTG or chronic primary open-angle glaucoma (POAG), compared with the normal controls. The patients with NTG also had significantly slower mean flow velocities than those with chronic open-angle glaucoma.

A similar study by Rankin and associates also found...
that both POAG and NTG patients had significantly reduced blood flow velocities compared with normal controls. In this study patients with chronic open-angle glaucoma showed a statistically significant decrease in mean diastolic velocity and an increase in the mean resistance index (RI) in the central retinal artery and the short posterior ciliary arteries. The resistance index was calculated as $RI = (PSV - EDV) / PSV$. Patients with NTG showed similar changes, most notably in the central retinal arteries, compared with normal subjects. However, unlike in the previous study, there were no statistically significant differences in any measure of ocular blood flow between the patients with chronic open-angle glaucoma and those with NTG. Harris and associates found similar results, and that vasodilator therapy, by increasing $P_{CO_2}$, reversed the increased vascular resistance.

A study by Diuirm and associates evaluated the retinal and choroidal hemodynamics in normal control subjects and patients with ocular hypertension, POAG, and NTG. Contrary to the reports of Rojanapongpun and Rankin, the retinal arteriovenous velocity was significantly slower in patients with POAG, but not in patients with NTG, compared with normal controls. The researchers concluded that the choroidal and retinal vascular systems behave differently in POAG and NTG and that these differences may be important in the management of glaucoma. However, the conflicting findings in these studies illustrate the complexity of the relationship between IOP and ocular hemodynamics.

**Ocular Blood Flow in Untreated Glaucoma**

Because most studies of ocular hemodynamics involve glaucoma patients using ocular hypertensive agents, it is difficult to determine if these agents have a confounding effect on the blood flow parameters measured. Several studies in recent years have used color Doppler imaging to study blood flow in untreated patients. One such study evaluated untreated patients with POAG or NTG, compared with a group of normal controls, and found that the EDV in the central retinal artery was significantly lower in patients with POAG than in normal subjects. Patients with POAG had significantly greater ophthalmic artery PSVs than patients with NTG or normal subjects. The resistance indices of both the ophthalmic and central retinal arteries were significantly greater in patients with POAG than in normal subjects, and the central retinal artery RI was significantly greater in NTG patients than normal subjects. The investigators concluded that there was an increased resistance to blood flow in the central retinal artery of untreated POAG and NTG patients and also in the ophthalmic artery of patients with POAG. In addition, the ophthalmic artery peak systolic velocity was elevated in untreated POAG patients.

A later study supported the conclusion that there is a definite pattern of altered ocular circulation in patients with glaucoma. There was a significant reduction in choroidal and short posterior ciliary artery circulation in untreated POAG patients compared with ocular hypertensive patients. Moreover, these patients were matched for age and IOP, thus removing 2 demonstrated confounding factors in an attempt to identify any IOP-independent changes in blood flow in POAG patients. Interestingly, even after controlling for factors known to affect perfusion pressure, the investigators found evidence of reduced ocular blood flow in POAG compared with ocular hypertension. The ocular pulse amplitude, pulsatile ocular blood flow, and pulse volume were significantly lower in the POAG group compared with the ocular hypertension group.

**The Effect of Trabeculectomy on Ocular Hemodynamics**

The hypothesis that vasospasm is involved in the pathogenesis of glaucoma is supported by many recent studies. O'Brien and Butt reported that patients with NTG had significantly reduced finger blood flow after immersion in cold water, compared with patients with untreated POAG and normal controls, as well as significantly longer recovery time to pre-immersion flow. Moreover, the POAG patients also had a significantly prolonged recovery time, relative to normal controls. Other studies have reported an increased incidence of migraine in patients with NTG and an association between NTG and an increased incidence of vasospasm, significantly reduced blood flow in the fingers, and a pathologic blood cell velocity. Faulty autoregulation of blood flow may also be characteristic of circulatory irregularity in patients with glaucoma. Evans and associates compared measures of retrobulbar hemodynamics in patients during postural change. When changing from the upright to the supine position, both glaucomatous patients and normal controls demonstrated significant increases in ophthalmic artery EDV and significant decreases in ophthalmic artery RI. Normal subjects also showed a significant decrease in central retinal artery RI, but glaucoma patients did not. The investigators concluded that these findings indicate that posture change exposes a vascular autoregulatory deficit in glaucoma patients, with the most prominent deficit in the vessels distal to the central retinal artery.

The possibility of an autoregulatory deficit in glaucoma patients is also supported by a large community-based screening of 5,308 individuals over the age of 40.9 In this survey, POAG was defined by demonstrable ocular nerve damage, without consideration of IOP. In this study, systolic and diastolic blood pressures were positively related to...
POAG, and this relationship was modified by age, with a stronger association found among older subjects. Lower perfusion pressure was also strongly associated with an increased prevalence of POAG. The investigators concluded that these findings suggest that POAG is associated with a breakdown of autoregulation and alterations in factors related to ocular blood flow.

**INTRAOCULAR PRESSURE AND OCULAR HEMODYNAMICS**

Abnormally elevated IOP has long been associated with the progression of glaucomatous damage. However, the relationship between IOP and blood flow velocities in the ocular vessels has yet to be clearly defined. Michelson and Harazny attempted to quantify the relationship between ocular vessels has yet to be clearly defined. Michelson and Harazny attempted to quantify the relationship between ocular pulse pressures and retinal vessel velocities using pulsed Doppler sonography. The relationship between the pulse-curves of the blood velocity in the ophthalmic artery, the central retinal vein and artery, and the IOP in 23 eyes of healthy subjects was evaluated. In all eyes, the researchers found a significant linear relationship between the blood velocity in the central retinal vein and IOP.

The effect of moderate changes in IOP on ocular hemodynamics was further evaluated by Findl and colleagues. In this study, elevations in IOP of 10 mm Hg and 20 mm Hg were induced by a suction cup in 10 healthy patients. Blood flow velocities in the central retinal artery and in the ophthalmic artery were measured by Doppler sonography, while ocular fundus pulsations in the macula and the optic disc were measured by laser interferometry. The investigators reported that as IOP was artificially increased, blood flow velocity in the central retinal artery and in the ophthalmic artery was reduced by both 10 mm Hg and 20 mm Hg elevations in IOP. The RI in the central retinal artery was significantly increased at both 10 mm Hg and 20 mm Hg. An increase in IOP was also found to correlate with significant reductions in fundus pulsations, which were more pronounced in the macula. In contrast, increasing IOP did not affect blood flow parameters in the ophthalmic artery.

A later study evaluated the autoregulatory capacity of the ciliary arteries in response to acutely elevated IOP. In this study, color Doppler imaging was performed on the short posterior ciliary arteries of 10 normal subjects at baseline and at incrementally increasing IOP. With use of a scleral suction cup, IOP was elevated to 25, 30, 40, and 50 mm Hg. Systolic and diastolic flow velocities were measured and resistivity indexes were calculated. The investigators reported that both systolic and diastolic flow velocities significantly decreased linearly with each incremental increase in IOP, while the RI increased linearly with each incremental increase in IOP. On the basis of these results, they concluded that the normal healthy eye is unable to autoregulate blood flow velocities in response to sharp elevations in IOP.

Although the previously mentioned studies clearly demonstrate a linear relationship between IOP and changes in ocular blood flow, the subjects were all normal. This selection of normal subjects may limit the applicability of their findings to patients with glaucoma. One of the few studies to use patients with glaucoma in an evaluation of the effects of acute IOP elevations was conducted by Quaranta and colleagues in 1994. This study, using patients with NTG and normal controls, found that although there were significant decreases in pulsatile ocular blood flow in both groups with IOP elevations of either 5 or 10 mm Hg, the decrease was significantly greater in the patients with NTG. The researchers concluded that these findings indicate an altered response of the vascular system with NTG, perhaps due to faulty myogenic autoregulation in reply to increased perfusion pressure.

Although the previous studies all describe the effect of elevated IOP on ocular hemodynamics, it is important to note that numerous studies report altered ocular blood flow in patients with low-tension glaucoma and NTG.

**THE EFFECT OF OCULAR HYPOTENSIVE AGENTS ON OCULAR HEMODYNAMICS**

In recent years, numerous studies have illustrated the effects of a wide range of ocular hypotensive agents on ocular blood flow. Turaci and coworkers investigated the effect of betaxolol, a beta-1-selective adrenoreceptor antagonist, on ocular blood flow and visual function in patients with NTG (n = 36 eyes). After 1 year of treatment with 0.5% betaxolol hydrochloride, the resistivity of the ophthalmic artery was significantly reduced and visual fields were significantly improved. The RIs in the central retinal artery and posterior ciliary artery were also improved but not to a statistically significant extent. These findings seem to indicate that ocular hemodynamics and visual function may be improved by long-term use of betaxolol in patients with NTG.

However, these findings were contradicted by a later study by Harris and colleagues. This study examined whether or not dosages of betaxolol and dorzolamide sufficient to lower IOP significantly in NTG patients (n = 9) had a comparable or a dissimilar impact on the retinal and retrobulbar circulation. In this open-label, 4-week, crossover study, both betaxolol and dorzolamide significantly lowered IOP, but only dorzolamide significantly accelerated arteriovenous passage of fluorescein dye in the inferior temporal quadrant of the retina, as measured by scanning laser ophthalmoscopy. Neither drug affected arteriovenous passage in the superotemporal retina or the central retinal or ophthalmic artery flow velocity (as measured by CDI) in this short-term study.
The Effect Of Trabeculectomy On Ocular Hemodynamics

that any effects of betaxolol on ocular blood flow are seen only after long-term use in patients with NTG.

These findings would seem to conflict with those of Arend and associates,63 who evaluated the effect of topical beta-adrenoreceptor blocking agents on circulation in the retina and optic nerve head. In this study, betaxolol, levobunolol, and timolol were each given to 12 subjects on separate occasions at least 2 weeks apart. Macular capillary blood velocity, epipapillary blood velocities, arteriovenous passage times, and arterial and venous diameters were measured by digital image analysis of scanning laser fluorescein angiograms before the drugs were instilled and 2 hours later. All 3 drugs, despite their differing beta-adrenergic properties, increased blood velocities in the epipapillary and retinal capillaries, while decreasing arteriovenous passage time by approximately 25%. There were no changes in arterial and venous diameters as measured by digital image analysis scanning laser fluorescein angiograms. The investigators concluded that the increased blood velocities in retinal and epipapillary capillaries, in concert with decreased retinal arteriovenous passage time, with constant retinal arterial and venous diameters, may indicate improved retinal perfusion after drug treatment. It is important to note that healthy, nonglaucomatous patients were used in this study, whereas the evaluation by Harris and colleagues, reporting that short-term use of betaxolol did not affect retinal hemodynamics, used patients with NTG. This disparity of results may highlight the confounding nature of extrapolating findings in normal controls to patients with glaucoma.

The impact of dorzolamide on ocular pulse amplitude in POAG patients was evaluated by Schmidt and coworkers,64 who reported that there were significant reductions in both IOP and ocular pulse amplitude after treatment with dorzolamide for 2 days compared with baseline measures.

Interestingly, prescription medications are not the only substances found to alter ocular blood flow. A recent Phase I clinical trial65 reported that ginkgo biloba extract, 40 mg taken orally 3 times daily for 2 days, significantly increased end diastolic velocity in the ophthalmic artery when compared with placebo-treated baseline in 11 healthy volunteers. No side effects were reported, and IOP was not altered.

Although numerous ocular hypotensive agents have been found to affect ocular hemodynamics in both healthy persons and glaucoma patients, a causal relationship between decreased IOP and improved ocular blood flow has not been proved. In fact, ocular blood flow appears to be unaffected by brimonidine tartrate, which is comparable to timolol in ocular hypotensive efficacy.66,67 Lachkar and associates68 found that hemodynamics in the posterior segment of the eye, as measured by color Doppler ultrasound, were not altered by short-term brimonidine therapy. Although IOP was significantly reduced by a mean 17.7%, velocities and resistivity indices in the ophthalmic artery, central retinal artery, nasal artery, and temporal ciliary arteries showed no statistically significant differences between brimonidine 0.2% and placebo, nor were there any significant changes from baseline. These findings were supported by a later study,69 which also found no significant changes in retinal capillary blood flow in ocular hypertensive subjects treated with brimonidine, despite a 16.2% to 17.9% reduction in IOP.

TRABECULECTOMY AND OCULAR HEMODYNAMICS

Trabeculectomy is commonly performed in patients with chronic open-angle glaucoma, since it appears to be the best surgical method for preservation of the visual field.70 The effect of trabeculectomy, with its corresponding decrease in IOP, on ocular hemodynamics has only begun to be studied. One of the few studies evaluating this relationship used CDI in a prospective population of 20 patients about to undergo trabeculectomy.71 Patients were evaluated before surgery and then at 2-, 5-, and 14-week intervals after surgery. At nearly all postoperative evaluations, there were statistically significant increases in the mean and end diastolic velocity and a significant reduction in the vascular resistance of the central retinal artery and both short posterior ciliary arteries. Although the velocity increased in the ophthalmic artery at all time points, only one of 3 postoperative intervals for mean velocity and 2 of the 3 intervals for EDV were statistically significant. There were no significant changes in resistance. The investigators concluded that these findings were consistent with increased blood flow through the central retinal artery and short posterior ciliary arteries with the reduction in IOP after trabeculectomy.

In contrast, James72 reported finding no significant change in pulsatile ocular blood flow, as measured in patients in a reclined position, despite a significant reduction in IOP following surgery. However, when ocular blood flow was evaluated with patients in a standing position, there were significant increases in pulsatile ocular blood flow at 3 and 6 months after trabeculectomy. James hypothesized that these findings may reflect a return to more normal autoregulatory ability in patients who have undergone a dramatic reduction in IOP. It is important to note that the patients in this study, as well as in the previous report, were using a variety of topical ocular hypotensive medications at the time of surgery. As previously summarized, certain antiglaucoma medications may influence ocular hemodynamics and thus may have a confounding effect on the postsurgical evaluation.

The purpose of the present investigation is to evaluate the ocular hemodynamics of naturally elevated IOP in patients with primary open-angle glaucoma as well as the
effects of glaucoma filtration surgery and the lowering of IOP on ocular hemodynamics.

METHODS

PATIENTS

Seventeen patients (19 eyes) with POAG who were assessed to have IOP too high for their degree of optic nerve cupping and visual field loss were recruited from the glaucoma services of 2 hospitals for trabeculectomy surgery. Included patients had POAG, NTG, or pigmentary or pseudoexfoliative glaucoma with IOPs of 32 mm Hg or less with their current medical therapy. Patients using topical or oral antiglaucoma medications were washed out using the following schedule: topical beta blockers and latanoprost, 4 weeks; brimonidine or other alpha adrenergics, 2 weeks; topical miotics, 2 weeks; oral or topical carbonic anhydrase inhibitors, 1 week. Patients were excluded if they had either primary or secondary angle-closure glaucoma, a cup-to-disc ratio greater than 0.9, split fixation on recent visual fields, a visual field defect approaching the central 5 degrees of fixation, previous intraocular surgery on the study eye, or a history of orbital or ocular trauma, or if any alterations in ongoing systemic vasoactive medication regimens were anticipated.

All patients signed an informed consent statement outlining the risks of washout from antiglaucoma medication and blood flow measurement that had been reviewed and approved by the University Institutional Review Board.

PROCEDURES

Prior to surgery, all patients underwent a comprehensive examination. A thorough ocular examination was conducted that included visual acuity, biomicroscopy, and fundoscopy. IOP, using Goldmann applanation tonometry, was also measured. Blood pressure was measured with a standard sphygmomanometer, and heart rate was measured by taking the pulse at the radial artery with patients in a seated position.

Hemodynamics in the ophthalmic artery, short posterior ciliary arteries, and central retinal artery were evaluated by using color Doppler imaging. Each patient was seated in a reclined position and asked to relax. A sterile, ophthalmic methylcellulose gel was then applied to the closed eyelid to act as a coupling agent for the ultrasound transducer. Ultrasound waves of known frequency were then sent out from the transducer (Quantum 2000, 7.5-MHz linear array transducer). The returning reflected waves were analyzed for frequency shifts, and these frequency shifts were then extrapolated into a range of colors and shades on a video screen. These colors and shades correspond to direction and velocity, respectively. From these data, 3 measurements were obtained: the peak systolic velocity, the end diastolic velocity, and the resistance index.

The Heidelberg retina flowmeter (Heidelberg Engineering, Heidelberg, Germany), based on scanning Doppler flowmetry, was used to measure perfusion within peripapillary and optic disc capillary beds. The HRF utilized a low-intensity infrared laser beam to scan the fundus. Moving red blood cells striking the beam caused a portion of the light to be Doppler shifted. Shifts within the reflected light were analyzed to determine the blood velocities present within the scanned tissue. Using the amplitude of the Doppler shifts, the volume of moving blood was determined. The data regarding velocity and volume were then combined to compute total blood flow, and a physical map of flow volumes contained in the retina was created. Interpretation of these flow maps was done using an original, previously described HRF measurement method by Kagemann, Harris, and coworkers. All measurement points of sufficient image quality were displayed by histogram, and cumulative percentage landmarks were used to describe the shape of the flow distribution within the retina. This technique also allows for discrimination of perfused and avascular tissue, producing measurements of the degree of vascularity of the fundus.

Each patient then underwent a trabeculectomy utilizing current trabeculectomy techniques. For all procedures, a limbus-based conjunctival and Tenon's flap was dissected superiorly. In most cases, mitomycin-C was given at a concentration of 0.2 mg/cc for 2 minutes beneath the conjunctival and Tenon's flaps. When mitomycin-C was used, the surgical site was subsequently irrigated generously with balanced salt solution. An approximately 3 x 3 mm rectangular scleral trabeculectomy flap was fashioned and dissected anteriorly into clear cornea. Hemostasis was achieved with wet-field cautery. A parametasis was performed through clear cornea. The trabeculectomy block was excised utilizing a combination of a blade and scissors. A peripheral iridectomy was performed. The scleral flap was sutured into position with 2-10-0 nylon sutures posteriorly, with placement of additional sutures as necessary to control the egress of aqueous. The conjunctival and Tenon's flaps were closed in a two-layered fashion with running Vicryl suture on a vascular needle. The anterior chamber was re-formed with a combination of balanced salt solution and viscoelastic as needed. If the anterior chamber remained formed with no visible leaking from the bleb, the procedure was concluded, and a combination antibiotic-steroid ointment and patch were applied to the eye. Postoperative medications dispensed included a topical corticosteroid, antibiotics, and cycloplegics as indicated.

In addition to having routine postoperative evaluations, each patient returned for a comprehensive examination at month 1 and months 3, 6, and 12. All procedures...
followed at the preoperative examination and described above were repeated for each of these evaluations. Eyes were excluded from follow-up if any subsequent ocular surgery, such as cataract surgery, was required.

**STATISTICAL ANALYSIS**

Student's t tests were used to evaluate all IOP, heart rate, blood pressure, color Doppler imaging, and Heidelberg flowmetry data. Bonferroni's correction was applied for multiple t tests from the same data set. The target sample size of 15 eyes would provide 90% power to detect a difference of 10%. The a priori alpha level was .05 for all tests.

**RESULTS**

Of the enrolled patients, 58.8% (10/17) were female, 88.2% (15/17) were white, and 76.5% (13/17) had a diagnosis of POAG. The mean age of the study population was 62.1 years (+ SD, 13.4; range, 41-85). The most commonly used systemic medications were Glucophage (3/17; 17.6%), Glucotrol (2/17; 11.8%), Synthroid (2/17; 11.8%), estrogens (2/17, 11.8%), and albuterol (2/17; 11.8%; Table I). During the study, 94.1% of patients (16/17) either had no alterations in their ongoing vasoactive medication regimen or did not use vasoactive medications. One patient underwent cardiac bypass surgery 5 months after trabeculectomy and discontinued vasoactive medication.

As expected, there were highly significant reductions in IOP from presurgical baseline measures in the surgical eyes. At 3 months, there was a mean IOP reduction of 17.1 mm Hg (62.3%; P < .001). At the 6- and 12-month evaluations, the mean IOP reductions were 15.7 mm Hg (57.3%) and 15.5 mm Hg (56.5%), respectively (P < .001). Interestingly, there were also small reductions in IOP in the fellow eyes, but these reductions were not statistically significant (P ≥ .139; Fig 1). There were no significant changes in heart rate or blood pressure from baseline measures at any study visit.

Despite the significant decrease in IOP following trabeculectomy, there were no significant changes in the peak systolic velocity, end diastolic velocity, or resistive index in the ophthalmic artery (Table II). The PSV, EDV, and RI in the central retinal artery also remained unchanged from pretrabeculectomy measures at all study visits (Table III). There were no significant changes in any parameters in the fellow eyes at any follow-up visit.

There were also no significant changes in hemodynamic measures in the nasal and temporal posterior ciliary arteries following trabeculectomy (Tables IV and V, respectively). There were no statistically significant changes in PSV, EDV, or RI in either vessel in either the surgical or fellow eyes.

There were also no significant changes in blood flow in the peripapillary or optic disc capillary beds, as measured by HRF (Table VI).
**TABLE II: BLOOD FLOW IN THE OPHTHALMIC ARTERY AT PRESURGERY BASELINE AND AT EACH STUDY VISIT WITH P VALUES FOR CHANGE FROM BASELINE**

<table>
<thead>
<tr>
<th></th>
<th>PEAK SYSTOLIC VELOCITY</th>
<th>END DIASTOLIC VELOCITY</th>
<th>RESISTIVE INDEX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN (SD) N P</td>
<td>MEAN (SD) N P</td>
<td>MEAN (SD) N P</td>
</tr>
<tr>
<td>Baseline</td>
<td>30.74 (13.04) 19</td>
<td>7.82 (3.12) 19</td>
<td>.73 (0.06) 19</td>
</tr>
<tr>
<td>Month 3</td>
<td>31.13 (10.22) 15 .924</td>
<td>8.17 (2.48) 15 .724</td>
<td>.73 (0.04) 15 .980</td>
</tr>
<tr>
<td>Month 6</td>
<td>28.22 (10.05) 15 .541</td>
<td>7.44 (2.94) 15 .725</td>
<td>.73 (0.07) 15 .831</td>
</tr>
<tr>
<td>Month 12</td>
<td>27.72 (7.0) 11 .485</td>
<td>6.96 (2.15) 11 .429</td>
<td>.75 (0.06) 11 .642</td>
</tr>
</tbody>
</table>

**TABLE III: BLOOD FLOW IN THE CENTRAL RETINAL ARTERY AT PRESURGERY BASELINE AND AT EACH STUDY VISIT WITH P VALUES FOR CHANGE FROM BASELINE**

<table>
<thead>
<tr>
<th></th>
<th>PEAK SYSTOLIC VELOCITY</th>
<th>END DIASTOLIC VELOCITY</th>
<th>RESISTIVE INDEX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN (SD) N P</td>
<td>MEAN (SD) N P</td>
<td>MEAN (SD) N P</td>
</tr>
<tr>
<td>Baseline</td>
<td>6.50 (2.12) 19</td>
<td>1.41 (0.49) 19</td>
<td>.76 (0.10) 19</td>
</tr>
<tr>
<td>Month 3</td>
<td>7.21 (2.21) 15 .35</td>
<td>1.66 (0.63) 15 .212</td>
<td>.77 (0.05) 15 .841</td>
</tr>
<tr>
<td>Month 6</td>
<td>7.05 (1.58) 15 .411</td>
<td>1.87 (0.74) 15 .098</td>
<td>.74 (0.07) 15 .403</td>
</tr>
<tr>
<td>Month 12</td>
<td>7.10 (1.47) 11 .418</td>
<td>1.74 (0.38) 11 .152</td>
<td>.75 (0.03) 11 .830</td>
</tr>
</tbody>
</table>

**TABLE IV: BLOOD FLOW IN THE NASAL POSTERIOR CILIARY ARTERIES AT PRESURGERY BASELINE AND AT EACH STUDY VISIT WITH P VALUES FOR CHANGE FROM BASELINE**

<table>
<thead>
<tr>
<th></th>
<th>PEAK SYSTOLIC VELOCITY</th>
<th>END DIASTOLIC VELOCITY</th>
<th>RESISTIVE INDEX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN (SD) N P</td>
<td>MEAN (SD) N P</td>
<td>MEAN (SD) N P</td>
</tr>
<tr>
<td>Baseline</td>
<td>6.91 (2.16) 16</td>
<td>1.59 (0.36) 16</td>
<td>.75 (0.10) 16</td>
</tr>
<tr>
<td>Month 3</td>
<td>7.72 (5.10) 14 .568</td>
<td>2.32 (1.69) 14 .133</td>
<td>.70 (0.08) 14 .109</td>
</tr>
<tr>
<td>Month 6</td>
<td>5.82 (1.83) 13 .158</td>
<td>1.93 (1.03) 13 .319</td>
<td>.64 (0.22) 13 .088</td>
</tr>
<tr>
<td>Month 12</td>
<td>6.45 (1.68) 8 .607</td>
<td>1.59 (0.26) 8 .991</td>
<td>.74 (0.80) 8 .763</td>
</tr>
</tbody>
</table>

**TABLE V: BLOOD FLOW IN THE CENTRAL RETINAL ARTERIES AT PRESURGERY BASELINE AND AT EACH STUDY VISIT WITH P VALUES FOR CHANGES FROM BASELINE**

<table>
<thead>
<tr>
<th></th>
<th>PEAK SYSTOLIC VELOCITY</th>
<th>END DIASTOLIC VELOCITY</th>
<th>RESISTIVE INDEX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN (SD) N P</td>
<td>MEAN (SD) N P</td>
<td>MEAN (SD) N P</td>
</tr>
<tr>
<td>Baseline</td>
<td>6.64 (2.26) 16</td>
<td>2.08 (1.45) 16</td>
<td>.665 (0.16) 16</td>
</tr>
<tr>
<td>Month 3</td>
<td>6.56 (2.26) 8 .940</td>
<td>2.13 (1.80) 8 .919</td>
<td>.62 (0.27) 8 .200</td>
</tr>
<tr>
<td>Month 6</td>
<td>6.82 (2.13) 10 .834</td>
<td>2.23 (1.36) 10 .787</td>
<td>.70 (0.09) 10 .995</td>
</tr>
<tr>
<td>Month 12</td>
<td>5.52 (1.58) 7 .250</td>
<td>1.71 (1.40) 7 .522</td>
<td>.63 (0.28) 7 .256</td>
</tr>
</tbody>
</table>

**TABLE VI: HEIDELBERG RETINAL FLOWMETRY DATA WITH P VALUES FOR CHANGES FROM BASELINE**

<table>
<thead>
<tr>
<th></th>
<th>10% COUNT</th>
<th>25% COUNT</th>
<th>50% COUNT</th>
<th>75% COUNT</th>
<th>90% COUNT</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>MEAN P</td>
<td>MEAN P</td>
<td>MEAN P</td>
<td>MEAN P</td>
<td>MEAN P</td>
</tr>
<tr>
<td>Baseline</td>
<td>95.39</td>
<td>224.47</td>
<td>440.96</td>
<td>709.95</td>
<td>1012.65</td>
</tr>
<tr>
<td>Month 3</td>
<td>100.60</td>
<td>238.22</td>
<td>461.70</td>
<td>742.63</td>
<td>1049.27</td>
</tr>
<tr>
<td>Month 6</td>
<td>100.88</td>
<td>235.36</td>
<td>458.85</td>
<td>760.47</td>
<td>1077.31</td>
</tr>
<tr>
<td>Month 12</td>
<td>107.28</td>
<td>226.04</td>
<td>428.24</td>
<td>673.59</td>
<td>946.72</td>
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</table>
DISCUSSION

For more than a century, elevated IOP has been considered to be the primary cause of visual loss in patients with open-angle glaucoma. Current treatments focus overwhelmingly on lowering IOP in glaucomatous patients, preferably below 20 mm Hg. While a reduction in IOP is clearly beneficial for the preservation of the visual field, the progression of visual field loss and glaucomatous optic nerve damage has been well documented in the absence of abnormally elevated IOP. Vascular factors have long been considered in the etiology of glaucoma, with the central thesis being that faulty autoregulation or inappropriate vasospasm or vasoconstriction causes inadequate perfusion of the optic nerve head and or retina, resulting in tissue death and visual field loss.

The findings of the present study illustrate that although ocular hemodynamics may be influenced by elevated IOP, dramatic chronic decreases in IOP produced by trabeculectomy in untreated eyes do not lead to improved ocular blood flow as measured by the techniques utilized in this study. This result contrasts sharply with those of several recent studies that reported a direct relationship between changes in IOP and altered ocular hemodynamics. By using a suction cup, Findl and Strenn increased IOP by 10 and 20 mm Hg in normal subjects. In that study, a 20 mm Hg increase in IOP caused a significant reduction in the mean flow velocity in the central retinal artery. Moreover, the RI in the central retinal artery increased significantly, with IOP elevation of just 10 mm Hg. In the present study, there were mean reductions in IOP of 15.5 to 17.1 mm Hg, with no significant change in ocular blood flow in the central retinal artery. Hemodynamics in the ophthalmic artery remained unchanged in both studies, despite significant reductions in IOP.

Acute changes in IOP have also been found to alter ocular blood flow in the posterior ciliary arteries. Joos and associates reported that artificially elevating IOP to 25, 30, 40, and 50 mm Hg reduced blood flow, clearly demonstrating that there is an inverse linear relationship between IOP and blood flow in these vessels. In contrast, the results of the present study suggest that the movement of blood in the posterior ciliary arteries is not dependent on chronic reductions of IOP.

There are several possible explanations for the findings in the present study, compared with previously published works. First, the previously cited studies using scleral suction cups to induce artificially acute IOP elevations were all in normal subjects, with normal baseline IOPs. For instance, in the study by Joos and associates, the mean baseline IOP was 15 (+5) mm Hg. In contrast, the mean baseline IOP of subjects in the current study was 27.4 (+6.5) mm Hg. Additionally, the single study that used patients with glaucoma to evaluate the effect of acute pressure change on ocular blood flow enrolled only patients with NTG, thus limiting the applicability of the findings to patients with NTG or POAG. The extrapolation of findings in a small number of normal subjects to a larger population of patients with glaucoma may be limited by the exclusion in each of these studies of normals with comorbid conditions prevalent in glaucoma patients, such as diabetes and hypertension.

Interestingly, there was also a significant mean reduction in IOP in the fellow eye of patients following trabeculectomy. Though not statistically significant, this reduction may be due to an increase in compliance to previously prescribed treatment regimens of ocular hypotensive agents in the nonsurgical eye following surgery.

The findings of the present study are contrary to those reported by Trible and colleagues, who found that trabeculectomy resulted in significant improvements in blood velocity in the central retinal artery and short posterior ciliary arteries, but are similar to the findings of James, who reported that trabeculectomy failed to produce significant improvements in pulsatile ocular blood flow when evaluated in a reclined position. It may be important to note that patients in the previous studies were using ocular hypotensive medications at the time of surgery, and thus the effect on ocular blood flow of these medications may have acted as a confounding influence. In contrast, the present study had only patients who were not using ocular hypotensive medications at the time of surgery owing to the inability to tolerate the medications, lack of efficacy, or completion of an appropriate washout period prior to surgery.

Numerous studies have documented that reducing IOP does not necessarily halt the progression of visual field loss in glaucoma patients, although greater IOP reductions have been associated with a reduced risk of visual field deterioration. The extent to which IOP must be lowered to reduce the risk of visual field loss is unclear. Recent research that evaluated the correlation between interocular difference in the progression of glaucomatous damage and interocular differences in the retrobulbar blood flow found that interocular differences in the progression of visual field damage were not related to IOP. Moreover, eyes with more marked damage had lower mean blood flow velocities in the ophthalmic artery, higher RIs in the central retinal artery, and higher PSV in the ophthalmic artery. However, it may be important to note that these patients were also taking a variety of ocular hypotensive medications and that the possible effect of these medications on the preservation of the visual field was not taken into consideration. In addition, it has been reported that glaucoma patients with progressive visual
field loss show altered hemodynamics in the short posterior ciliary arteries and the central retinal artery, especially in the absence of increased ocular pressure, and that patients with low-tension glaucoma exhibit significantly lower pulsatile ocular blood flow than normal controls.

Although numerous studies have evaluated the effect of acute IOP changes on ocular hemodynamics, the effects of chronically elevated pressures are still unclear. The results of the present study, in which IOP was reduced chronically without any significant changes in ocular hemodynamics, suggest either that chronically elevated IOP has no effect on reducing blood flow or that any pressure-induced changes are irreversible when the IOP is reduced. Although the latter hypothesis is not currently supported by published reports, there is some evidence that the eye may autoregulate in response to changes in IOP within a certain range. Pillunat and associates in normal eyes measured the average velocity, the number of moving erythrocytes, and the volume of flow in the capillary bed of the optic disc at spontaneous levels of IOP and at pressures artificially elevated to 25, 35, 45, and 55 mm Hg. Of the 10 patients evaluated, 7 maintained their baseline blood flow across the lower range of IOP but showed a reduction in flow at both 45 and 55 mm Hg. In contrast, 2 subjects exhibited a linear decline in blood flow with even slight elevation in IOP. These 2 subjects were reevaluated on 6 additional occasions and consistently exhibited the same lack of autoregulation. However, autoregulation was evident at other locations on the discs of these individuals. The investigators concluded that their findings supported the theory that in most individuals, the optic nerve head is able to maintain a constant blood flow over a range of elevated IOP.

The elimination of the possible confounding effects of ocular hypertensive agents in this study may have influenced the observed lack of significant change in ocular blood flow parameters following chronic reduction of IOP. Although numerous studies have found that ocular hypertensive medications alter ocular hemodynamics, it is not possible to determine if the changes in ocular blood flow are due to a vascular effect of the drug or to the acute reduction in IOP. Moreover, if the eye autoregulates over a period of time, it is possible that even the drug effects on ocular blood flow that are often seen with chronic therapy are true vascular effects of the drug and not necessarily related to decreases in IOP.

**SUMMARY**

The findings of this study suggest that chronically decreasing IOP alone may not improve ocular hemodynamics in glaucoma patients, suggesting that IOP is a risk factor for optic nerve head damage independent of the effects of elevated IOP on ocular blood flow. Moreover, although the evaluation of the effect of acute changes in IOP on ocular hemodynamics may provide some insight into the mechanisms of the pathology, it is possible that the eye may not be evident from short-term studies. As glaucoma is a long-term disease, the contribution of IOP, ocular hemodynamics, or other variables that contribute to either visual field stability or progression of glaucoma may best be understood by considering their chronic influence throughout the course of the disease.

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The Effect Of Trabeculectomy On Ocular Hemodynamics


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