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Effect of Brimonidine on Retinal Vascular Autoregulation and Short-term Visual Function in Normal Tension Glaucoma

GILBERT T. FEKE, PETER J. BEX, CHRISTOPHER P. TAYLOR, DOUGLAS J. RHEE, ANGELA V. TURALBA, TERESA C. CHEN, MARTIN WAND, LOUIS R. PASQUALE

Massachusetts Eye & Ear Infirmary (G.T.F., D.J.R., A.V.T., T.C.C., L.R.P.) and Schepens Eye Research Institute (P.J.B., C.P.T.), Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts; and Consulting Ophthalmologists (M.W.), Farmington, Connecticut.

Abstract

- **PURPOSE:** To assess whether brimonidine 0.15% alters retinal vascular autoregulation and short-term visual function in normal tension glaucoma patients who demonstrate retinal vascular dysregulation.
- **DESIGN:** Nonrandomized clinical trial.
- **METHODS:** In this prospective study, 46 normal tension glaucoma patients not previously treated with brimonidine underwent retinal vascular autoregulation testing and visual function assessment using frequency doubling technology perimetry and equivalent noise motion sensitivity testing. We measured blood flow in a major temporal retinal artery with subjects seated and then while reclined for 30 minutes. Patients having a change in retinal blood flow with posture change outside the range previously found in healthy subjects were classified as having retinal vascular dysregulation. They were treated with brimonidine 0.15% for 8 weeks and designated for retesting.
- **RESULTS:** Twenty-three patients demonstrated retinal vascular dysregulation at the initial visit. Younger age ($P = .050$) and diabetes ($P = .055$) were marginally significant risk factors for retinal vascular dysregulation. After the 8-week course with brimonidine, 14 of the 17 patients who completed the study showed a return of posture-induced retinal blood flow changes to levels consistent with normal retinal vascular autoregulation ($P < .0001$). We found no significant changes in frequency doubling technology perimetry or in motion detection parameters following treatment with brimonidine ($P > .09$ for all tests performed).
- **CONCLUSIONS:** Brimonidine significantly improved impaired retinal vascular autoregulation in normal tension glaucoma patients, but short-term alteration in visual function could not be demonstrated.

Inquiries to Louis R. Pasquale, Massachusetts Eye & Ear Infirmary, Harvard Medical School, 243 Charles Street, Boston, MA 02114; Louis_Pasquale@meei.harvard.edu.

Douglas J. Rhee is currently at the Department of Ophthalmology and Visual Sciences, University Hospitals Case Medical Center and Case Western Reserve University School of Medicine, Cleveland, Ohio.

Author contributions:

design of the study (G.T.F., L.R.P.); conduct of the study (G.T.F., P.J.B., C.P.T., L.R.P.); collection, management, and analysis of the data (G.T.F., P.J.B., C.P.T., L.R.P.); interpretation of the data (G.T.F., P.J.B., L.R.P.); preparation of the manuscript (G.T.F., P.J.B., L.R.P.); review and approval of the manuscript (G.T.F., P.J.B., D.J.R., A.V.T., T.C.C., M.W., L.R.P.).

BRIMONIDINE IS AN ALPHA2 ADRENOCEPTOR agonist that modulates retinal vascular tone by altering nitric oxide signaling.¹ The effect of brimonidine on retinal vessel tone is consistent with the observation that retinal vessels are not innervated.² Interestingly, phakic patients receiving topical brimonidine have vitreous brimonidine levels sufficient to mediate retinal vascular modulatory effects.^{3,4}

There is compelling evidence supporting the role of impaired nitric oxide signaling in primary open-angle glaucoma (POAG). When soluble guanylate cyclase, the intracellular receptor for nitric oxide, is knocked out in a murine model, intraocular pressure (IOP) increases nominally (~1–2 mm Hg), there is abnormal retinal vascular reactivity to nitric oxide donors, and optic nerve degeneration ensues.⁵ With the exception of 1 study,⁶ several research groups^{7–12} found positive associations between *NOS3* (coding for endothelial nitric oxide synthase) genetic polymorphisms or other biomarkers of nitric oxide signaling in association with POAG. Furthermore, female reproductive health attributes, systemic hypertension, and cigarette smoking modify the relation between *NOS3* polymorphisms and POAG.^{13–15} Finally, polymorphisms in the genomic region corresponding to the caveolin genes, which code for proteins that reciprocally control *NOS3* activity in endothelial caveolar membranes,¹⁶ are also associated with POAG.^{17,18}

Previously, we demonstrated that some normal tension glaucoma (NTG) patients exhibit retinal vascular dysregulation and proposed that retinal blood flow instability induced by posture change could contribute to disc hemorrhage and progressive optic neuropathy.¹⁹ Furthermore, we showed that topical brimonidine corrected retinal vascular dysregulation in 6 NTG patients.²⁰ Correction of retinal vascular dysregulation may explain why topical brimonidine was superior to timolol in preserving visual field in NTG patients after 3 years of treatment, as reported in the Low Pressure Glaucoma Treatment Study.²¹

In this study, we prospectively evaluate the effect of brimonidine 0.15% on retinal hemodynamics in NTG patients with retinal vascular dysregulation who have not been previously exposed to this agent. Secondly, we assessed whether brimonidine improved visual function in these patients. Glaucoma patients exhibit selective deficits in processing moving or flickering stimuli.²² Therefore, we chose motion sensitivity²³ and frequency doubling technology perimetry,²⁴ 2 tests that leverage this particular aspect of visual function, in our analysis.

METHODS

• PATIENTS:

This is a prospective, nonrandomized clinical trial of POAG patients with a history of untreated IOP <22 mm Hg. We recruited patients from the practices of 5 of the authors (D.J.R., A.V.T., T.C.C., M.W., and L.R.P.). Prior to study commencement, the Institutional Review Board at Massachusetts Eye & Ear Infirmary approved all aspects of this investigation. Each subject signed written informed consent to participate in the trial, which was registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (identifier:).

POAG patients aged 35–80 years old were eligible for the study. All patients had untreated IOP <22 mm Hg and open angles on gonioscopy in both eyes. There were at least 2 reliable Humphrey 24–2 (Zeiss-Humphrey Instruments, Inc, San Leandro, California, USA) Swedish Interactive Threshold Algorithm visual fields showing reproducible glaucomatous loss in at least 1 eye. Patients were excluded from the study if there was: a history of prior brimonidine treatment; use of more than 2 IOP-lowering medications; evidence of exfoliation or pigment dispersion syndrome; diabetic retinopathy; or history of ocular laser/incisional surgery in either eye. In order to facilitate the retinal blood flow measurements, we included only subjects with refractive error between –10 and +10 diopters, no lens opacities greater than 1+ cortical spokes or 2+ nuclear sclerosis, and pupillary dilation of at least 6 mm following mydriasis.

Forty-six patients met study eligibility criteria; 25 were untreated while the remaining 21 received topical glaucoma medications (latanoprost [n = 8], bimatoprost [n = 4], travoprost [n = 4], timolol [n = 2], timolol + latanoprost [n = 1], timolol + bimatoprost [n = 1], and timolol + travoprost [n = 1]). The left eye underwent hemodynamic testing in 44 patients; the right eye was used in the remaining 2 patients.

• RETINAL VASCULAR AUTOREGULATION TESTING PROTOCOL:

At approximately 10 AM, we allowed subjects to sit for 15 minutes and then measured blood pressure and heart rate using a Keller Vital Signs Monitor (Keller Medical Specialties, Antioch, Illinois, USA). We measured seated IOP in both eyes using Goldmann applanation tonometry (Haag Streit USA, Mason, Ohio, USA) and 1 eye was dilated with tropicamide 1%. Baseline seated ocular perfusion pressure (OPP) was estimated using the standard formula: $OPP = \frac{2}{3} MAP - IOP$, where MAP refers to mean arterial pressure. The factor of two-thirds adjusts for the decline in blood pressure between the brachial and ophthalmic artery with the subject sitting.²⁵ We used the Canon CLBF 100 Laser Blood Flowmeter (Canon Inc, Tokyo, Japan) to measure baseline retinal arterial blood column diameter and centerline blood speed, which allows for automatic calculation of the blood flow rate.²⁶ We chose a site along either the inferior temporal retinal artery (29 subjects) or the superior temporal retinal artery (17 subjects) adjacent to the optic disc for baseline measurements. Prior work demonstrates that seated measures of retinal blood flow with the CLBF are valid and reproducible.²⁶

Following the baseline measurements, the subjects assumed a posture typically used for face-on x-rays, reclining on their right side with their head supported by a foam wedge making a 24-degree angle from the horizontal. Subjects reclined for 30 minutes while brachial blood pressure and heart rate were automatically measured at 5-minute intervals. Laser Doppler blood flow measurements were obtained from the same arterial site that was used at baseline after approximately 15 and 30 minutes of reclining. A 30-minute reclining time ensures that a new equilibrium condition is reached. Previous studies^{25,27} have indicated that a period of at least 5–8 minutes is required for the retinal vasculature to adjust to an altered OPP. Immediately following the 30-minute laser Doppler measurement, with the subject still reclining, we used the Perkins handheld applanation tonometry (Haag Streit USA) to remeasure IOP in the eye undergoing hemodynamic testing. In the reclined

position, OPP was estimated using the following formula: $OPP_{\text{reclining}} = MAP_{\text{reclining}} - IOP_{\text{reclining}}$, where $MAP_{\text{reclining}}$ is the mean brachial artery blood pressure measured in the left arm with the subject reclining on the right side.²⁸ In a clinical trial comparing Goldmann and Perkins applanation tonometry,²⁹ IOP was approximately 1 mm Hg lower using Perkins compared to Goldmann applanation tonometry. Thus, any difference between Goldmann and Perkins applanation tonometry has minimal impact on the calculation of $OPP_{\text{reclining}}$. Subsequently, blood pressure, heart rate, and laser Doppler measurements were repeated after the subjects were resealed for 15 minutes.

Only patients who exhibited retinal vascular dysregulation continued in the study. We defined retinal vascular dysregulation based on the percentage change between the retinal blood flow measured while reclining for 30 minutes and the baseline seated measures. Previously,¹⁹ we found that healthy subjects exhibited a $+6.5\% \pm 12\%$ blood flow change induced by 30 minutes of reclining. Thus, we defined the normal range of blood flow autoregulation as within 2 standard deviations of the mean percentage change found in this group, or -17.5% to $+30.5\%$. Patients with a retinal blood flow change induced by posture outside this range were classified as exhibiting retinal vascular dysregulation. These patients began an 8-week course of brimonidine 0.15% 3 times a day in both eyes. Subsequently, they returned at 10 AM and repeated the testing protocol described above. We obtained retinal hemodynamic measurements at the same retinal arterial site used during the initial visit. Designations of retinal vascular dysregulation and normal retinal vascular autoregulation are reproducible.¹⁹ In our study each patient served as his or her own control in that we measured hemodynamic changes at the same site of the same eye both before and after treatment with brimonidine. Similarly each patient underwent visual function testing, described below, in the eye that had hemodynamic studies both before and after 8-week treatment with brimonidine 0.15%.

• VISUAL FUNCTION TESTING PROTOCOLS:

At each study visit, prior to retinal vascular autoregulation testing, we performed frequency doubling technology perimetry²⁴ and equivalent noise motion sensitivity tests.²³ For frequency doubling technology perimetry, we used the full-threshold N-30 protocol to determine the visual field mean deviation, pattern standard deviation, and test duration in the eye that had hemodynamic testing.

The equivalent noise method²³ measures internal noise and sampling efficiency, which are respectively associated with the dysfunction and the nonfunction of retinal ganglion cells. A PC microcomputer with Matlab (MacBook Pro, Apple, Cupertino, California) and the Psychophysics Toolbox³⁰ was used to present stimuli on a 21-inch View-sonic GS790 CRT monitor (ViewSonic, Walnut, California). We set the monitor's spatial resolution to 1024×768 (subtending $36^\circ \times 27^\circ$) with a refresh rate of 100 Hz and a mean luminance of 50 cd/m^2 . With the subjects positioned in a chin and forehead rest, they viewed the screen situated 57 cm in front of the eye that had hemodynamic testing while the fellow eye was patched. If necessary, patients wore spectacles for their best-corrected near vision.

Random dot motion stimuli were presented within 1 of 3 circular apertures with a radius of 4 degrees. The apertures were centered at 0 degrees (fovea) and at 8 degrees eccentricity in the

inferior and superior visual field. Dot directions were drawn from a normal distribution whose mean and standard deviation were varied by a computer staircase. Random dot noise stimuli were composed of 100 independent black or white dots with a Michelson contrast of 75% that maintained a constant mean luminance level. Each dot subtended 0.19 degrees (6 pixels) in diameter and was initially randomly positioned within a circular region that subtended 4 degrees in diameter. The position of each dot was updated every 3 video frames (40 msec). If a dot's displacement would take it to a position outside the aperture, its position was wrapped to the opposite side of the aperture. Each dot had a lifetime of 3 displacements (120 msec), after which it was randomly repositioned within the aperture. The initial lifetime was random to avoid all dots expiring simultaneously. Stimuli were presented for 500 msec with abrupt onset and offset. The direction of motion of each dot was drawn from a wrapped Gaussian circular uniform distribution whose mean and standard deviation were under computer control.³¹

The subject's task was to maintain fixation on a central dot and to identify whether the mean direction of the moving dots was clockwise or counterclockwise from the 12 o'clock (upwards) position. The fixation point provided feedback that was white following a correct trial and black following an incorrect trial. Subjects provided their responses with a mouse, but if they were uncomfortable with using the mouse, the experimenter recorded their verbal responses.

Motion sensitivity was tested with an equivalent noise paradigm²³ that was used to estimate internal noise and sampling efficiency for each observer. Under equivalent noise analysis, performance is represented by

$$\frac{\sigma_i^2 + \sigma_e^2}{N_{\text{samp}}} = \sqrt{\sigma_{\text{obs}}}$$

where σ_{obs} is the observed direction discrimination threshold, σ_i^2 is internal noise (the directional uncertainty in the observer's visual system), σ_e^2 is external noise (the variance of the direction distribution from which dot directions were drawn), and N_{samp} is the number of dots used by the observer to estimate the global direction of all dots. A FAST procedure³¹ was used to select the cue angle and the standard deviation of the direction distribution of each trial. This method selects the test parameters in each trial that maximizes information gain and provides significant increases in the efficiency of data collection. The test was repeated twice with 100 trials at each test location. At the end of testing, internal noise and sampling efficiency were estimated with the FAST toolbox,³¹ along with 95% confidence intervals on all parameters.

• SAMPLE SIZE CALCULATION:

Data from our initial retinal vascular autoregulation study¹⁹ were analyzed in order to arrive at an appropriate sample size. Assuming a 2-sided test with $\alpha = 0.05$, we determined that 20 patients would provide a statistical power of 80%–90%. The study was also powered to detect differences in motion detection testing before and after treatment with brimonidine, assuming a variation in the motion detection assay of 20%. We estimated that one-half of the

patients would exhibit normal autoregulation at initial testing. Therefore, 40 patients would need to be tested to end up with 20 patients completing the study.

- **STATISTICAL ANALYSIS:**

For the initial retinal vascular autoregulation analysis, results obtained after 30 minutes of reclining were used for comparisons with the baseline, seated measurements. Logistic regression analysis and unpaired *t* tests were used to determine which factors were related to retinal vascular dysregulation at the initial testing visit. For the retinal vascular autoregulation analysis, paired *t* tests were used to determine the significance of differences in the measured parameters prior to and following brimonidine treatment. We used a χ^2 test to assess brimonidine's impact on retinal vascular autoregulation in the patients who exhibited retinal vascular dysregulation at baseline. For the visual function analysis, paired *t* tests on log values prior to and following brimonidine treatment were used in order to equate proportional increases and decreases compared with baseline performance. Results are expressed as mean $\pm$ standard deviation. All tests were 2-tailed, and *P* values less than .05 were considered to be statistically significant.

RESULTS

- **INITIAL VISIT RESULTS:**

Univariate analyses showed no statistically significant differences in the demographic and ocular factors between the patients with or without retinal vascular dysregulation (Table 1). Eighteen patients with retinal vascular dysregulation demonstrated increases in retinal blood flow while reclined vs seated ranging from 31% to 104%, while 5 patients showed blood flow decreases ranging from -24% to -76%. The remaining 23 patients had blood flow changes that were within the normal range (-17.5% to +30.5%), as defined in our initial retinal vascular autoregulation study.¹⁹

We performed a logistic regression analysis to identify factors related to retinal vascular dysregulation. Younger age (odds ratio [OR] = 1.09; 95% confidence interval [CI]: 1.00–1.18, *P* = .0496) and presence of diabetes (OR = 11.89; 95% CI: 0.95–149.04, *P* = .055) were marginally related to retinal vascular dysregulation.

- **POST-TREATMENT VS PRETREATMENT RETINAL HEMODYNAMIC RESULTS:**

Of the 23 patients with retinal vascular dysregulation who began brimonidine treatment, 5 withdrew from the study prior to completing the 8-week treatment period. Three patients had allergic reactions to brimonidine and 2 patients had symptoms associated with low systemic blood pressure. A sixth patient completed the treatment period, but the post-brimonidine measurement was not completed owing to technical issues. Pre- and post-brimonidine data analysis was completed on the remaining 17 patients. There were no significant differences in the seated measures of IOP, MAP, OPP, retinal arterial diameter, blood speed, or blood flow following the 8-week treatment period with brimonidine (Table 2).

Fourteen of the 17 patients who demonstrated retinal vascular dysregulation at the initial visit showed posture-induced retinal blood flow changes to levels consistent with normal

retinal vascular autoregulation after an 8-week treatment period with brimonidine ($P < .0001$) (Table 3). The post-brimonidine improvements in the blood flow responses occurred without any corresponding differences in the posture-induced changes in IOP, MAP, or OPP before brimonidine vs after brimonidine. IOP while reclining increased by $14.2\% \pm 6.2\%$ before brimonidine and by $17.9 \pm 7.9\%$ after brimonidine ($P = .17$). Brachial artery MAP while reclining decreased by $16.0\% \pm 6.0\%$ before brimonidine and by $14.7\% \pm 5.9\%$ after brimonidine ($P = .51$). OPP while reclining increased by $31.5\% \pm 11.9\%$ before brimonidine and by $31.0\% \pm 14.4\%$ after brimonidine ($P = .91$). Removal of the 4 patients with type 2 diabetes mellitus did not materially alter the results of the analyses using all 17 patients. Ten of the remaining 13 patients showed a return of the posture-induced retinal blood flow change to levels consistent with normal retinal vascular autoregulation ($P = .0003$). Of the 10 previously untreated NTG patients with retinal vascular dysregulation, 7 showed a return of the posture-induced retinal blood flow change to levels consistent with normal retinal vascular autoregulation ($P = .005$).

• VISUAL FUNCTION RESULTS:

There were no significant differences in visual field mean deviation or pattern standard deviation as determined by frequency doubling technology perimetry, or in the time required for the patients to complete the test following the 8-week treatment period with brimonidine in the 17 patients with retinal vascular dysregulation (Table 4). Shown in Figure 1 are box plots of the log of the internal noise parameter measured after treatment minus the log of that measured before treatment in the foveal area, the parafoveal inferior visual field, and the parafoveal superior visual field. We computed paired t tests on log values in order to equate proportional increases and decreases compared with baseline performance. The differences in the log values were not statistically different from zero (foveal area, $P = .2463$; inferior field, $P = .2183$; and superior field, $P = .5433$), indicating that there was no significant change in internal noise following 8 weeks of brimonidine treatment. Similarly, shown in Figure 2 are box plots of the log of the sampling efficiency parameter measured after treatment minus the log of that measured before treatment at each eccentricity. Again, the differences in the log values were not statistically different from zero (foveal area, $P = .1104$; inferior field, $P = .0936$; and superior field, $P = .9813$). There was no significant change in sampling efficiency following 8 weeks of brimonidine treatment.

DISCUSSION

IN THIS STUDY, 14 OF 17 NTG PATIENTS WITH RETINAL vascular dysregulation showed a return of the posture-induced retinal blood flow change to levels consistent with normal retinal vascular autoregulation following an 8-week treatment period with brimonidine 0.15%. These results are consistent with our prior retrospective study showing similar findings in 6 NTG patients with retinal vascular dysregulation prior to treatment with brimonidine.²⁰

As in our retrospective study,²⁰ we found (Table 2) that the seated measures of retinal arterial diameter, blood speed, and blood flow rate were not significantly different before and after brimonidine treatment. This finding is also consistent with earlier reports,^{32,33}

where no differences in central retinal artery hemodynamic parameters were noted in POAG patients after brimonidine treatment. Furthermore, other studies reported that brimonidine treatment did not alter intraretinal circulatory parameters in ocular hypertensive patients³⁴ or in healthy volunteers.³⁵ The mean post-brimonidine seated IOP was ~ 1 mm Hg lower than the mean pre-brimonidine seated IOP. This finding is consistent with the ~ 1 mm Hg IOP reduction reported among 62 NTG patients treated with brimonidine in the Low Pressure Glaucoma Treatment Study.²¹ Yet, in that study after 3 years of follow-up, brimonidine preserved visual function, as assessed with standard automated perimetry, better than timolol. We believe that the relative preservation of visual function following brimonidine in that study was likely related to the normalization of retinal vascular autoregulation following brimonidine, as shown in our current study. However, we were unable to demonstrate an improvement in psychophysical parameters after an 8-week course of brimonidine.

Recently Hein and associates reported that human retinal arterioles respond to increases in blood flow in a nitric oxide-dependent manner.³⁶ Of note, the increase in retinal vascular OPP that occurs when subjects recline provides the stimulus for increased flow and the flow-induced dilation mechanism. The ability of brimonidine to influence retinal vascular autoregulation is likely rooted in its interaction with the nitric oxide signaling cascade.

We also found that there were no significant differences in the posture-induced changes in IOP, MAP, or OPP measured before brimonidine vs after brimonidine. The magnitudes of the posture-induced changes in IOP and OPP were similar to those recently reported in subjects measured while lying on their right side (lateral decubitus position) compared to the sitting position.³⁷

Our finding from logistic regression analysis that diabetes was a marginally significant risk factor for retinal vascular dysregulation is not surprising. It is known that patients with type 2 diabetes have vascular endothelial dysfunction and altered retinal vascular reactivity.³⁸ In fact, Shoshani and associates suggested that the impaired retinal vascular autoregulation in diabetes could contribute to glaucomatous damage.³⁹ To allow our findings to be more generalizable, we included 8 patients with type 2 diabetes mellitus and no retinopathy. Removal of these patients did not materially affect the results of any of the analyses.

This study has strengths and limitations that need to be considered. The definition of normal retinal vascular autoregulation is based on a small number of controls; yet, the definition is uniformly applied to all subjects. Furthermore, patients with retinal vascular dysregulation generally had large positional changes in retinal blood flow that responded dramatically to brimonidine. For example, Patient 4 had a 65% increase in retinal blood flow with positional change that, upon treatment with brimonidine, was changed to a 3.4% decrease in flow with positional change (Table 3). The study was not powered to detect determinants of retinal vascular dysregulation and this represents another weakness. One strength of our study is that patients were compared to themselves in terms of their retinal hemodynamic and visual function responses to treatment, although we did not employ a comparison arm consisting of another agent. Another strength is that we assessed the effect of brimonidine on retinal blood flow homeostasis using a stimulus (posture change from a seated to a reclined position) that is completely physiologic in nature. Conversely, while the study showed that brimonidine

improved the retinal vascular autoregulatory response to positional change, we could not demonstrate a concomitant improvement in motion detection, a functional attribute of retinal ganglion cells. There are myriad reasons for this, including the fact that our tests were insensitive to detect such improvements or that we did not allow enough time to detect such changes. Alternatively, it is possible that reversal of visual dysfunction could not be realized in this population.

In conclusion, although these data are not tantamount to changing clinical management of POAG, they do lend support to careful consideration of brimonidine in the treatment of NTG.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST.

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Biosketch

Gilbert T. Feke, PhD, FARVO, is currently at the Massachusetts Eye & Ear Infirmary, Department of Ophthalmology, Harvard Medical School in Boston, MA. Trained as a physicist at the Massachusetts Institute of Technology in Cambridge, MA, Dr Feke's laboratory developed the laser Doppler instrument used in this study. He has published widely in the biomedical optics and ophthalmology literature with a focus on the retinal circulation in glaucoma, diabetes, age-related macular degeneration, and Alzheimer's disease.

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FIGURE 1.

Motion sensitivity in patients with normal tension glaucoma. Box plots of the logarithm of the internal noise parameter measured following 8 weeks of treatment with brimonidine 0.15% 3 times a day in both eyes minus the logarithm of that measured before brimonidine treatment in the foveal area, the parafoveal inferior visual field, and the parafoveal superior visual field in patients with normal tension glaucoma. Horizontal lines, bottom to top: 25th, 50th (median), and 75th percentiles. Upper and lower vertical lines indicate data within 1.5 IQR (interquartile range) of the upper and lower quartiles. Data outside these ranges are plotted as points.

FIGURE 2.

Motion sensitivity in patients with normal tension glaucoma. Box plots of the logarithm of the sampling efficiency parameter measured following 8 weeks of treatment with brimonidine 0.15% 3 times a day in both eyes minus the logarithm of that measured before brimonidine treatment in the foveal area, the parafoveal inferior visual field, and the parafoveal superior visual field in patients with normal tension glaucoma. Horizontal lines, bottom to top: 25th, 50th (median), and 75th percentiles. Upper and lower vertical lines indicate data within 1.5 IQR (interquartile range) of the upper and lower quartiles. Data outside these ranges are plotted as points.

TABLE 1.

Normal Tension Glaucoma Patient Demographic and Ocular Characteristics Stratified According to Retinal Vascular Autoregulatory Status at Visit 1 Prior to Treatment With Brimonidine

	Normal RVA	Abnormal RVA	
	N = 23	N = 23	P Value ^a
Age (y)	60.7 ± 9.9	57.1 ± 10.8	.25
Sex (male/female)	10/13	11/12	.77
Race (white/black/Asian)	22/0/1	17/3/3	.10 ^b
Systemic hypertension (Y/N)	5/18	7/16	.46
Diabetes (Y/N)	3/20	5/18	.45
Family history of glaucoma (Y/N)	15/8	13/10	.54
Glaucoma treatment (Y/N)	11/12	10/13	.77
Seated MAP (mm Hg)	88.9 ± 10.6	91.0 ± 11.3	.53
Seated IOP (mm Hg) ^c	14.4 ± 2.9	15.2 ± 2.3	.32
Seated OPP (mm Hg) ^c	44.9 ± 7.2	45.5 ± 7.2	.78
Mean deviation ^d (dB) ^c	-2.51 ± 2.46	-3.56 ± 4.54	.36
Pattern standard deviation ^e (dB) ^c	3.62 ± 3.45	4.69 ± 4.07	.36
Cup-to-disc ratio ^c	0.68 ± 0.10	0.73 ± 0.11	.15

IOP=intraocular pressure; MAP=mean brachial arterial pressure; OPP 1/4 ocular perfusion pressure; RVA 1/4 retinal vascular autoregulation.

^aUnpaired *t* test.

^bANOVA.

^cRefers to the eye that underwent retinal hemodynamic and specialized visual function testing.

^dHumphrey 24-2 SITA mean deviation.

^eHumphrey 24-2 SITA pattern standard deviation.

TABLE 2.

Baseline Physiologic and Retinal Hemodynamic Values While Seated in Normal Tension Glaucoma Patients Before and Following an 8-Week Treatment Period With Brimonidine 0.15%

	Pre Brimonidine, Mean $\pm$ SD	Post Brimonidine, Mean $\pm$ SD	P Value ^a
	N = 17	N = 17	
IOP (mm Hg)	15.6 $\pm$ 2.2	14.6 $\pm$ 3.0	.12
MAP (mm Hg)	90.4 $\pm$ 11.9	87.1 $\pm$ 11.8	.30
OPP (mm Hg)	44.6 $\pm$ 7.2	43.5 $\pm$ 6.5	.55
Arterial diameter (μ m)	114 $\pm$ 15	112 $\pm$ 16	.39
Blood speed (mm/s)	37.2 $\pm$ 11.4	37.0 $\pm$ 10.4	.96
Blood flow (μ l/min)	11.5 $\pm$ 4.6	11.3 $\pm$ 4.7	.90

IOP = intraocular pressure; MAP = mean brachial arterial pressure; OPP = seated ocular perfusion pressure.

^a Paired *t* test.

Normal Tension Glaucoma Patient Demographic Characteristics, Pre-brimonidine Treatment Status, and Percentage Change in Retinal Arterial Blood Flow While Reclining for 30 Minutes Compared to Sitting Before and Following an 8-Week Treatment Period With Brimonidine 0.15%

TABLE 3.

Patient	Age (y)	Race	Sex	Diabetes (Yes/No)	Pre-brimonidine Rx	% Blood Flow Pre Brimonidine	% Blood Flow Post Brimonidine
1	56	W	M	No	Travoprost	47.3	14.2
2	50	W	F	No	Untreated	-23.8	-8.2
3	55	W	F	No	Travoprost	32.1	-6.7
4	42	Asian	M	No	Untreated	65.4	-3.4
5	54	B	F	Yes	Latanoprost	42.2	13.4
6	55	W	M	No	Bimatoprost	63.9	27.5
7	37	W	M	No	Untreated	-76.1	16.7
8	54	W	M	No	Untreated	64.4	89.5
9	59	W	F	No	Untreated	52.4	23.1
10	60	W	M	No	Travoprost	75.6	1.3
11	36	W	F	No	Untreated	-24.8	-2.9
12	48	W	F	No	Untreated	31.0	31.2
13	67	W	M	Yes	Untreated	104.3	-13.2
14	60	W	F	No	Untreated	41.4	31.0
15	73	B	M	Yes	Untreated	-33.0	12.1
16	64	W	F	Yes	Timolol + Bimatoprost	73.7	20.0
17	52	Asian	M	No	Travoprost	64.3	-3.4

B = black; W = white.

TABLE 4.

Frequency Doubling Technology Perimetry Values Before and Following an 8- Week Treatment Period With Brimonidine 0.15% in Normal Tension Glaucoma Patients

	Pre Brimonidine, Mean $\pm$ SD	Post Brimonidine, Mean $\pm$ SD	
	N = 17	N = 17	<i>P</i> Value ^a
Mean deviation (dB)	-2.03 $\pm$ 3.50	-2.77 $\pm$ 5.03	.28
Pattern standard deviation (dB)	6.44 $\pm$ 2.89	6.78 $\pm$ 2.66	.44
Test duration (s)	268 $\pm$ 21	270 $\pm$ 21	.67

^a Paired *t* test.