Investigative Ophthalmology & Visual Science, Vol. 33, No. 3, March 1992
Copyright © Association for Research in Vision and Ophthalmology

Color Doppler Ultrasound of Orbital and Optic Nerve Blood Flow: Effects of Posture and Timolol 0.5%

G. M. Baxter,* T. H. Williamson,† G. McKillop,‡ and G. N. Dutton†

Color Doppler ultrasound allows simultaneous imaging with real-time ultrasound and superimposed color-coded vascular flow, allowing visualization of vessels previously beyond the resolution of conventional imaging, such as those in the orbit. With this technique, 20 healthy volunteers were studied. Three regional vessels named 1, 2, and 3 were identified. No significant difference in maximum or minimum blood velocity or resistive index was detected between vessels 1 and 2, although significant differences were noted between both these vessels and vessel 3 ($P < 0.01$ and $P < 0.001$, respectively). These regional variations are unaffected by small but significant rises in pulse ($P < 0.05$) and diastolic blood pressure ($P < 0.01$) induced by postural change. No significant change within each vessel was recorded in response to posture, reflecting autoregulation within these vessels. Using a similar technique, 10 healthy volunteers were studied at baseline and at 2 hr and 3 d following the unilateral instillation of 0.5% timolol eye drops. A fall in resistive index was recorded in vessel 3 for both eyes ($P < 0.05$, timolol administered eye; $P < 0.01$ timolol-free eye). This effect was independent of any simultaneous fall in intraocular pressure that occurred only in the eye receiving timolol drops ($P < 0.01$). These results support the presence of B receptors in the vessels at the optic nerve head (vessel 3). A fall in resistive index should not compromise the blood supply in this region, and may even increase it. Thus, color Doppler ultrasound is a suitable noninvasive method of imaging the retrobulbar vasculature and may play a role in the diagnosis and management of vascular eye disease. Invest Ophthalmol Vis Sci 33:604–610, 1992

Doppler ultrasound provides a reliable noninvasive method for analyzing velocity of blood flow. The introduction of color Doppler ultrasound has, for the first time, allowed a combination of a real-time image of anatomic structures with superimposed color-coded vascular flow. It also has permitted, in many cases, imaging of blood flow in vessels that cannot be resolved by real-time ultrasound alone, such as in the orbit. The potential application of this technique, with respect to the retrobulbar vasculature, recently has been described,[1] although the exact site within the orbit at which reliable and reproducible Doppler interrogation of these vessels can be performed has not yet been determined. If this can be done, the Doppler technique potentially provides the opportunity to investigate a wide range of disorders that affect vascular perfusion of structures within the orbit and it may play a role in their management.

Many techniques have been used to study the blood flow analysis of the eye. Some of these, such as the use of labelled and unlabelled microspheres, are restricted to animal models.[2,3,4,5,6] Others, although applicable to human subjects, have limitations and disadvantages in their own right. Laser Doppler velocimetry relies on direct visualization of the vasculature and therefore is restricted primarily to the retinal vasculature.[7,8] Furthermore, this method may be unsuitable for monitoring the pharmacologic actions of drugs on blood velocity because of the need for topical mydriatics, which may have a direct effect on the orbital vasculature.[9] Blue field entoptic techniques are restricted to macular blood vessels and interpretation is extremely subjective.[10] Alternative techniques, including oculo-oscillo-dynamography[11] and ocular pneumoplethysmography,[12] provide recordable indices of perfusion pressure in the retinal and ciliary arteries, while compression ophthalmodynamometry[13] provides an index of blood pressure at the optic nerve head. Unfortunately, these methods require abnormal physiologic circumstances such as pressure on the globe to provide recordings.

Color Doppler ultrasound obviates many of these problems and can be used to examine orbital blood vessels not amenable to other methods of investigation. It also has the advantage of not requiring additional pharmacologic agents or abnormal physiologic circumstances to perform an examination.

From the *Department of Radiology and †Tennent Institute of Ophthalmology, Western Infirmary, and the ‡Department of Radiology, Victoria Infirmary, Glasgow, Scotland.

Submitted for publication: May 8, 1991; October 21, 1991.

Reprint requests: Dr. G. M. Baxter, Department of Radiology, Western Infirmary, Glasgow, G11 6NT, Scotland, UK.

In this study, color Doppler ultrasound has, for the first time, been used to evaluate the velocity of arterial blood flow in the orbit. Initially, regional locations were identified within the orbit from which repeatable measurements of blood velocity could be recorded. The effect of posture on these vessels then was examined. Finally, the effect of topical timolol 0.5% on the orbital vasculature was assessed.

Patients and Methods

Color Doppler Ultrasound—Technique

Thirty normal volunteers underwent color Doppler ultrasound examination of the eye using a 7.5 MHz probe (Acuson 128 Computed Tomography, Mountain View, CA). Twenty of this group had a noninvasive assessment of their retrobulbar vasculature with respect to posture. The remaining 10 had this assessment before and after the topical administration of timolol 0.5%. Informed consent was obtained in all cases after the procedure was explained fully.

After an initial pilot study, it became obvious that we could reliably and reproducibly measure a Doppler frequency shift spectrum from three separate areas behind the globe, which we arbitrarily named vessels 1, 2, and 3. Scanning was performed in a transverse and longitudinal axis. The transverse axis proved the most practicable and reproducible. Vessel 1 was situated adjacent to the optic nerve at a mean distance of 17 mm behind the globe (Fig. 1, top left). Vessel 2 was adjacent to the medial orbital wall and 15 mm posterior to the globe (Fig. 1, top right). Vessel 3 was adjacent to the vessels around the optic nerve head, 5 mm behind the choroid (Fig. 1, left). It is presumed that vessel 1 identifies the ophthalmic artery, vessel 2 the branch of the ophthalmic artery that enters the ethmoid air cells, and vessel 3 a combination of the central retinal artery and posterior ciliary vessels.

The maximum Doppler frequency shift was calculated from each of the above three positions (Fig. 2). No angle correction was applied because these vessels have a very small diameter and are extremely tortuous. Any errors in measurement were likely to be as great, if not magnified, if an angle correction technique were used. Maximum and minimum velocities were recorded from all Doppler waveforms, although, for the reasons mentioned above, these were not absolute values. To overcome this, the resistive index also was recorded:

$$\text{Resistive Index (RI)} = \frac{\text{systolic velocity} - \text{diastolic velocity}}{\text{systolic velocity}}$$

Determination of Posture on Color Doppler Recordings

Twenty volunteers—12 males, eight females, age range 20–60 yr (mean 34.6)—were examined. Exclusion criteria for entry were a past history of eye disease or surgery, cardiovascular or neurological history, current drug therapy, or refractive errors of more than 3 diopters of myopia or hypermetropia.

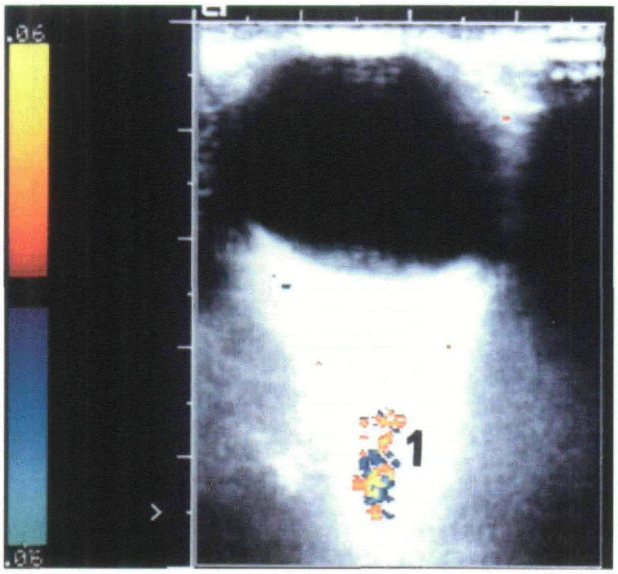
Initially, each subject was asked to lie supine for five min. The blood pressure and pulse rate then were recorded automatically using a digital recording device (Copal Digital Sphygmomanometer; Andrew Stephens Co., West Yorkshire, UK). Maximum Doppler frequency shifts were recorded from each of the three retroorbital regions from either the left or right eye, according to a pre-determined random number sequence. Three Doppler indices (maximum and minimum velocity and resistive index) were calculated for each vessel. Each subject then was asked to sit up and all recordings were repeated two minutes later. Next, the subject was asked to stand for an additional two minutes, and all recordings were repeated once more.

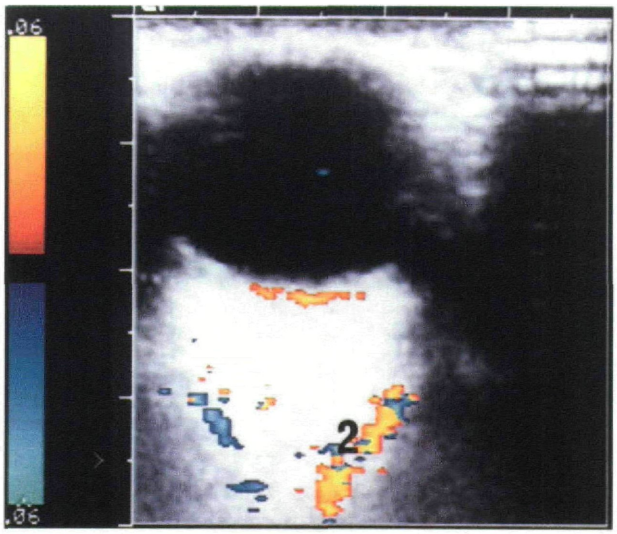
Effects of Topical Timolol 0.5% on Color Doppler Recordings

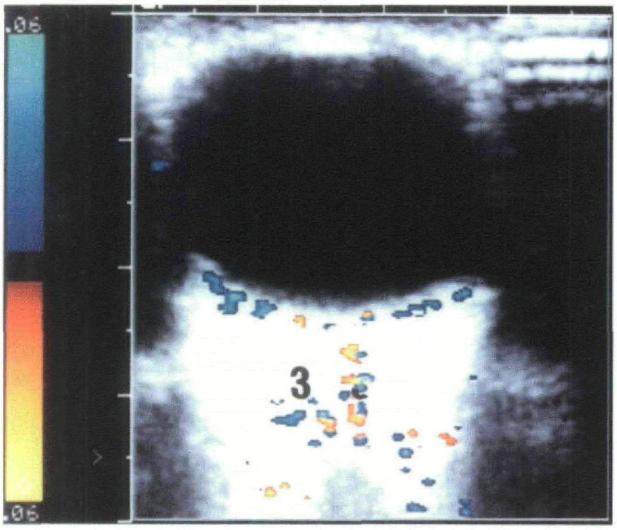
Ten normotensive volunteers—eight males, two females, age range 28–52 years (mean 31.8)—were examined. The same exclusion criteria as above were applied. Initially, a baseline intraocular pressure was taken using Goldmann's applanation tonometry. Each subject then was asked to lie down for five minutes. The pulse and blood pressure were determined, as described above, and color Doppler recordings were taken from both eyes at regions 1, 2, and 3. Next, topical timolol 0.5% was applied to one eye chosen at random. The clinician performing the color Doppler ultrasound examination was unaware of which eye had received treatment. Two hours later, intraocular pressure measurement and color Doppler ultrasound were repeated. Each subject continued to take topical timolol 0.5% two times a day in the same eye for a additional three days. Then, all recordings were repeated in the same manner.

Analysis

All data were analyzed over three cardiac cycles. Mean values of maximum velocity, minimum velocity, and resistive index were obtained to minimize error. Statistical analysis was by one-way analysis of variance followed by Student's t-test, where appropriate.







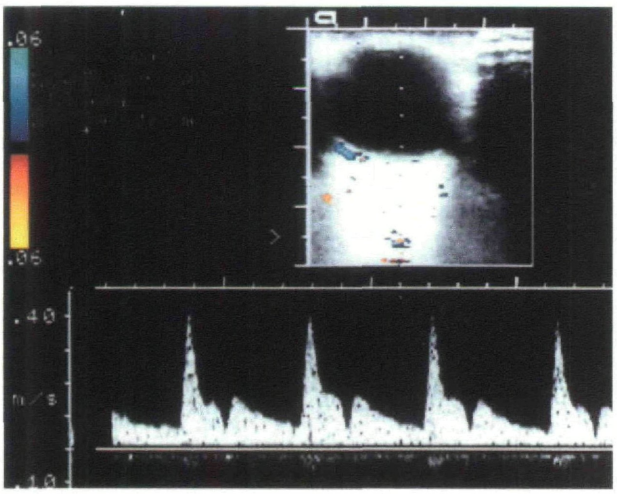


Fig. 2. A typical Doppler frequency shift waveform recorded in this case from vessel 1. Maximum systolic velocity and minimum end diastolic velocity are easily measured, and resistive index calculated simply as described in the text.

Fig. 1. (**Top left**) Color Doppler ultrasound scan of the orbit showing the position of vessel 1, presumed to be the ophthalmic artery. The scan has been performed in the transverse axis. (**Top right**) Color Doppler ultrasound scan in the transverse axis showing the position of vessel 2 running along the medial orbital wall. (**Left**) Color Doppler ultrasound scan of vessel 3 just posterior to the choroid. These vessels lie adjacent to the optic nerve head and are likely to represent a combination of the central retinal artery and posterior ciliary vessels.

Results

Regional Variations Within the Eye

Data was obtained for vessels 1, 2, and 3 as described in Methods. Doppler indices of maximum and minimum velocity and resistive index were measured in all regions in the supine position.

No significant difference was recorded between vessels 1 and 2. There were, however, significant differences between both of these vessels and vessel 3 ($P < 0.01$ and $P < 0.001$, respectively), for all 3 parameters measured (see Fig. 3).

Effect of Posture on Color Doppler Recordings

Table 1 summarizes the effects of change of posture on the pulse and blood pressure. No significant change was observed when subjects changed from the supine to sitting position. However, there was a small but significant rise in pulse and diastolic blood pressure between both of these positions and the erect position ($P < 0.05$ and $P < 0.01$ respectively).

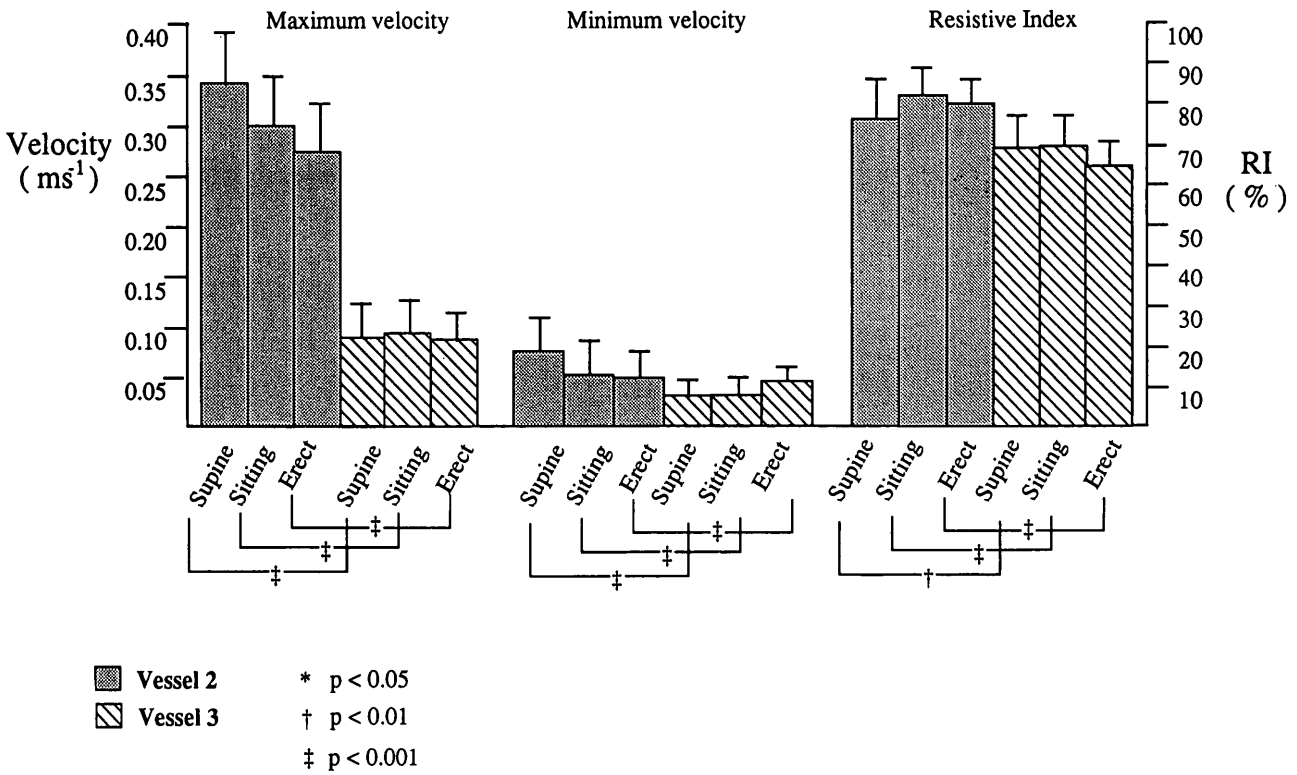


Fig. 3. The effects of posture on maximum and minimum velocities and resistive index of vessels 2 and 3. Mean values and one standard deviation have been plotted. There is no significant change in any of the above indices in response to postural change; however, there are significant differences in these indices between vessel 2 (and thus vessel 1—see text) and vessel 3 ($P < 0.01$ and $P < 0.001$) in all positions independent of posture.

Despite this small but significant hemodynamic response, no similarly significant change was recorded in the Doppler spectra of any of the three retrobulbar vessels studied (see Fig. 3). Regional differences were maintained between the three vessels and were independent of posture.

Effect of Topical Timolol 0.5% on Color Doppler Recordings

Table 1 gives the details of the mean pulse rate and diastolic and systolic blood pressures before and after the use of topical timolol 0.5%. None of these variables reached statistical significance.

Intraocular Pressure

Table 2 shows the effect of timolol 0.5% on intraocular pressure of the treated and contralateral untreated eye. A significant and sustained intraocular pressure reduction was obtained ($P < 0.01$) in the timolol-treated eye only, at 2 hr and at 3 d following timolol administration.

Table 1. Effects on pulse, systolic blood pressure (SBP), and diastolic blood pressure (DBP) of changes in posture (section A) and of administration of Timolol (section B)

	Pulse						*SBP (mmHg)*						*DBP (mmHg)*					
	Mean	*SD*	*Max*	*Min*	*F*	*P*	*Mean*	*SD*	*Max*	*Min*	*F*	*P*	*Mean*	*SD*	*Max*	*Min*	*F*	*P*
A																		
Supine	70.6	9.82	92.0	56.0			118.0	12.17	150.0	105.0			71.7	7.92	90.0	60.0		
Sitting	72.6	8.83	88.0	52.0	3.24	<0.05	113.5	13.80	140.0	96.0	0.83	NS	72.9	8.75	95.0	60.0	5.61	<0.01
Standing	78.6	12.12	104.0	60.0			114.0	10.37	140.0	98.0			79.8	8.00	95.0	70.0		
B																		
Baseline	67.7	11.44	88.0	52.0			120.5	11.03	133.0	94.0			72.3	7.66	81.0	58.0		
2 hour post	63.4	10.80	79.0	51.0	1.23	NS	121.8	11.49	135.0	96.0	0.62	NS	75.6	9.16	95.0	66.0	1.22	NS
3 days post	60.9	6.45	72.0	51.0			116.7	9.43	132.0	98.0			77.9	7.29	68.0	89.0		

Table 2. The effects on intraocular pressure of topical Timolol are shown for the Timolol-administered and nonadministered (free) eye

	T ad						*T free*					
	Mean	*SD*	*Min*	*Max*	*F*	*P*	*Mean*	*SD*	*Min*	*Max*	*F*	*P*
Baseline	11.9	2.51	10	18			11.9	2.38	10	18		
2 hours post	8.7	3.23	4	14	3.63	<0.05	11.7	4.14	5	18	0.135	NS
3 days post	9.1	2.88	6	14			12.5	3.98	8	20		

Abbreviations: T ad, Timolol administered; T free, Timolol free.

Comparisons between the Timolol-treated and untreated eyes showed a significant difference ($P < 0.05$) between the intraocular pressure values at 2 hr and 3 d.

Color Doppler Assessment

Timolol was found to have no significant effect upon any of the Doppler parameters measured at vessels 1 and 2, although there was a nonsignificant trend to a lower resistive index in these vessels at 2 hr. This was maintained at 3 d for both the timolol-administered and timolol-free eye. Similarly, vessel 3 showed no significant change in the maximum or minimum velocities following timolol administration in either eye over the 3 d time course, as Table 3 shows. However, a significant reduction in resistive index was obtained at vessel 3, 2 hr following the commencement of timolol administration ($P < 0.05$, timolol-treated eye; $P < 0.01$, timolol-free eye). This effect was observed in both eyes and was maintained at the final 3 d reading ($P < 0.01$, timolol-administered eye; $P < 0.01$, timolol-free eye). No significant change was recorded for resistive index between the 2 hr and 3 d readings.

Discussion

In the present study, color Doppler ultrasound was found to be a noninvasive method of assessing retrobulbar hemodynamics. Intra- and interpatient detection of blood flow was reproducible at three sites. Because there were no antecedent guidelines, Doppler spectral readings were measured at these three definable loci so repeat measurements in the same patient or in cohort studies could be performed. Regions 1 and 2 appear to represent blood velocity within a single vessel, ie the ophthalmic artery and a major branch artery, respectively, while vessel 3 probably provides an index of blood flow in the central retinal artery and the posterior ciliary arteries. Clinical studies on patients with selective, occlusive vascular dis-

Table 3. Comparison of Timolol-administered and Timolol-free eye—effects on maximum velocity, minimum velocity, and resistive index (RI) in vessel 3

	T ad				*T free*			
	Mean	*SD*	*Max*	*Min*	*Mean*	*SD*	*Max*	*Min*
A Maximum velocity ($msec^{-1}$)								
Baseline	0.104	0.027	0.157	0.059	0.141	0.170	0.620	0.059
2 hours post	0.093	0.023	0.048	0.117	0.121	0.060	0.249	0.063
3 days post	0.141	0.182	0.653	0.045	0.102	0.057	0.242	0.049
F		0.556				0.319		
P		NS				NS		
B Minimum velocity ($msec^{-1}$)								
Baseline	0.104	0.027	0.157	0.069	0.026	0.008	0.039	0.016
2 hours post	0.037	0.009	0.051	0.025	0.036	0.011	0.051	0.022
3 days post	0.034	0.009	0.049	0.023	0.056	0.048	0.169	0.022
F		0.252				2.929		
P		NS				NS		
C Resistive index (%)								
Baseline	67.6	8.10	81.7	55.6	68.5	6.66	84.2	59.4
2 hours post	59.4	9.14	77.5	44.7	58.5	8.34	71.3	45.7
3 days post	58.8	7.56	68.5	48.4	57.3	7.17	71.2	46.4
F		3.554				6.818		
P		<0.05				<0.01		

Abbreviations: T ad, Timolol administered; T free, Timolol free.

ease of the retinal or ciliary vasculature will be required to establish the contribution of each component. Thus, we intend to use the same reference points in future clinical studies.

The failure to identify any change in the blood velocity spectrum in response to posture and its effect on pulse and blood pressure provides indirect evidence of an autoregulatory mechanism. Such mechanisms previously have been described only in the optic nerve head[3,4] and retinal circulation[7] and, to our knowledge, have not been previously identified in the other orbital arteries. A reduction in pulsatile ocular blood flow when position is changed from erect to supine has been shown,[14] although this may be a result of an over-riding effect of the choroidal circulation, which does not show autoregulatory characteristics.[15]

Reduction of intraocular pressure with maintenance and enhancement of optic nerve head perfusion and preservation of visual fields has been the principal goal in treating glaucoma. However, loss of visual field[16] and progressive glaucomatous change in the optic nerve head[17] may continue despite intraocular pressure "control" with timolol. To date, the results of hemodynamic studies are conflicting. Laser Doppler velocimetric analysis of retinal veins has indicated that topical L-timolol reduces velocity in the rabbit but that D-timolol has a converse effect.[18] In a similar study in humans, an increased blood velocity has been reported.[19]

Timolol is known to reduce oxygen tension in the anterior chamber of the cat, so a relative local hypercapnia may explain the increased blood flow observed in man.[19] In addition, compression ophthalmodynamometric comparisons of timolol-treated and untreated eyes show a slight but significant increase in central retinal artery perfusion pressure in the treated eye, independent of any effect on intraocular pressure.[13] However, a decrease in pulse amplitude in response to topical timolol led Colloton and Perkins[20] to conclude that intraocular blood flow is decreased after local administration. Video angiographic and blue field entoptoscopic studies show an increase in retinal circulation time after timolol administration.[21]

Topical timolol may reduce heart rate and systolic and diastolic pressure[22] but our study and the studies of others[23,24,25] showed no statistically significant change. Also, in accordance with the findings of Martin and Rabineau,[26] we failed to find a significant reduction in intraocular pressure in the contralateral eyes of the normal subjects we investigated.

Timolol uniformly reduces intraocular pressure by suppressing aqueous humor formation,[27] but the exact mechanism is unknown. In this study, after timolol administration, the resistive index was found to be significantly decreased in the treated and untreated eyes at vessel 3 adjacent to the optic nerve head. Beta adrenergic binding sites recently have been detected in the retinal vasculature.[28] Therefore, timolol may directly affect the retinal vasculature. Indeed, topical timolol recently has been shown to lead to constriction of the retinal arterial vasculature.[9] As flow of a liquid in a tube is related to velocity and cross-sectional areas, the fall in resistive index and the relatively increased diastolic flow to systolic flow—detected at the optic nerve head in this study—may be compensating for the vasoconstriction induced by timolol. This hypothesis would agree with the observation that timolol probably does not decrease overall blood flow at the optic nerve head, as shown by its failure to impair optic nerve head conduction as a sequel to raised intraocular pressure.[29]

In the present study, the contralateral untreated eye also showed a reduction in resistive index at the optic nerve head (vessel 3). This effect occurred in the absence of a fall in intraocular pressure or significant change in pulse or blood pressure. Therefore, these changes at the optic nerve head may be a result of the local effect of timolol on the blood vessels at this location.

Visual loss in primary open angle glaucoma may be a sequel to microvascular ischemia at the optic nerve head. Therefore, it must be determined whether the influence of timolol on optic nerve head perfusion is potentially beneficial or detrimental to nerve fiber survival. Further studies are required to assess the effect of timolol and other beta blockers on vascular perfusion of the optic nerve, in normal subjects and in patients with glaucoma.

In conclusion, we have shown that color Doppler ultrasound provides an effective way to measure blood velocity in the orbit. We have described a novel technique for orbital scanning and have shown significant regional variations in blood velocity that provide a possible future role for color Doppler in the diagnosis and management of certain vascular conditions. We also have shown no significant change in these values in response to the physiological changes of posture that reflect the known mechanism of autoregulation. Finally, we have shown a statistically significant change in the resistive index in vessel 3 in both eyes after the unilateral administration of timolol 0.5%. We believe this supports the findings of B receptors within the eye because we have have shown these effects to be independent of any accompanying reduction in intraocular pressure. We also believe that the reduction in resistive index induced by 0.5% timolol,

for the reasons discussed earlier, is likely to maintain or have a beneficial effect on optic nerve head blood flow.

Key words: color Doppler, ophthalmic artery, optic nerve, posture, timolol

References

1. Canning CR and Restori M: Doppler ultrasound studies of the ophthalmic artery. Eye 2:92, 1988.
2. Malik AB, vanHeuven WAJ, and Satler LF: Effects of isoproterenol and norepinephrine on regional ocular blood flows. Invest Ophthalmol 15:492, 1976.
3. Weinstein JM, Bradford Duckrow R, Beard D, and Brennan RW: Regional optic nerve blood flow and its autoregulation. Invest Ophthalmol Vis Sci 24:1559, 1983.
4. Geijer C and Bill A: Effects of raised intraocular pressure on retinal, prelaminar, laminar and retrolaminar optic nerve blood flow in monkeys. Invest Ophthalmol Vis Sci 18:1030, 1979.
5. Capriolo J and Miller JM: Measurement of optic nerve blood flow with iodoantipyrine: Limitations caused by diffusion from the choroid. Exp Eye Res 47:641, 1988.
6. Alm A: The effect of topical l-epinephrine on regional ocular blood flow in monkeys. Invest Ophthalmol Vis Sci 19:487, 1980.
7. Riva CE, Grunwald GE, Sinclair SH, and Petrig BL: Blood velocity and volumetric flow rate in human retinal vessels. Invest Ophthalmol Vis Sci 26:1124, 1985.
8. Robinson F, Riva CE, Grunwald JE, Petrig BL, and Sinclair SH: Retinal blood flow autoregulation in response to an acute increase in blood pressure. Invest Ophthalmol Vis Sci 27:722, 1986.
9. Martin XD and Rabineau PA: Vasoconstrictive effect of topical timolol on human retinal arteries. Arch Clin Exp Ophthalmol 227:526, 1989.
10. Sinclair SH, Azar-Cavanagh M, Soper KA, Tuma RF, and Mayrovitz HN: Investigation of the source of blue field entoptic phenomenon. Invest Ophthalmol Vis Sci 30:722, 1989.
11. Ulrich WP and Ulrich C: Oculo-oscillo-dynamography: A diagnostic procedure for recording ocular pulses and measuring retinal and ciliary artery blood pressures. Ophthalmic Res 17:308, 1985.
12. Gee W, Oller DW, and Wylie EJ: Non-invasive diagnosis of carotid occlusion by ocular pneumoplethysmography. Stroke 7:18, 1976.
13. Grunwald JE and Furubayashi C: Effect of topical timolol on the ophthalmic artery blood pressure. Invest Ophthalmol Vis Sci 30:1095, 1989.
14. Trew DR and Smith SE: Postural studies on pulsatile ocular blood flow: 1. Ocular hypertension and normotension. J Ophthalmol 75:71, 1991.
15. Alm A and Bill A: Ocular and optic nerve blood flow at normal and increased intraocular pressures in monkeys (macaca irus): A study with radioactive labelled microspheres including flow determinations in brain and some other tissues. Exp Eye Res 15:15, 1973.
16. Jay WM, Aziz MZ, and Green K: Effect of topical epinephrine and timolol on ocular and optic nerve blood flow in phakic and aphakic rabbit eyes. Curr Eye Res 3:1199, 1984.
17. Nielson NV and Eriksen JS: Timolol in maintenance treatment of ocular hypertension and glaucoma. Acta Ophthalmol 57:1070, 1979.
18. Yan HY and Chiou GCY: Effects of l-timolol, d-timolol, haloperidol and domperidone on rabbit retinal blood flow measured with laser doppler method. Ophthalmic Res 19:45, 1987.
19. Grunwald JE: Effect of topical timolol on the human retinal circulation. Invest Ophthalmol Vis Sci 27:1713, 1986.
20. Colloton E and Perkins ES: The effect of timolol on the intraocular pulse pressure. Invest Ophthalmol Vis Sci 27(suppl):102, 1986.
21. Richard G and Weber J: Der einfluss der betablocker timolol und pindolol Auf die retinale hamodynamik-eine videoangiographische studie. Klin Monatsbl Augenheilkd 190:34, 1987.
22. Merte HJ and Merkle W: Timolol - augentropfen in der glaukombehandlung ergebnisse einer langzeitstudie. Klin Monatsbl Augenheilkd 177:562, 1980.
23. Katz IM, Hubbard WA, Getson AJ, and Gould AL: Intraocular pressure decrease in normal volunteers following timolol ophthalmic solution. Invest Ophthalmol 15:489, 1976.
24. Zimmerman TJ and Kaufman WE: A b-adrenergic blocking agent for the treatment of glaucoma. Arch Ophthalmol 95:601, 1977.
25. Krieglstein GK: Die wirkung von timolol-augentropfen auf den augen-innendruck. Klin Monatsbl Augenheilkd 172:677, 1978.
26. Martin XD and Rabineau PA: Intraocular pressure effects of timolol after unilateral installation. Ophthalmology 95:1620, 1988.
27. Coakes RL and Braubaker RF: The mechanism of timolol in lowering intraocular pressure in the normal eye. Arch Ophthalmol 96:2045, 1978.
28. Ferrari-Dileo G: Beta-1 and beta-2 adrenergic binding sites in bovine retina and retinal blood vessels. Invest Ophthalmol Vis Sci 29:695, 1988.
29. Pillunat LE, Stodmeister R, Wilmanns I, and Metzner D: Effect of timolol on optic nerve head autoregulation. Ophthalmologica 193:146, 1986.