European Journal of Ophthalmology / Vol. 14 no. 3, 2004 / pp. 226-235

Regulation of optic nerve head blood flow in normal tension glaucoma patients

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PURPOSE. *To investigate the regulation of the optic nerve blood flow (F_{onh}) in response to an increase of the perfusion pressure (PP_m) in normal tension glaucoma (NTG) patients and in age-matched normal volunteers.*
METHODS. *Measurements were performed in 16 eyes of NTG patients and in 10 eyes of age-matched controls. Laser Doppler flowmetry (LDF) was applied to calculate the relative flux of red blood cells at the temporal rim of the optic nerve head (ONH) in response to increases in PP_m. PP_m was raised through an increase in systemic blood pressure induced by isometric exercise. Before being tested, all patients had 3 weeks of washout of any local medication.*
RESULTS. *In the NTG group, mean ophthalmic arterial blood pressure increased during isometric exercise from 73 to 89 mmHg (22%), resulting in a 29% increase of the PP_m. This increase did not induce any significant change in mean F_{onh}. For the control group, the 28% increase of PP_m also did not significantly affect F_{onh}. There was a trend for a greater increase in vascular resistance during isometric exercise in the NTG than in the normal control group (47% versus 25%).*
CONCLUSIONS. *The LDF parameters, measured in the ONH, did not indicate an abnormal F_{onh} regulation in response to an increase of the PP_m in either normal subjects or NTG patients. The maintenance of constant blood flow is achieved by an increase in local vascular resistance. Our data show a greater percent increase in vascular resistance in the NTG patients compared to the normal subjects for a similar percent increase in PP_m in both groups during squatting. This suggests some alteration of the vessel tone regulatory mechanisms in NTG patients. (Eur J Ophthalmol 2004; 14: 226-35)*

KEY WORDS. *Laser Doppler flowmetry, Optic nerve head, Isometric exercise, Vascular regulation, Vascular resistance, Perfusion pressure*

Accepted: March 10, 2004

INTRODUCTION

Vascular alterations, such as a reduction of the blood supply or a dysregulation of blood flow to the optic nerve head (ONH), have been implicated in the pathogenesis of glaucomatous optic neuropathy (1-4), in particular in normal tension glaucoma (NTG) (5). Hypoperfusion of the ONH during nocturnal systemic hypotension (6-8), in the presence of other vascular risk factors, may reduce the ONH blood flow below a critical level and be a significant factor by compromising blood supply, resulting in progressive glaucoma-

1120-6721/226-10$15.00/0

tous damage. The understanding of the etiology of NTG requires a better knowledge of the role of ONH blood flow and its regulation.

The ONH is part of the nervous system. As such, this tissue requires high metabolic activity and oxygen consumption to maintain neuronal activity. Nutrition and oxygenation of the ONH depend on blood flow to this tissue (9), which in turn depends upon the perfusion pressure (PP_m) and vascular resistance (R). The mean perfusion pressure is defined as the mean ophthalmic artery blood pressure (MOAP) minus the intraocular pressure (IOP). The vascular resistance depends upon the contractile state of the smooth muscle of the arterioles irrigating the ONH and, potentially, of the pericytes of the ONH capillary network (10). This contractile state is regulated by circulating vasoactive substances and local metabolic factors such as partial pressure of oxygen (PO_2), carbon dioxide (PCO_2), pH, metabolic products, and endothelium derived substances (endothelin, nitric oxide [NO], and prostaglandins) (11, 12). By adaptation of the vascular resistance (vasodilation or vasoconstriction), the above regulatory factors ensure constant blood flow (F_{onh}) (13, 14) and constant oxygen supply (15-17) in spite of variations of PP_m (regulation). In addition, experimental data indicate a constant ONH oxygen supply during the inhibition of endothelial NO release (16), suggesting that the lack of NO release should be compensated by the release of some other substances, such as vasodilating prostaglandins.

Most of the studies performed so far in animals (17-20) and humans (13, 14) with the aim of assessing the regulatory behavior of the ONH circulation have documented the response of F_{onh} to decreases in PP_m achieved by raising the IOP. The investigation of the effect of increases in PP_m induced by raising the systemic blood pressure is more recent (21) and has demonstrated in normal volunteers that F_{onh} is maintained constant over a broad range of PP_m increases.

Patients with high-tension and normal tension primary open-angle glaucoma have a reduced retrobulbar vessels blood flow velocity (22). Furthermore, laser Doppler flowmetry (LDF) measurements suggest a reduction of the optic disk perfusion in patients with open angle glaucoma (23-26). The hypothesis has been made that, in these patients, systemic diseases affect F_{onh} regulation (5). To our knowledge, however, direct, quantitative data supporting an alteration of this regulation are lacking. At best, the findings of Grunwald et al (27) showing an abnormal autoregulation of macular retinal blood flow in open-angle glaucoma when PP_m is decreased by increasing the IOP suggest some similar behavior of the optic disk circulation. With regard to the regulation of F_{onh} when PP_m is increased, to our knowledge, no data are available in eyes with pathologic alterations.

This investigation reports the response in F_{onh} during an increase in PP_m induced by isometric exercise. Responses in NTG patients were compared to those obtained in age-matched volunteers.

MATERIALS AND METHODS

Subjects and patients

The study was performed in 10 healthy adult volunteers (2 male, 8 female, control group), whose age ranged from 52 to 80 years (mean 67 ± 10 standard deviation [SD]) and in 16 NTG patients (5 male, 11 female) ranging in age from 50 to 78 years (mean 66 ± 5). The diagnosis of NTG was based on the presence of glaucomatous optic disk damage (mean cup/disc ratio = 0.74 ± 0.12) and reproducible visual field defects (mean visual field defect = –12.7 ± 7.06). IOP prior to the measurements was normal (14.0 ± 2 mm Hg), and no patient had a measured IOP higher than 21 mmHg. Seven NTG eyes had undergone filtering surgery to further lower the IOP. Among the NTG patients, two had systemic hypertension.

In 11 of the 16 NTG patients LDF measurements were performed in both eyes. In the remaining 5 NTG patients and in all normal subjects, only one eye was measured. We compared the mean values of the LDF parameters of the most affected eye (the one with the greater damage of the ONH and larger mean defect of the visual field) to those obtained from the less affected eye.

Before the LDF measurements, patients on the beta-blockers, latanoprost and/or dorzolamide had a 3-week washout of these topical eye medications. Additionally, in the two systemic hypertensive patients, the oral treatment by calcium blockers was also stopped 48 hours before the measurements. Six eyes had no ocular hypotensive medication.

In the control group, subjects had no history of sys-

temic or ocular diseases and the results of the ocular examination were normal. Subjects and patients were asked to abstain from caffeine, alcohol, and nicotine 12 hours before being tested. The eyes of each subject were dilated with one or two drops of 1% tropicamide.

The experimental procedure, approved by the Ethical Committee of the Medical Faculties of the University of Geneva, Lausanne, and Angers, followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects after the nature and possible consequences of the study had been fully explained to them.

Measurement of ONH blood flow by LDF

The LDF technique, as applied in this study, has been previously described (14, 21). In brief, measurements were performed using a Topcon based fundus camera LDF system (28). A probing laser beam (wavelength = 670 nm, power at the cornea = 60 μW) was directed at temporal rim areas of the disk, away from visible vessels. Diameter of the beam at the fundus was approximately 150 μm. The position of the laser beam was continuously monitored by the operator. The laser light scattered from the tissue and red blood cells (RBCs) was collected by an optical fiber with its input aperture focused at the image plane of the fundus camera and centered on the probing laser. The effective diameter of this aperture at the disk was approximately 180 μm. The collected laser light was guided to a photodetector, whose output signal was analyzed by a NeXT computer (29) to obtain relative measures of the following flow parameters: Vel_{onh}, the mean velocity of the RBCs, expressed in kHz, Vol_{onh}, the number of RBCs, and F_{onh}, the flux of RBCs in the volume sampled by the laser. F_{onh} is proportional to Vel_{onh} x Vol_{onh}. F_{onh} and Vol_{onh} are expressed in arbitrary units. The portion of the Doppler shift power spectrum between 32 and 2500 Hz was used for the determination of the flow parameters. The region between 2500 and 5000 Hz served to determine the shot noise level, which was subtracted from the spectrum before calculating the flow parameters.

The DC of the Doppler signal, which is proportional to the total amount of light reaching the detector, was also recorded and used to monitor the position of the camera and to remove the portions of recordings associated with blinks. Spikes occurring mainly in Vol_{onh} and lasting less than 0.1 sec were attributed to micro-saccadic eye motion and were also removed from the recording, as described elsewhere (21). Prior to the LDF measurements, a Polaroid fundus photograph was obtained from each eye for documentation of the measurement sites.

The MOAP was assumed to be 2/3 of the mean arterial blood pressure (MABP), and was calculated as $MOAP = 2/3\ [BP_{diast} + 1/3\ (BP_{syst} - BP_{diast})]$. BP_{diast} and BP_{syst} are the brachial artery blood pressures during diastole and systole, respectively.

Since isometric exercise does not induce a significant change of the IOP (21) the changes in PP_m were calculated based on the changes of MOAP, keeping constant the value of IOP. The mean vascular resistance, R, was defined as $R = PP_m / F_{onh}$.

Isometric exercise

Squatting was chosen to raise the MABP. Measurements of the LDF parameters were first performed with the subject standing up. The table holding the LDF system was placed on a platform at about 30 cm above ground and the subject maintained his or her head on the chin rest and against the forehead holder strap. It was then lowered at a rate of approximately 2 cm/sec, forcing the subject to squat, while maintaining the torso in a near vertical position. MABP was measured with a manual sphygmomanometer, before squatting and every 30 seconds during exercise and recovery. Heart rate was continuously measured by means of a transducer clamped to the subject's earlobe. When the subject wished to stop squatting, the table was raised again. The measurements of heart rate, blood pressure, and flow parameters were pursued for another 5 min.

Sensitivity of LDF parameters (for example, F_{onh}) was defined as SF_{onh}. This quantity represents the minimum change that can be detected by the LDF technique for a group of subjects. SF_{onh} was determined in each of the two groups of eyes (10 normal and 16 NTG) for the measurements at rest and for the last 10-20 sec of squatting using a procedure described in details elsewhere (21).

Mean changes in the blood flow parameters PP_m and R were assessed for statistical significance by paired t-test, corresponding to a significance level of 0.05.

RESULTS

Figure 1 shows a representative recording of DC, Vel_{onh}, Vol_{onh}, and F_{onh} obtained in one of the subjects at baseline, at the end of squatting, and recovery from squatting. In this particular subject, squatting induced a 31% increase in PP_m (64 to 85 mmHg). The LDF signals were recorded with a time constant of 0.047 sec and displayed with a time constant of 0.186 sec. Spikes associated with saccadic eye motions have been removed, as described elsewhere (21). During the recording segments highlighted in gray, the brachial artery blood pressure was measured and the variation of each flow parameter during the heart cycle was obtained by averaging each parameter over the marked segment, taking the phase of the heart cycle into account, as previously described (29). Such variations of the F_{onh} are shown below the LDF recordings, at baseline, just before the end of squatting, and about 80 sec after squatting was stopped.

Control group

Figure 2 shows the percentage changes of the LDF parameters at the end of squatting (approximately 3 min) for each subject relative to the baseline values. The average results obtained in the normal volunteers are summarized in Table I. Measured at the end of squatting, group average MOAP was 81 ± 6 mmHg, which is 22.3% above the baseline values of 66 ± 6 ($p < 0.05$). Average values of the LDF parameters of the control group did not change significantly during

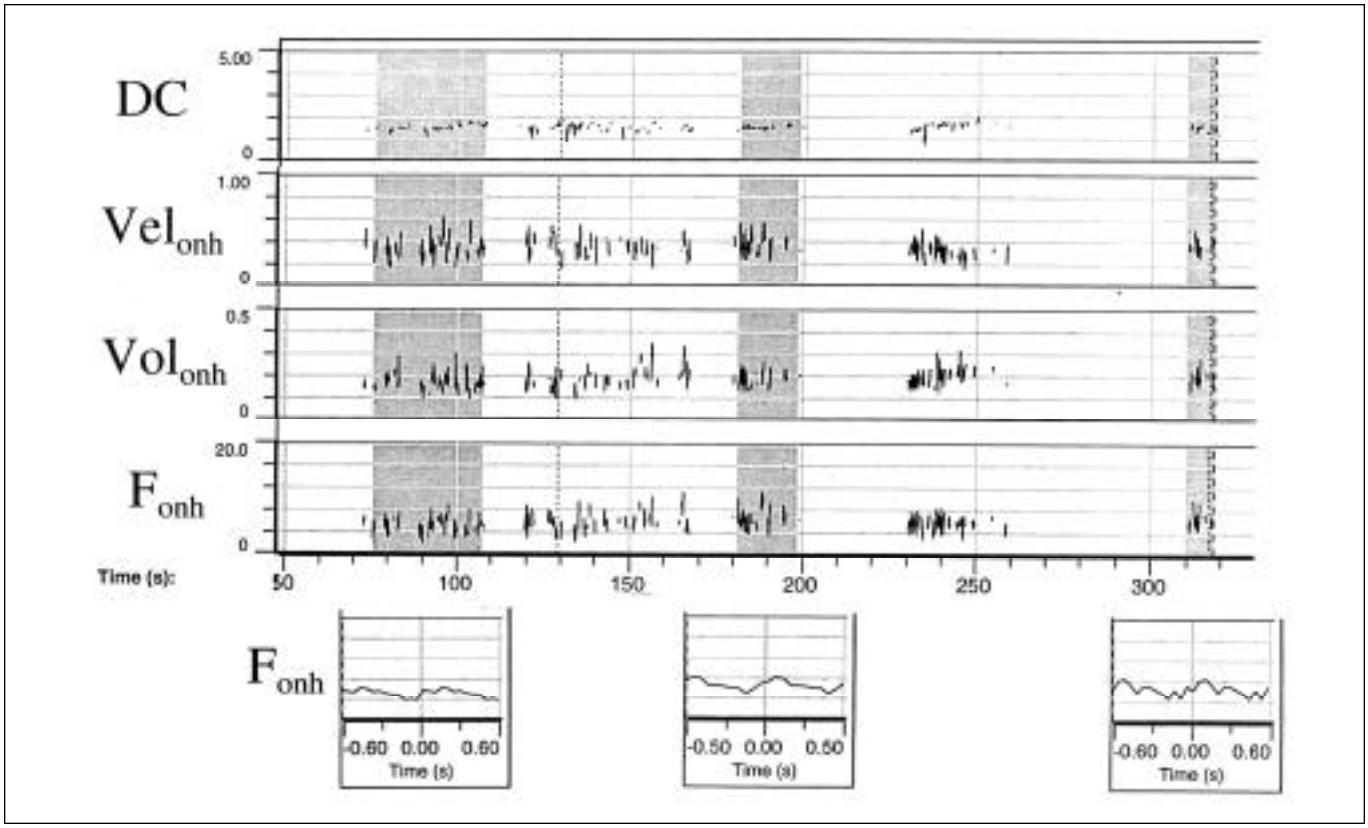

Fig. 1 - *Representative recording of DC, Vel_{onh}, Vol_{onh}, and F_{onh} obtained in one of the subjects at baseline, during squatting, and recovery from squatting. DC represents the intensity of the detected light and the laser Doppler flowmetry (LDF) flow parameters, Vel_{onh}, Vol_{onh}, and F_{onh}, are the mean velocity, volume, and flux of the red blood cells in the volume sampled by the laser beam, respectively. Highlighted are the recording segments that have been used to determine the average change of the flow parameters during the heart cycle, at baseline, during squatting, and approximately 80 sec during recovery from squatting. In this Figure, only the change in F_{onh} during the heart cycle is shown (three traces below the LDF parameter recordings).*

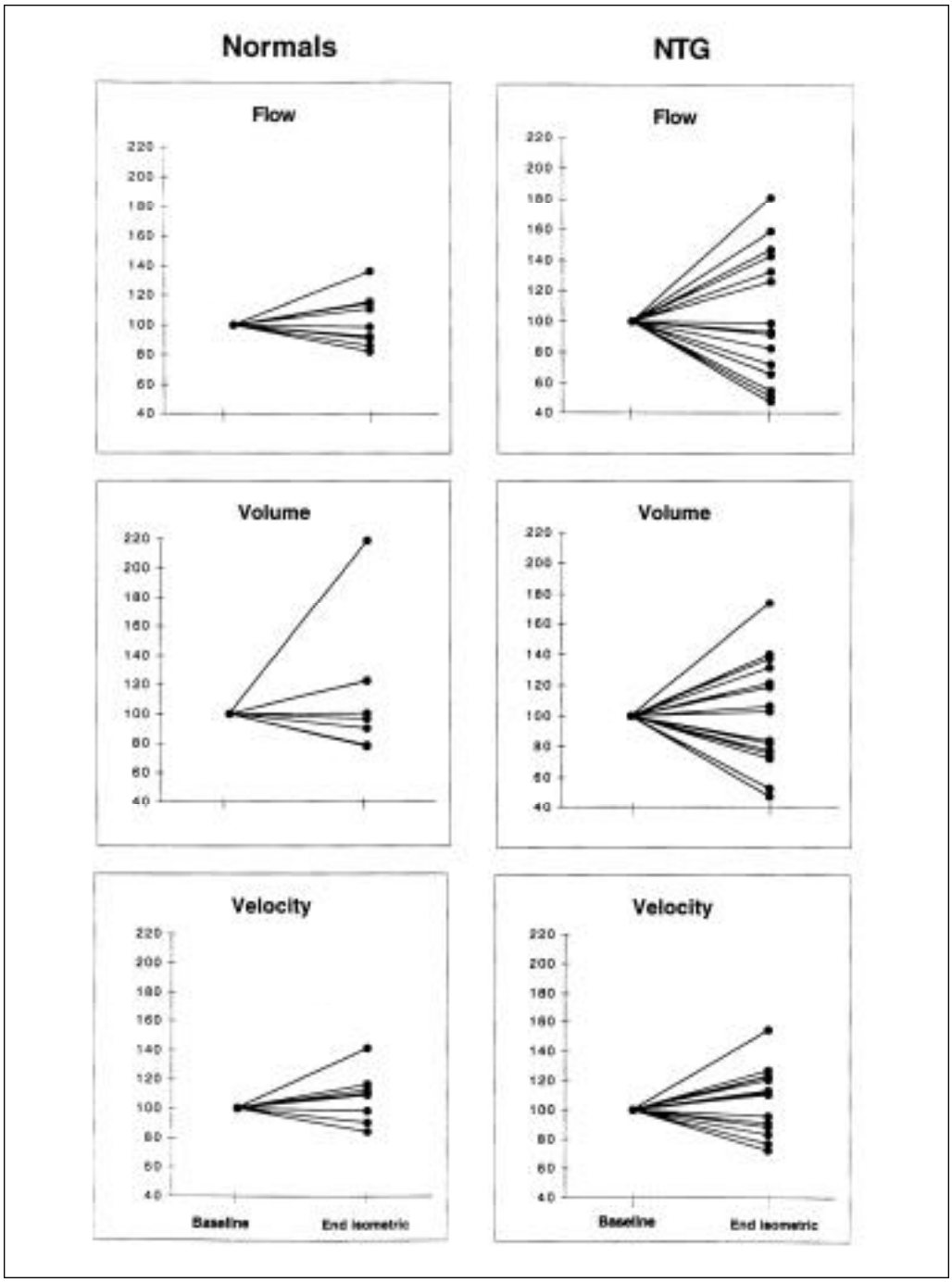

Fig. 2 - *Percentage changes of the laser Doppler flowmetry parameters at the end of squatting (approximately 3 min) relative to the baseline values for the normal subjects and the normal tension glaucoma group.*

squatting for Vel_{onh} (0.37 ± 0.07 to 0.40 ± 0.07), Vol_{onh} (0.30 ± 0.09 to 0.31 ± 0.09), and F_{onh} (9.84 ± 2.12 to 9.97 ± 1.54). When subjects stopped squatting, the mean LDF parameters Vel_{onh} (0.35 ± 0.05), Vol_{onh} (0.28 ± 0.12), and F_{onh} (8.83 ± 2.78) reached values that were not significantly different from baseline.

During squatting, PP_m increased from 52.4 ± 5.5 mm Hg to 66.9 ± 6.7 mm Hg, a 28.5% increase. Vascular resistance (R) increased significantly ($p < 0.001$) from 5.5 ± 1.3 at baseline to 6.9 ± 1.8 at the end of squatting (26.5%).

TABLE I - ISOMETRIC EXERCISE: MEAN LASER DOPPLER FLOWMETRY VALUES: NORMAL SUBJECTS (N = 10)

Values	Baseline	Isometric exercise	Recovery
MOAP (mmHg)	66 ± 6	81 ± 6	64 ± 7
Vel_{onh} (kHz)	0.37 ± 0.07	0.40 ± 0.07	0.35 ± 0.05
Vol_{onh} (AU)	0.30 ± 0.09	0.31 ± 0.09	0.28 ± 0.12
F_{onh} (AU)	9.8 ± 2.1	10 ± 1.5	8.8 ± 2.8

MOAP = Mean ophthalmic artery blood pressure; AU = Arbitrary units

TABLE II - ISOMETRIC EXERCISE: MEAN LASER DOPPLER FLOWMETRY VALUES: NORMAL TENSION GLAUCOMA PATIENTS (N = 16), WORSE EYE

Values	Baseline	Isometric exercise	Recovery
MOAP (mmHg)	73 ± 5	89 ± 9	72 ± 9
Vel_{onh} (kHz)	0.32 ± 0.06	0.34 ± 0.07	0.33 ± 0.09
Vol_{onh} (AU)	0.34 ± 0.15	0.30 ± 0.09	0.39 ± 0.08
F_{onh} (AU)	7.1 ± 2.6	7.4 ± 3.9	7.3 ± 3

MOAP = Mean ophthalmic artery blood pressure; AU = Arbitrary units

NTG group

The average results obtained in the more affected eye of the NTG patients are summarized in Table II. Figure 2 shows the percentage changes of the LDF parameters relative to baseline for each subject after 3 min of squatting. During this time, group average MOAP increased significantly ($p < 0.05$) from a baseline value of 73 ± 5 to 89 ± 9 mmHg (22%). Group average of the three LDF parameters did not change significantly during squatting (0.32 ± 0.06 to 0.34 ± 0.07 for Vel_{onh}, 0.34 ± 0.15 to 0.30 ± 0.09 for Vol_{onh}, 7.1 ± 2.6 to 7.4 ± 3.9 for F_{onh}). During recovery from squatting, these flow parameters also did not change significantly.

During the 3 min of squatting, PP_m increased significantly ($p < 0.001$) from 58.9 ± 5 mmHg to 75.7 ± 8.3 mmHg (28.9%). R_m also increased significantly from 9.1 ± 2.8 to 13.4 ± 7.6 (47%). The mean F_{onh} values ± SD and MOAP at baseline, during isometric exercise, and recovery for normal and NTG groups are shown in Figure 3.

In the 11 NTG patients, in whom the LDF parameters were measured in both eyes, the average MOAP for the better eye group increased significantly during isometric exercise from 72.9 ± 5.1 to 92.09 ± 8.32 mmHg, resulting in a significant increase of the PP_m from 59.5 ± 5.2 to 78.7 ± 8 mmHg (32%). Similarly, in the worse eyes group, the MOAP and PP_m increased significantly from 72.5 ± 5.9 to 87.3 ± 8.5 mmHg and

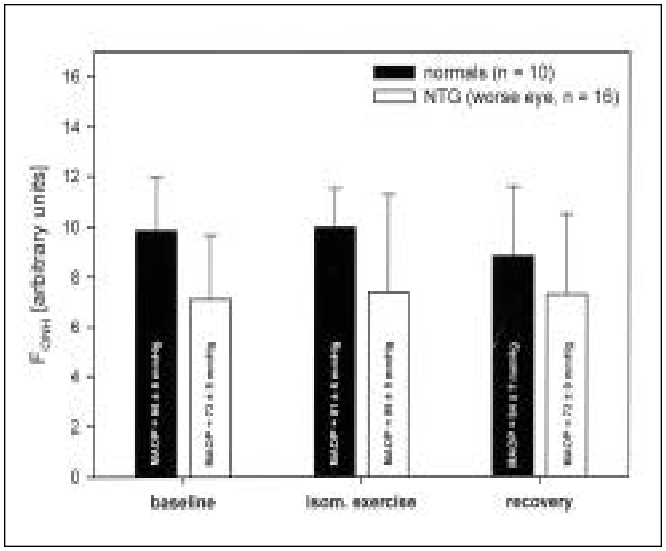

Fig. 3 - *Histogram of mean F_{onh} values ± SD at baseline, at the end of the isometric exercise and at recovery for normal and normal tension glaucoma groups. These values are not statistically different from each other.*

TABLE III - F_{onh} VALUES IN NORMAL TENSION GLAUCOMA PATIENTS DURING ISOMETRIC EXERCISE, BETTER VERSUS WORSE EYE (N = 11)

Eye	Baseline	Isometric exercise
Better eye		
MOAP (mmHg)	73 ± 5.3	92 ± 8.3
Vel_{onh} (kHz)	0.36 ± 0.08	0.37 ± 0.08
Vol_{onh} (AU)	0.32 ± 0.14	0.27 ± 0.09
F_{onh} (AU)	10 ± 6.3	8.8 ± 3.2
Worse eye		
MOAP (mmHg)	72 ± 6	87 ± 9
Vel_{onh} (kHz)	0.32 ± 0.06	0.35 ± 0.07
Vol_{onh} (AU)	0.28 ± 0.09	0.27 ± 0.13
F_{onh} (AU)	7.5 ± 2.8	8 ± 4

MOAP = Mean ophthalmic artery blood pressure;
AU = Arbitrary units

from 59.5 ± 5.4 to 74.3 ± 8.3 mmHg (25%), respectively.

Group average of the F_{onh} LDF parameters did not change significantly during squatting, from 10.2 ± 6.3 to 8.8 ± 3.4 for the better eyes, and from 7.5 ± 2.6 to 7.5 ± 4.1 for the worse eye group (Tab. III). In addition, the F_{onh} at baseline and end exercise were not significantly different in both groups. Similarly, average increases of R_m for the groups of better eyes (from 7.0 ± 3.6 to 10 ± 3.2) and worse eyes (from 8.7 ± 2.6 to 13.0 ± 8.8) were significant. These increases in R were not statistically different between the two groups, indicating a similar regulation for all patients of the NTG group.

From recordings obtained during the last minute of squatting, $SVel_{onh,sq}$, $SVol_{onh,sq}$, and $SF_{onh,sq}$ were equal to 4.8%, 9.4%, and 9.2%, respectively, for the group of normal subjects. For the NTG group, these sensitivities were equal to 8.8%, 14%, and 14%, respectively.

DISCUSSION

Alterations of F_{onh} appear to be of pathogenic relevance in patients with normal pressure glaucoma as optic nerve damage is weakly related to the level of the IOP (30). These have been hypothesized to result from an abnormal regulation of F_{onh} in response to changes in PP_m. Although retinal capillary blood flow appears to be dysregulated in chronic open-angle glaucoma (27), there are no data on ONH F_{onh} regulation in this disease. To reveal an abnormal regulation of F_{onh} requires either that the IOP be increased by suction cup to diminish PP_m or that the MOAP be increased to raise the PP_m. The latter procedure can be achieved by means of isometric exercise, which has the advantage of being noninvasive. In normal volunteers, F_{onh} remains constant, in spite of an average increase in PP_m of 30% (21). Beyond this value, F_{onh} increases in parallel with further increases of this pressure. Our working hypothesis was, therefore, that, in glaucoma, a deficient ONH blood flow regulation would lead to an observable increase in F_{onh} before reaching a 30% increase in PP_m. Our data, however, failed to confirm this hypothesis, since no significant difference in the response of F_{onh} was found between the NTG patients and the control subjects.

It is conceivable either that the regulation of F_{onh} in NTG during an increase of the PP_m is not different from that in normal subjects or that a larger increase in systemic blood pressure may be necessary in both normal subjects and patients to demonstrate a difference in their F_{onh} regulation. Clinically, however, this appears to be difficult to realize, particularly in view of the advanced age of the patients. In addition, an increase of the PP_m by more than 30% should induce a linear increase of the F_{onh} also in normal subjects (21) requiring a larger number of subjects to be able to detect differences in regulation between the NTG and normal groups. Another reason for our failure to confirm our hypothesis could be that the method used in this study is not sensitive enough to detect a difference between the normal and glaucoma groups.

Although altered blood flow regulation was not demonstrable in NTG patients, these patients had an average F_{onh} that was approximately 28% lower than the average F_{onh} of normal subjects, in agreement with previous LDF data in open-angle glaucoma (23-26). A decreased F_{onh} does not fully exclude, however, the possibility that this decrease could be due to changes in optical properties as a consequence of the tissue damage in the glaucomatous ONH, by modifying the scattering of the laser beam (31).

The findings of the present study are similar to those previously observed in a population of younger volunteers and indicate that, during isometric exercise, a regulatory mechanism operates to increase the vascular resistance in response to the increase in ocular perfusion pressure (21). This mechanism could involve factors external to the eye or act locally at the ONH vasculature.

Isometric exercises are known to increase heart rate, cardiac output, and MABP by stimulating sympathetic activity (32), an effect known to produce a vasoconstriction in a number of organs. In addition, squatting increases venous return caused by venous compression in the legs (33). An increase in the resistance of the ophthalmic artery and the vessels between this artery and the site of LDF measurements at the ONH, secondary to increased sympathetic activity, could be the main regulatory mechanism of the blood flow during isometric exercise (34). Whether such a vasoconstricting mechanism operates in the ONH is still unclear, since it is generally accepted that sympathetic innervation stops at the lamina cribrosa (35). Nevertheless, some studies have reported an autonomic innervation of the preretinal vessels in mammals (36).

In a previous study (37), it was reported that the MABP in the ophthalmic and brachial arteries rise in parallel during squatting, which suggests that the regulatory increase of the vascular resistance by vasoconstriction occurs distally to the ophthalmic artery, at the level of the ONH vasculature. The maintenance of a nearly constant Vol_{onh} value in the ONH capillary bed (Fig. 2) suggests that this vasoconstriction occurs outside of the sampled volume. Whether it takes place at the arterioles feeding or at the veins draining the blood from the ONH cannot be answered by LDF measurements.

An autoregulatory mechanism has already been shown to operate in the normal ONH in response to a stepwise decrease of the perfusion pressure induced by raising the IOP by suction cup (13, 14). A time course analysis of this response concluded that a metabolic rather than a myogenic process of autoregulation was operating (14), probably through the release of substances inducing vasodilatation of the resistance vessels of the ONH during a decrease of the PP_m.

Unexpectedly, the increase in vascular resistance in response to practically identical increases in PP_m during squatting appears to be more important in the NTG patients than in the normal subjects (46% versus 26%), although this difference did not reach statistical significance. This observation suggests some alteration of the vessel tone regulatory mechanisms in glaucoma, possibly through a higher plasma concentration of ET_1 (38). Whether a hyper-reactivity of the vascular resistance in these patients could lead, in the long term, to insufficient blood flow to the ONH and subsequent damage to the ONH tissue remains to be investigated.

In conclusion, these results did not reveal an abnormal F_{onh} regulation in response to an increase of the ocular perfusion pressure of approximately 30% in either normal controls or NTG patients. The maintenance of constant blood flow is achieved by an increase in vascular resistance in the vascular bed outside of the ONH vessels. Our results do not exclude an additional mechanism at the site of LDF measurements. The greater increase in vascular resistance in response to a similar increase in ocular perfusion pressure during squatting in the NTG patients suggests some alteration of the vessel tone regulatory mechanisms in glaucoma.

ACKNOWLEDGEMENTS

Supported by grant 3200-043157 from the Swiss National Science Foundation and Loterie Romande, Lausanne, Switzerland.

The authors thank François Riva for his contribution in the measurements and data analysis and Christine Strassberger for secretarial help.

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