Anterior Optic Nerve Blood Flow Decreases in Clinical Neurogenic Optic Atrophy

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Abstract: Anterior optic nerve blood flow was studied in nine patients with unilateral neurogenic optic atrophy using noninvasive techniques. Disk reflectometry measurements from temporal sites demonstrated a significant reduction in the index of blood volume in atrophic optic nerves as compared with the contralateral optic nerves ($P < 0.00001$). Laser Doppler measurements from the same temporal sites detected a significant reduction in the speed of blood ($P < 0.002$). On average, blood volume was decreased by 49% ± 11% and blood speed by 30% ± 17%. Combining the results of these two techniques yielded a relative index of blood flow that showed a significant reduction in the atrophic nerves ($P < 0.0001$), averaging 64% ± 14% temporally. Nasally there was less reduction in blood flow. The results correlated well with clinical assessment of the degree of optic nerve damage ($\rho = 0.92$, $P < 0.002$). This study demonstrates that clinical neurogenic optic atrophy induces significant reductions in overall anterior optic nerve blood flow that are detected by these noninvasive techniques. [Key words: blood flow, laser Doppler, optic atrophy, optic nerve, reflectometry.] Ophthalmology 93:858–865, 1986

The paucity of knowledge about the role of blood flow abnormalities in optic nerve disorders is due in part to a lack of noninvasive techniques for measuring anterior optic nerve blood flow in vivo.

Disk pallor in optic atrophy was once thought to result from decreased vascularity, but some recent studies, using histologic and angiographic techniques, found no decreased vascularity in optic atrophy.[1–5] However, Quigley and colleagues found an overall decrease in the number of capillaries and a 27% decrease in the cross-sectional area of remaining capillaries in experimental total neurogenic optic atrophy.[6] The decrease in number of capillaries was proportional to a decrease in nerve head substance, so that the number of vessels in relation to tissue volume was unchanged from normal. These workers concluded that there is a loss of capillaries in the anterior optic nerve that is secondary to nerve fiber loss. Thus, in vivo assessment of anterior optic nerve blood flow could reflect not only the circulatory status but also the degree of nerve fiber degeneration in the optic nerve. Furthermore, on the basis of Quigley's findings it is possible to predict that any in vivo measure of overall anterior optic nerve blood flow would show reductions in blood volume as well as reduced blood speed.

We have reported previously on two noninvasive techniques for measuring anterior optic nerve blood flow in vivo and noted the importance of evaluating blood volume and blood speed independently because each parameter can be affected differently in disease.[7,8] In an animal model of neurogenic optic atrophy, reflectometry techniques demonstrated a 51% decrease in estimated capillary blood volume, and laser Doppler showed a 53% decrease in the speed of blood flow.[9] The present study used these two techniques to evaluate human anterior optic nerve blood flow in vivo. The objective was to determine whether blood flow changes could be detected in clinical neurogenic optic atrophy. The results are consistent with predictions based on Quigley's morphologic studies and with our previous findings in experimental neurogenic optic atrophy.[6,9]

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Table 1. Clinical Characteristics of Patient Population

Patient No.	Age	Sex	Diagnosis	Visual Acuity	Ishihara	Visual Fields	IOP (mmHg)	Disk	NFL	Clinical Severity Index*	Ancillary Tests

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1	17	M	Optic neuritis	20/25	2/8	T P-C scotoma	16	Pallor T > N	Defects T Slits N	2.67	CT scan—normal
2	28	M	Optic neuritis	20/30	1/8	S C-C scotoma	18	Pallor ST Slight N	Defects ST, SN, IN	2.00	—
3	32	F	Optic neuritis	CF	0/8	Central scotoma	17	Pallor T	Defects ST, IT, IN	3.67	CT scan—normal
4	21	F	Optic neuritis	20/20	6/8	Arcuate scotomas IT > ST	15	Pallor T > N	Defect ST	3.33	CT scan—normal VER—abnormal
5	47	F	Optic neuritis	20/70	—	ST defect N constriction	19	Pallor IT > ST Slight N	Defect P-M Nodules ST, IT	2.00	CT scan—normal
6	41	F	Multiple sclerosis	20/20	1/8	S altitudinal defect	14	Pallor IT	Defect IT	1.33	VER—abnormal CSF—diagnostic
7	30	F	Optic neuritis	20/30	—	Arcuate scotoma IT	14	Pallor T	Slits T	1.67	—
8	29	M	Optic neuritis	20/20	6/8	Normal	16	Slight pallor T	Normal	0.67	—
9	37	M	Pituitary tumor	20/15	6/8	Defect SN	20	Pallor T Slight N	Defects SN, ST, IT	3.33	VER—abnormal OS normal OD

M = male; F = female; IOP = intraocular pressure; OS = left eye; OD = right eye; CF = count fingers; S = superior; I = inferior; T = temporal; N = nasal; ST = superotemporal; IT = inferotemporal; IN = inferonasal; SN = superonasal; P-C = paracentral; C-C = centrocaecal; P-M = papillo-macular; CT = computed tomography; VER = visual evoked response; CSF = cerebrospinal fluid.
* Values represent the mean of the grading of three observers: 0 = normal → 4 = most severe.

MATERIALS AND METHODS

PATIENT POPULATION

The nine patients with unilateral neurogenic optic atrophy ranged in age between 17 and 47 years; had no history of ocular disease, trauma, or surgery; and no diabetes, hypertension, or cardiovascular disease. Informed consent was obtained from each patient. A complete ophthalmologic examination was performed including color vision and visual field testing. Bilateral mydriasis was induced using phenylephrine 5% and tropicamide 0.5%, and intraocular pressures were measured after pupil dilatation. Color and red-free monochromatic fundus photographs with magnified views of the disks were obtained, and fluorescein angiography, laser Doppler, and reflectometry were performed. The clinical findings are shown in Table 1.

The patients were ranked with respect to the severity of optic nerve damage on a clinical basis. Three experienced clinicians independently examined color slides of the disks and peripapillary fundi of both eyes in all patients and graded the severity of disease from 0 to 4 (0 = normal, 4 = most severe) based on the degree and extent of optic nerve head pallor and the degree of nerve fiber layer dropout. These evaluations were done in a masked fashion, and the scores averaged into a clinical severity index (Table 1).

LASER DOPPLER TECHNIQUE

The theoretical aspects of the application of the laser Doppler technique to measurements of blood speed in the anterior optic nerve have been described in detail.[9] Briefly, when a region of tissue perfused by capillaries is illuminated by laser light, the superposition of the light scattered by red cells of different velocities and at different angles causes a broadening of the frequency spectrum $S(\Delta f)$ of the backscattered light. A theory predicting the shape of the Doppler-broadened frequency spectrum was developed by Stern and Lappe, who showed that the low frequency portion of $S(\Delta f)$ can be expressed as

$$S(\Delta f) = -K \log (\Delta f/\alpha) \qquad (1)$$

where K is a measure of the spectrum's amplitude, and the frequency α is a measure of the spectrum's broadening, which is proportional to the red blood cell speeds that are present.[10]

During data acquisition, patients were positioned before a fundus camera apparatus equipped with a helium-neon laser light source ($\lambda = 633$ nm) and a scanning fiberoptic-photomultiplier detector assembly that collects the scattered light.[11,12] The incident laser beam was directed into the eye and positioned onto the optic disk. Examination with red-free light enabled the identification of vessels on the disk surface, which were avoided to ensure that measurements were obtained from regions of disk tissue perfused only by capillaries.

Measurement sites were approximately 180 μm in diameter, as determined by the fiberoptic entrance aperture and the camera magnification. The photocurrent signal from the detector was recorded continuously on a Honeywell 5600 C Recorder/Reproducer for approximately 1 minute. The mean value of the photocurrent, a measure of the intensity of the scattered light, was continuously displayed on a strip chart recorder. The photocurrent signal was also channelled through a loudspeaker. The audio signal from the disk tissue is easily distinguished from that of an individual vessel and is a useful guide in maintaining the position of the incident beam only on anterior optic nerve tissue during the measurement.

All data analysis was performed without prior knowledge of the clinical diagnosis. For data analysis, the portion of tape recorded during optimal conditions of eye stability, incident beam alignment, and detector alignment was identified as that portion exhibiting the least fluctuation in the mean photocurrent. The frequency spectrum $S(\Delta f)$ of the photocurrent was then obtained using a Federal Scientific UA 500 ubiquitous real-time spectrum analyzer. Spectra were obtained using a 5 kHz full-scale range with an averaging time of 6.4 seconds. The results were recorded on an X-Y plotter. Amplitude and log frequency data in the range 70 to 500 Hz at 25 Hz intervals were entered into a computer for determination of α. All spectra were fit either to the single logarithmic form predicted by the theory or to the sum of two logarithmic curves. In the latter case, an average value of α was determined as previously described.[9] It has been shown previously that using this approach for data acquisition and analysis there is typically a ±7% standard deviation about the mean for α values determined from spectra obtained during successive measurements from the same optic disk site.[7]

OPTIC DISK REFLECTOMETRY

Spectral reflectometry of the optic disk was used to estimate in vivo the amount of blood present in the tissue of the optic nerve head. The method consists of measuring the reflectance $R\lambda$ of a discrete area of the optic disc at three appropriate wavelengths λ_0 = 569 nm, λ_1 = 559 nm, and λ_2 = 585 nm. Reflectance ratios $r_1 = R\lambda_1/R\lambda_0$ and $r_2 = R\lambda_2/R\lambda_0$ are calculated to eliminate the influence of variations in the incident light intensity.

Theoretical considerations, which were given in detail in a previous paper, show that the reflectance ratio can be expressed by:

$$r_\lambda = [1 + \beta(\lambda - \lambda_0)] \cdot \frac{1 - \gamma K_\lambda}{1 - \gamma K_{\lambda_0}} \qquad (2)$$

where γ is a measure for the amount of blood (cm), K_λ is the known absorption coefficient of hemoglobin (1/cm), and β is a wavelength-independent parameter.[9] The index γ is proportional to the volume fraction of blood in the tissue and inversely proportional to the scattering coefficient of the tissue. The determination of γ therefore does not allow, a priori, differentiation between changes in blood volume and changes in the scattering properties of the tissue. The term in square brackets is the reflectance ratio for the bloodless disk ($\gamma = 0$), and accounts for the spectral variation of the reflectance of the optic disk and of the double transmission of light through the ocular media.

Each reflectance ratio r_i and r_2 can be related to γ and β by equation (2), but with $\lambda = \lambda_1$ and $\lambda = \lambda_2$. The unknown index γ is solved, by elimination of β, to give:

$$\gamma = \frac{w(r_1 - 1) - r_2 + 1}{K_0(w \cdot r_1 - r_2) - K_1 \cdot w + K_2} \qquad (3)$$

where W = (585 − 569/559 − 569), and K_0, K_1, and K_2, the absorption coefficients at 569, 559, and 585 nm, respectively. Each absorption coefficient is the product of the specific absorption coefficient (at a given oxygen saturation of the blood), and the hemoglobin concentration.[13] Oxygen saturation of blood was assumed to be 80% for all disks, and hemoglobin concentration to be 15 g/100 ml. Under these assumptions, values K_0 = 237 cm^{-1}, K_1 = 202 cm^{-1}, and K_2 = 153 cm^{-1} were found and used in equation (3) to calculate γ. A change of 10% saturation from the assumed value (80%) causes an inverse change of 7% in γ. This dependence affects measurements on all disks such that the ratio of γ for atrophic and normal disks are not critically affected (less than 2%) if the blood oxygen saturation in both disks is the same. Changes in hemoglobin concentration also affect the γ values, but not the ratio of γ values, as the hemoglobin concentration of blood in both disks can be assumed to be the same.

Data acquisition consists of reflectance measurements, at the three wavelengths, from selected areas of the anterior optic disk. The Retinal Vessel Oximeter, operated in its reflectometry mode, is used for that purpose.[14] The fundus was illuminated over an area of about 5° successively at three wavelengths (λ_0 = 569, λ_1 = 559, and λ_2 = 585 nm), and the light reflected from a 250 × 250 μm area of the optic disk was detected. Microcomputer control of the instrument allows signal averaging, and the calculation every 3 seconds of the intensity of the reflected light signal at the three wavelengths and the reflectance ratios r_1 and r_2. Typically, about 20 such 3-second measurements were made and averaged for each optic disk site. Measurement of light intensities reflected from a magnesium oxide reflectance standard allows correction of the disk data to account for differences in illumination intensities and detection sensitivities at the three wavelengths. The average reflectance ratios r_1 and r_2 are then used to compute the index γ using equation (3). This parameter is expressed in units of microns representing the thickness of an equivalent blood layer.

INDEX OF BLOOD FLOW

The two parameters γ and α were combined into an index of blood flow

$$F = \gamma \cdot \alpha \qquad (4)$$

where γ is the index of blood volume as measured by

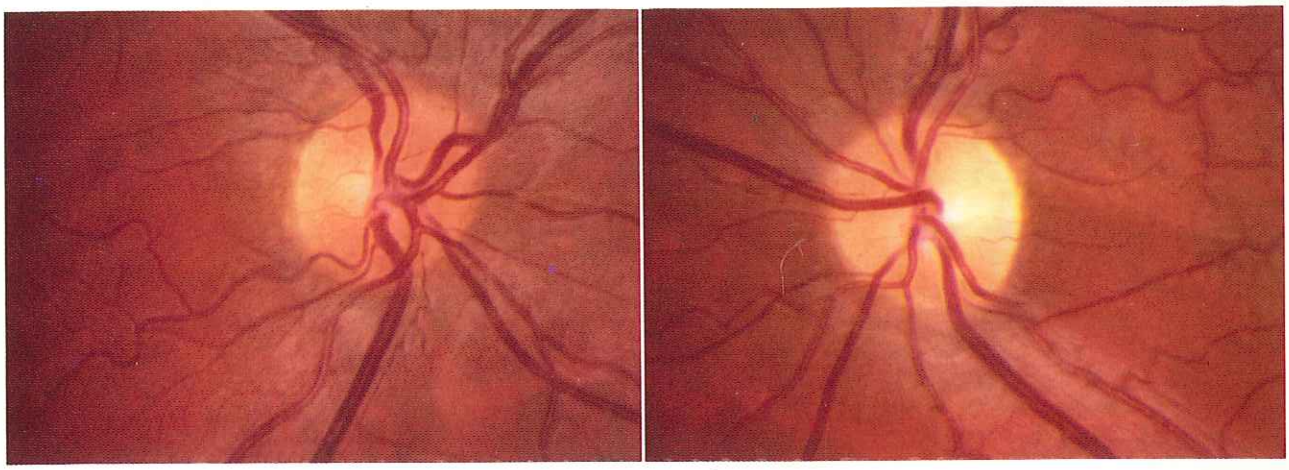

Fig 1. Case 1. There is marked pallor of the temporal disk in the left eye (*right*). Severe temporal nerve fiber layer dropout is present with slits in the nasal nerve fiber layer of the left eye.

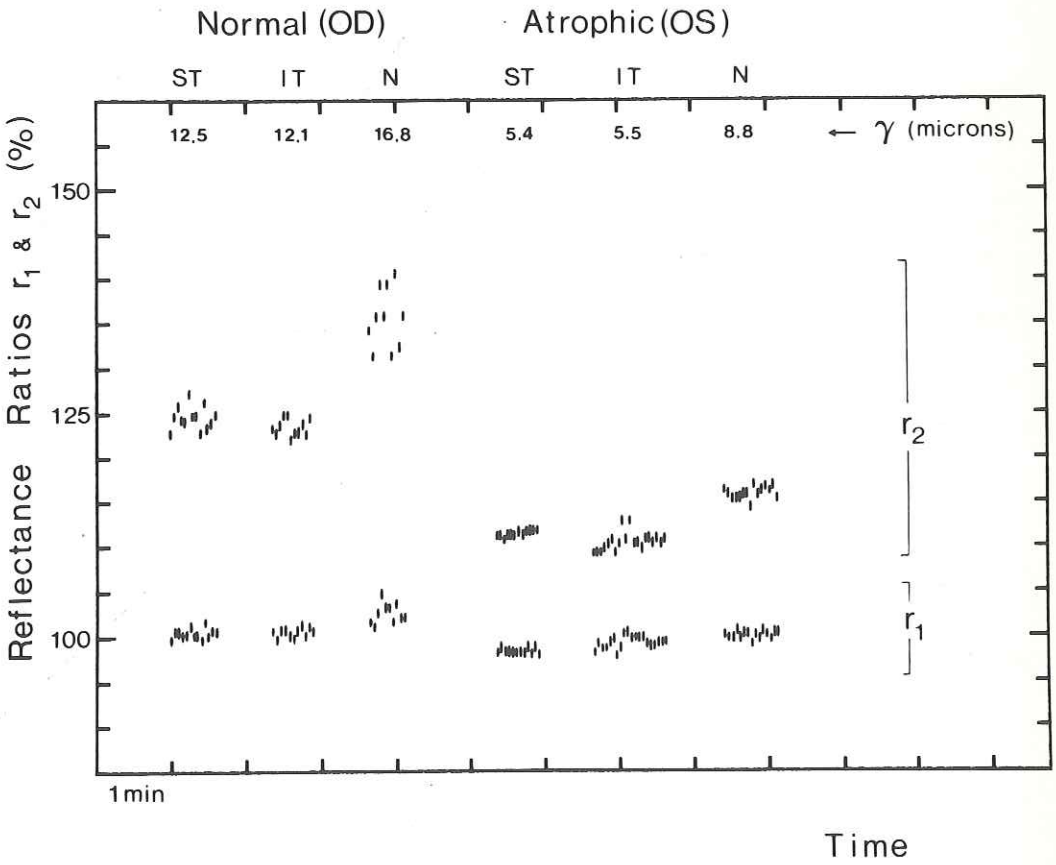

Fig 2. Disk reflectometry measurements, case 1. All data points measured at the superotemporal (ST), inferotemporal (IT), and nasal (N) disk sites in the normal (right; OD) and affected (left; OS) eyes are shown. The six groups of data points at the bottom correspond to the ratios of reflectances measured at 559 nm/569 nm (r_1), and the six at the top to the ratios at 585 nm/569 nm (r_2). These ratios, especially r_2, were lower at all three sites in the eye with optic atrophy than in the normal eye. The values for γ, the index of blood volume, calculated from these data using equation (3), are shown at the top.

reflectometry, and α is the index of the speed of blood flow as measured by laser Doppler. Equation 4 is valid when used for comparisons of blood flow in the atrophic optic nerve with the fellow eye, under the assumption that changes in the scattering coefficient of atrophic optic nerve tissue are small compared to the circulatory changes.

RESULTS

One case is presented as an example of the results obtained using the two techniques, and then the results for the total population are given.

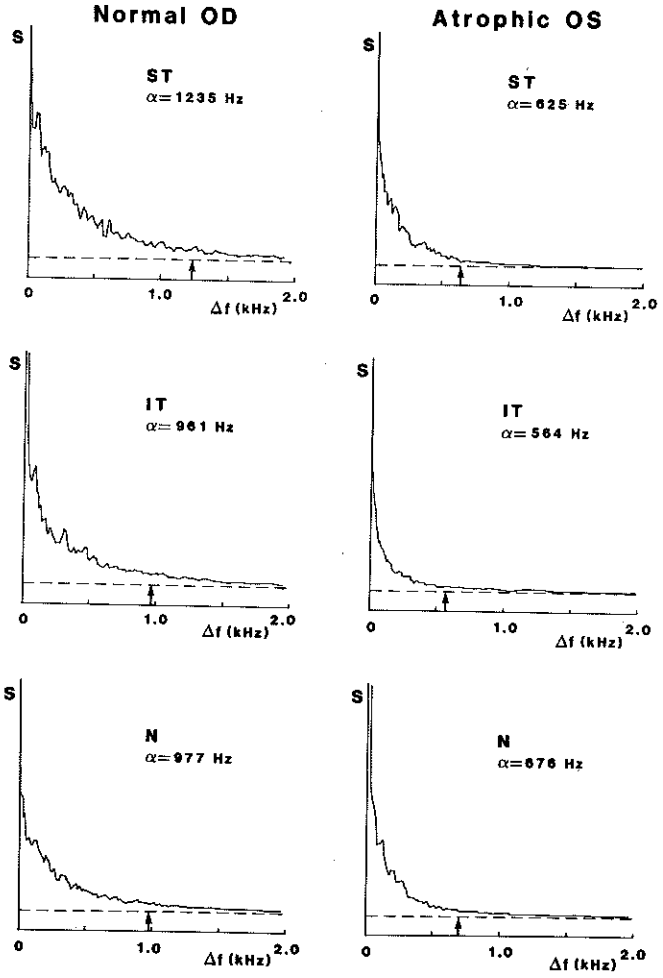

Fig 3. Laser Doppler measurements, case 1. The Doppler-broadened frequency shift spectra obtained from the superotemporal (ST), inferotemporal (IT), and nasal (N) disk sites are shown for the normal (right; OD) and affected (left; OS) eyes. The ordinate is amplitude in arbitrary units. The spectra were narrower at all sites in the affected eye than at corresponding sites in the normal eye. The values for α, the index of blood speed, are shown for each spectrum (arrows).

Case 1. A 17-year-old white male experienced two episodes of decreased vision in the left eye over a period of eight months. During the first episode, visual acuity decreased to 20/400; a CT scan was normal. During the second episode, vision was worsened by exercise or heat (positive Uhtoff sign). Past medical and ocular histories were negative.

On examination, visual acuity was 20/20 in the right eye and 20/25 in the left. The anterior segment was normal in both eyes and intraocular pressure was 16 mmHg. There was an afferent pupillary defect in the left eye. Color vision evaluation demonstrated 75% red desaturation in the left eye on confrontation testing, and the patient could identify only 2/8 Ishihara plates with this eye. Goldmann visual field testing demonstrated a temporal paracentral scotoma in the left eye. There was marked pallor of the temporal disk and slight pallor of the nasal disk in that eye (Fig 1). There was severe nerve fiber layer dropout on the temporal side and slits in the nerve fiber layer on the nasal side of the left disk (Fig 1). Fluorescein angiography demonstrated normal filling of the disk and peripapillary choroidal vasculature.

Table 2. Reflectometry and Laser Doppler Results

	Reflectometry γ (μm)		Laser Doppler α (Hz)	
Patient No.	Normal	Atrophic	Normal	Atrophic
Temporal				
1	12.3	5.4	1098	594
2	11.1	4.8	881	708
3	12.7	4.8	832	421
4	12.0	5.3	1230	715
5	11.4	6.4	926	552
6	16.5	8.8	745	666
7	10.4	5.7	839	818
8	15.3	11.7	933	745
9	12.7	6.1	1148	661
Mean ± SD	12.7 ± 2.0	6.6 ± 2.3	959 ± 163	653 ± 117
	$P < 0.00001$		$P < 0.002$	
Nasal				
1	16.8	8.8	977	676
2	13.8	13.4		
3	17.5	12.1	1023	666
4	11.6	10.2	572	545
5	14.4	11.8	733	708
6	14.5	10.5	938	813
7	10.5	12.7	832	663
8	17.7	16.9	943	726
9	11.6	11.9	751	552
Mean ± SD	14.3 ± 2.7	12.0 ± 2.3	846 ± 153	669 ± 88
	$P = 0.06$, NS		$P < 0.004$	

NS = not significant; SD = standard deviation.

Temporal data are the averages of superotemporal and inferotemporal results whenever both were available for an eye. Nasal data are the results of one set of measurements in each eye of all patients. Significance levels were determined using the parametric two-tailed paired t-test. There were no statistically significant differences between temporal and nasal measurements in the normal eyes.

Reflectometry and laser Doppler measurements were obtained in the superotemporal, inferotemporal, and nasal regions of the disk in each eye (Figs 2, 3). Compared with corresponding sites in the contralateral eye, the affected eye showed substantial reductions in both the index of blood volume γ and the index of speed α at all sites (Figs 2, 3). Whenever two temporal measurements were available, as in this case, the results were averaged into a single value for all subsequent data analysis.

TOTAL POPULATION

The results obtained from temporal and nasal measurements in each optic nerve of all nine patients using the two techniques are shown in Table 2. The percent decreases in these results for the atrophic optic nerves as compared with the corresponding sites in the contralateral eye of each patient are shown in Table 3.

Temporal disk measurements with each technique demonstrated decreases in γ and α in the atrophic nerve as compared with the contralateral nerve in each patient. In the unaffected eyes, reflectometry measurements resulted in a mean value for γ of 12.7 ± 2.0 μm temporally. This was quite close to the mean value obtained in another study of 15 normal subjects where γ = 12.5 ± 2.7 μm

Table 3. Percent Decrease in Blood Volume (γ), Blood Speed (α), and Blood Flow (F) in the Atrophic Anterior Optic Nerves as Compared with the Contralateral Normal Optic Nerves

Patient No.	Volume (γ)	Speed (α)	Flow (F)
Temporal			
1	56	46	76
2	57	20	65
3	62	49	81
4	56	42	74
5	43	40	66
6	47	11	52
7	45	3	47
8	24	20	39
9	52	42	72
Mean ± SD	49 ± 11	30 ± 17	64 ± 14
Nasal			
1	48	31	64
2	3	—	—
3	31	35	55
4	12	5	16
5	18	3	21
6	28	13	37
7	−20	20	4
8	5	23	26
9	−2	26	24
Mean ± SD	13 ± 20	20 ± 12	31 ± 20

SD = standard deviation.

Percent decreases in γ and α showed no statistically significant linear correlations with each other, for either the temporal or nasal data.

(unpublished data). The mean value for γ in atrophic optic nerves, 6.6 ± 2.3 μm, was significantly lower than that in the contralateral normal nerves ($P < 0.00001$). The average of the individual decreases was 49 ± 11%, as listed in Table 3.

Temporal laser Doppler measurements in the unaffected eyes yielded a mean value for α = 959 ± 163 Hz, which compared favorably with the results of previous studies in 20 eyes of 10 normal young subjects, where α = 969 ± 153.[8] The mean value for α in atrophic optic nerves, 653 ± 117 Hz, was significantly lower than that in the contralateral normal nerves ($P < 0.002$). The average of the individual decreases as listed in Table 3 was 30% ± 17%.

When the data for γ and α were combined into the blood flow index F (using equation [4]), the mean value of F in atrophic optic nerves was significantly lower than that in the contralateral normal nerves ($P < 0.0001$). The average decrease in this index of blood flow was 64 ± 14% (Table 3).

Nasal disk measurements did not, in general, reflect the results obtained temporally. In particular, the mean value of γ in the atrophic optic nerves, although lower, was not significantly different from the value in the contralateral normal nerves ($P = 0.06$). The average decrease in γ was 13 ± 20%, which was significantly different from the temporal result (paired t-test, $P < 0.001$). The mean value for α in the atrophic nerves was significantly lower than that in the normal nerves ($P < 0.004$). The average decrease in α was 20 ± 12%, which was not significantly different from the temporal result (paired t-test, $P = 0.12$). The blood flow index F in the atrophic nerves was significantly lower than that for the normal nerves ($P < 0.02$). The average decrease in F was 31 ± 20%, which was significantly different from the temporal result (paired t-test, $P < 0.002$).

The results of reflectometry and laser Doppler measurements from temporal sites are compared to the clinical index of disease severity (Table 1) in Figure 4. A statistically significant correlation is seen between the clinical assessment of optic nerve damage and both the blood volume index ($\rho = 0.73$, $P < 0.04$), and the blood speed index ($\rho = 0.82$, $P < 0.02$). The two techniques seemed to differ in the pattern of correlation with severity of optic nerve damage. Reflectometry results showed 40 to 50% decreases in the index of blood volume (γ) for grades 1 and 2 severity and exceeded 60% reduction in grade 4. Laser Doppler showed a more graded correlation, with a 10 to 20% reduction in the blood speed index (α) for grades 1 and 2 and 40 to 50% for grades 3 and 4. The index of blood flow F also correlated significantly with the severity index ($\rho = 0.92$, $P < 0.002$). For the nasal sites, similar analyses showed no significant correlations.

DISCUSSION

The results reported herein demonstrate that reflectometry and laser Doppler techniques are applicable to the study of human optic nerve disease. The 64% decrease in blood flow through the temporal anterior optic nerve microcirculation detected in clinical neurogenic optic atrophy is in agreement with our previous findings in an animal model.[9] In this animal study of experimental neurogenic optic atrophy, histologic microsphere studies confirmed the noninvasive findings of a decrease in anterior optic nerve blood flow. This suggests that changes in tissue scattering as well as tissue loss due to atrophy did not artifactually influence blood flow measurements by the noninvasive techniques of reflectometry and laser Doppler. In humans, the index of temporal anterior optic nerve blood volume was found to be 49% lower than in the contralateral optic nerves, consistent with the reduction in the overall number of capillaries demonstrated by Quigley.[6] The index of temporal anterior optic nerve blood speed was found to be 30% lower than controls, most likely due to the decrease in the cross-sectional area of the capillaries remaining in the atrophic optic nerve head shown by Quigley.[6]

The volume changes detected temporally by reflectometry were greater than the changes detected nasally, while laser Doppler detected similar speed changes both temporally and nasally. Overall blood flow was reduced to a greater extent temporally, consistent with the clinical observation that in optic neuritis the temporal disk is usually more severely affected than the nasal disk.[15] This is supported by the histologic finding that following optic neu-

ritis due to multiple sclerosis, optic atrophy involves predominantly the temporal portion of the optic nerve.[16]

The finding that in optic atrophy the speed of blood nasally was not significantly different from temporally indicates that even though the disease is most prominent temporally, a generalized decrease in the speed of blood flow occurs throughout the anterior optic nerve. The finding that the blood volume index γ is lower temporally than nasally is probably due to the fact that there is greater tissue loss temporally and thus a greater reduction in the number of capillaries. It cannot be ruled out, however, that scattering changes may be more prominent temporally. Thus, at the present time one must exercise caution in attempting to draw conclusions concerning the exact pathogenic mechanisms underlying the changes detected by these techniques. Further studies must be performed to evaluate the ways in which tissue scattering changes induced by gliosis and loss of nerve fibers influence the measurements. In addition, the use of two different wavelength ranges by these two techniques may influence the depth of penetration of incident light at the level of the anterior optic nerve such that combining the results of the two techniques into an index of blood flow may be misleading. Nevertheless, the sensitivity of these techniques in detecting changes induced by clinical neurogenic optic atrophy is readily apparent.

Although the case ranking by clinical severity of optic nerve damage was based on relatively crude clinical assessments, the results correlated remarkably well with the blood flow measurements. The more severe cases of neurogenic optic nerve damage had greater reductions in anterior optic nerve blood flow, suggesting that these measurements could be helpful in providing an objective clinical assessment of the degree of optic nerve fiber degeneration. Further experimental and clinical investigation correlating histologic optic nerve fiber counts and/or more refined clinical assessment of optic nerve damage with these noninvasive blood flow measurements in vivo should establish whether this hypothesis is indeed true. It is interesting to note, however, that in the most "severe" cases (by clinical criteria) the temporal blood volume index (γ) was reduced by 50 to 60%, whereas the speed index (α) was reduced by 40 to 50% as compared with controls. This finding is in close agreement with similar measurements made in the animal model of total neurogenic optic atrophy where γ was reduced by 51% ± 18% and α was reduced by 53% ± 20%.[9] This suggests that blood flow reduction in *severe* clinical neurogenic optic atrophy is approximately the same as that observed in *total* neurogenic optic atrophy in the animal model. The comparison of human blood flow measurements with the clinical severity of disease (Fig 4) suggests that these techniques are sensitive to a broad range of disease severity, including cases with minimal clinical manifestations. Further investigations should identify whether these techniques are able to detect minimal changes in blood flow due to mild or early optic nerve fiber degeneration secondary to a variety of optic neuropathies.

These techniques seem to hold promise for providing safe, objective, noninvasive clinical evaluation of the an-

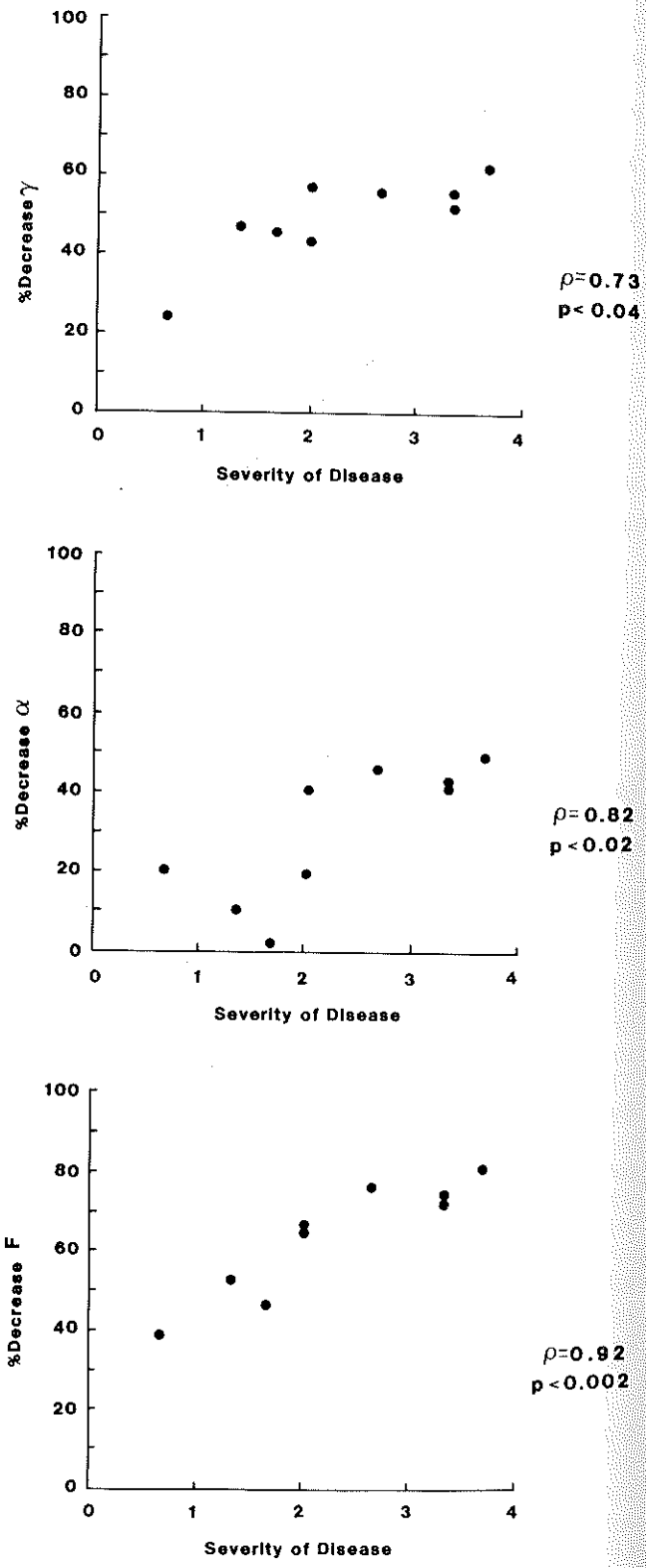

Fig 4. Comparison of noninvasive blood flow measurements with the clinical severity index. Percent decreases in γ (index of blood volume), in α (index of blood speed), and in F (index of blood flow) measured from temporal disk sites are shown as a function of the clinical severity index. All three parameters correlated with the clinical severity of optic nerve damage as shown by the Spearman rank correlation coefficients (ρ) and the significances (p).

terior optic nerve. This approach may allow earlier diagnosis of optic nerve damage in diseases such as glaucoma, enabling earlier treatment and providing an objective means of monitoring the response to therapy.

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REFERENCES

1. Cogan DG. Neurology of the Visual System. Springfield Ill: Charles C Thomas, 1966; 133.
2. Walsh FB, Hoyt WF. Clinical Neuro-Ophthalmology, 3rd ed. Baltimore: Williams & Wilkins, 1969; 635.
3. Henkind P, Bellhorn R, Rabkin M, Murphy ME. Optic nerve transection in cats. II. Effects on vessels of optic nerve head and lamina cribosa. Invest Ophthalmol Vis Sci 1977; 16:442–7.
4. Quigley HA, Anderson DR. The histologic basis of optic disk pallor in experimental optic atrophy. Am J Ophthalmol 1977; 83:709–17.
5. Radius RL, Anderson DR. The mechanism of disc pallor in experimental optic atrophy; a fluorescein angiographic study. Arch Ophthalmol 1979; 97:532–5.
6. Quigley HA, Hohman RM, Addicks EM. Quantitative study of optic nerve head capillaries in experimental optic disk pallor. Am J Ophthalmol 1982; 93:689–99.
7. Feke GT, Sebag J, Delori FC, et al. Laser Doppler measurement of optic disc blood flow in experimental optic atrophy and related clinical entities. ARVO Abstracts. Invest Ophthalmol Vis Sci 1984; 25(Suppl):9.
8. Sebag J, Feke GT, Delori FC, et al. Laser Doppler and disk reflectometry studies of anterior optic nerve blood flow in humans. ARVO Abstracts. Invest Ophthalmol Vis Sci 1985; 26(Suppl):244.
9. Sebag J, Feke GT, Delori FC, Weiter JJ. Anterior optic nerve blood flow in experimental optic atrophy. Invest Ophthalmol Vis Sci 1985; 26:1415–22.
10. Stern MD, Lappe DL. Method and apparatus for measurement of blood flow using coherent light. U.S. Patent No. 4,109,647, 1978.
11. Feke GT, Riva CE. Laser Doppler measurements of blood velocity in human retinal vessels. J Opt Soc Am 1978; 68:526–31.
12. Green GJ, Feke GT, Goger DG, McMeel JW. Clinical application of the laser Doppler technique for retinal blood flow studies. Arch Ophthalmol 1983; 101:971–4.
13. Van Assendelft OW. Spectrophotometry of Hemoglobin Derivatives. Springfield IL: Charles C Thomas, 1970.
14. Delori FC, Rogers FJ, Bursell SE, Parker JS. A system for non-invasive oximetry of retinal vessels. In: Potvin AR, Potvin JH, eds. Frontiers of Engineering in Health Care; Proceedings of the Fourth Annual Conference, 1982. New York: Institute of Electrical and Electronics Engineers, 1982; 296–9.
15. Miller NR. Walsh and Hoyt's Clinical Neuro-Ophthalmology, 4th ed. Baltimore: Williams & Wilkins, 1982; 231.
16. Gärtner S. Optic neuropathy in multiple sclerosis; optic neuritis. Arch Ophthalmol 1953; 50:718–26.