Effects of Optic Atrophy on Retinal Blood Flow and Oxygen Saturation in Humans

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• **Retinal blood flow and oxygen saturation were evaluated in patients with unilateral inner retinal degeneration secondary to neurogenic optic atrophy. Arteriovenous O_2 saturation for temporal and nasal vascular segments of the affected eyes, evaluated by retinal vessel oximetry, was 12% ± 9% higher than in the fellow eyes (seven patients). Blood flow in the temporal retinal arteries of the affected eyes, measured by the laser Doppler technique, was 48% ± 20% lower than in the fellow eyes (four patients). The combination of these results indicated a 40% ± 29% reduction in O_2 delivery in the affected eyes (four patients), thereby quantifying the decrease in retinal metabolism that resulted from inner retinal degeneration.**

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Abnormal retinal metabolism can accompany a variety of disorders of the retina and adjacent structures. Since alterations in retinal metabolism can affect retinal oxygen consumption, evaluating O_2 delivery can provide a means to monitor the level of retinal metabolic activity. Patients with primary neurogenic optic atrophy and retrograde retinal degeneration provide a good clinical model in which to study the influence of inner retinal degeneration on retinal metabolism.

We combined the noninvasive techniques of laser Doppler and retinal vessel oximetry to evaluate human retinal metabolism in vivo. The laser Doppler technique,[1,2] combined with measurements of vessel diameter,[3] measures the retinal blood flow rate at discrete, selected points in the retinal vasculature. Retinal vessel oximetry[4,5] measures O_2 saturation at selected points in the retinal circulatory system. The combination of these parameters was used to calculate retinal O_2 delivery in a group of patients with unilateral inner retinal degeneration secondary to neurogenic optic atrophy.

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PATIENTS AND METHODS

Seven patients with unilateral neurogenic optic atrophy and retrograde inner retinal degeneration were studied. These patients were selected by chart review of the files of several neuro-ophthalmologists in the community (see the "Acknowledgment" section). Inclusion criteria were as follows: less than 50 years of age (to minimize the risk of arteritic ischemic optic neuropathy), the presence of unilateral disease, no evidence of ischemic optic neuropathy (normal erythrocyte sedimentation rate or normal temporal artery biopsy results, and a diagnosis of optic neuritis of probable demyelinating disease origin with or without cerebrospinal fluid analysis.

There were four women and three men ranging in age from 17 to 47 years. There was no history of ocular trauma, surgery, diabetes, hypertension, or cardiovascular disease. The clinical characteristics of this population are summarized in Table 1. All but one patient (No. 3) had discernible defects in the retinal nerve fiber layer of the affected eye (by ophthalmoscopy and examination of fundus photographs).

These patients have all been previously studied with respect to the effects of neurogenic optic atrophy on anterior optic nerve blood flow. As part of that study,[6] a clinical index of disease severity was determined as follows: Three experienced clinicians independently examined color slides of the disc and peripapillary fundus of each eye in all patients and graded the severity of disease from 0 to 4 based on the degree and extent of optic nerve head pallor and the degree of nerve fiber layer dropout. Normal fundi were graded as 0. The most severe case of optic disc pallor and nerve fiber layer dropout in this group was graded as 4. All other fundi were ranked in order of severity of pallor and nerve fiber layer defects and were graded from 0 to 4 based on the relative (to one another) degrees of pallor and nerve fiber layer defects. The evaluations were performed in a masked fashion, and the scores from the three graders were averaged into a clinical index of disease severity for each eye (Table 1). This same clinical index of disease severity in the same patients has been previously published.

Noninvasive Measurements

Written informed consent for all noninvasive testing was obtained from each patient. The pupils were dilated using topical phenylephrine hydrochloride (2.5%) and tropicamide (1.0%). Measurements of O_2 saturation, blood flow, and retinal vessel width were performed at comparable sites of the retinal vasculature for the atrophic and fellow eyes. Measurement sites, preselected by reviewing fundus photographs, were along superotemporal, inferotemporal, and nasal vessel segments that had a corresponding vessel in the fellow eye that subserved the same quadrant of the fundus, and were at the same number of branches from the central retinal artery or vein.

Blood O_2 Saturation.—The retinal vessel oximeter[4,5] was used to measure O_2 saturation and vessel diameters of the preselected retinal veins in both eyes of each patient. The oximetry technique uses scanning fundus reflectometry to measure vessel densities at three wavelengths (λ = 558, 569, and 586 nm). The method compensates for light scattering by the red blood cells (RBCs), and partially for reflections and light scattering in the media and vessel walls. The three measured vessel densities ($D\lambda$) are combined in ratio R, defined as:

$$R = (D_{569} - D_{558})/(D_{569} - D_{586}), \quad (1)$$

which is then used to calculate the O_2 saturation by the algorithm:

$$O_2\ \text{Saturation} = 100 \cdot \{(E_{r,569} - E_{r,558}) + (E_{r,586} - E_{r,569})\} \cdot R/\{(\Delta_{558} - \Delta_{569}) + (\Delta_{569} - \Delta_{586})\} \cdot R, \quad (2)$$

where $\Delta\lambda = E_{o,\lambda} - E_{r,\lambda}$, and $E_{o,\lambda}$ and $E_{r,\lambda}$ are the specific extinction coefficients of oxygenated and deoxygenated hemoglobin, respectively.

The arteriovenous O_2 saturation difference (Δ O_2 saturation) is required to calculate O_2 delivery in a vascular segment. However, no measurements of arterial O_2 saturation were made in this study. Instead, since various studies have reported that arterial O_2 saturation varies between 96% and 98% between subjects,[7,8] we assumed, for simplicity, a constant arterial O_2 saturation of 97% for both eyes

Table 1.—Clinical Characteristics of Study Subjects*

Patient/ Age, y/Sex	Diagnosis	Visual Acuity	Visual Fields	IOP, mm Hg	Disc Pallor	Nerve Fiber Layer	Clinical Severity Index†
1/30/F	Optic neuritis	20/30	Arcuate scotoma, IT	14	T	Slits, T	1.67
2/37/M	Pituitary tumor	20/15	Defect, SN	20	T, slight N	Defects, SN, ST, and IT	3.33
3/29/M	Optic neuritis	20/20	Normal	16	Slight T	Normal	0.67
4/32/F	Optic neuritis	CF	Central scotoma	17	T	Defects, ST, IT, and IN	3.67
5/21/F	Optic neuritis	20/20	Arcuate scotoma, IT > ST	15	T > N	Defects, ST	3.33
6/47/F	Optic neuritis	20/70	ST defect, N constriction	19	IT > ST, slight N	Defect, P-M; nodules, ST and IT	2.00
7/17/M	Optic neuritis	20/25	T P-C scotoma	16	T > N	Defects, T; slits, N	2.67

*IOP indicates intraocular pressure; I, inferior; T, temporal; S, superior; N, nasal; CF, counting fingers; P-M, papillomacular; and P-C, paracentral.
†Values represent the mean of the grading of three observers; 0, normal, to 4, most severe.

of each patient. The ΔO_2 saturation is thus given by:

$$\Delta O_2 \text{ Saturation} = 97 - (\text{Venous } O_2 \text{ Saturation}) \quad (3)$$

Since our analysis always involves a comparison between the two eyes of each patient, the intersubject variability in arterial O_2 saturation does not affect the difference in ΔO_2 saturation between eyes and minimally affects the percent difference (see below) in ΔO_2 saturation between eyes. The magnitude of any difference in arterial O_2 saturation between the two eyes of a patient is difficult to assess but is likely to be small.

Retinal Blood Flow.—The laser Doppler system and technique of data analysis used in this study provided measurements of the speed of RBCs flowing at discrete, selected sites in the retinal vasculature; the technique has been described in detail elsewhere.[2] Doppler-shifted frequency spectra of laser light that is scattered from RBCs flowing through individual retinal vessels exhibit large fluctuations in spectral power up to a clearly measureable frequency shift (Δf_{max}). This shift arises from scattered light, Doppler shifted by RBCs flowing at the maximum speed (V_{max}) at the center of the vessel. When the light scattered by the RBCs is detected simultaneously in two distinct directions, a pair of spectra are obtained. The centerline speed is calculated as

$$V_{max} = \kappa \cdot (\Delta f_{max1} - \Delta f_{max2})/\text{cosine } \beta, \quad (4)$$

where κ is an instrumental constant, and β is the angle between the direction of V_{max} and its projection on the plane defined by the two scattering directions.

To calculate the blood flow rate in retinal arteries, it is necessary to determine the time-averaged value of V_{max} during the cardiac cycle, $\overline{V}_{max}$. We have previously presented[2] experimental data leading to the derivation of the relationship between $\overline{V}_{max}$ and the RBC speeds measured in retinal arteries during the minimum diastolic and maximum systolic phases of the cardiac cycle. We found that

$$\overline{V}_{max} = V_{max}(\text{Diastole}) + k \cdot \{V_{max}(\text{Systole}) - V_{max}(\text{Diastole})\}, \quad (5)$$

where $k = 0.48 \pm 0.04$.

Table 2.—Venous Diameter and A-V Oxygen (O_2) Saturation Difference in Affected and Fellow Eyes*

Patient	Site	Venous Vessel Diameter, μm: Fellow Eye	Affected Eye	% Difference	A-V O_2 Saturation Difference, % O_2 Saturation: Fellow Eye	Affected Eye	% Difference
		Temporal Data†					
1	IT	123	137	+2	52	53	+10
	ST	133	122		49	59	
2	IT	117	91	−13	49	55	+13
	ST	148	142		36	42	
3	IT	133	111	−10	39	58	+30
	ST	113	109		57	64	
4	IT	122	130	−4	47	45	+12
	ST	124	108		43	55	
5	IT	121	108	−11	58	53	−2
	ST	124	110		60	63	
6	IT	134	143	+0	41	58	+23
	ST	152	143		42	48	
7	IT	161	157	+5	52	48	+1
	ST	114	128		59	65	
Mean ± SD significance‡	...	130 ± 15	124 ± 19	−4 ± 7 ($P = .14$)	49 ± 6	54 ± 5	+12 ± 11 ($P = .028$)
		Nasal Data					
1	SN	104	100	−4	61	68	+12
2	IN	99	92	−7	56	59	+5
3	SN	98	115	+16	59	71	+20
4	IN	92	99	+8	56	63	+12
5	SN	117	96	−18	64	71	+12
6	IN	122	111	−9	53	59	+12
7	SN	136	136	+0	57	61	+7
Mean ± SD significance‡	...	110 ± 16	107 ± 15	−2 ± 11 ($P = .66$)	58 ± 3	65 ± 5	+11 ± 5 ($P = .001$)

*A-V indicates arteriovenous; IT, inferotemporal; ST, superotemporal; SN, superonasal; and IN, inferonasal.
†For the temporal data, the percent difference is the average of the percent differences for the two sites of each patient.
‡Significance was determined using a two-tailed one-sample *t* test that compared the percent difference with zero.

The blood flow (F) rate is calculated as:

$$F = (\overline{V}_{max}/2) \cdot S, \quad (6)$$

where S is the cross-sectional area of the vessel at the measurement site.[2] The value S is calculated from the measured arterial blood column diameter, assuming a circular cross section. The arterial blood column diameter is determined by measuring the width of the vessel image on the negatives of monochromatic (575-nm) fundus photographs (projection micrometry).[3]

O_2 Delivery.—Oxygen delivery was derived from ΔO_2 saturation and blood flow measurements under the assumption that the selected arteries and veins constituted closed vascular segments. Oxygen delivery, expressed in microliters of O_2/min, was

Table 3.—Vessel Diameter, Blood Speed, and Blood Flow in Retinal Arteries in Affected and Fellow Eyes*

Patient	Site	Arterial Vessel Diameter, μm: Fellow Eye	Affected Eye	% Difference	Arterial Blood Speed, cm/s: Fellow Eye	Affected Eye	% Difference	Segmental Blood Flow, μL/min: Fellow Eye	Affected Eye	% Difference
1	IT	124	121	+2	6.8	4.2	−38	24.5	14.5	−35
	ST	119	126		6.6	4.1		21.9	15.3	
2	IT	127	102	−8	8.1	3.4	−53	30.6	8.3	−59
	ST	104	107		6.5	3.4		16.6	9.2	
3	IT	106	102	−2	8.1	6.7	−25	21.4	16.4	−28
	ST	100	100		8.8	6.0		20.7	14.1	
4	IT	121	103	−15	8.4	3.4	−60	29.0	8.4	−71
Mean ± SD significance†										
...	...	114 ± 11	109 ± 10	−6 ± 7 (P = .20)	7.6 ± 1.0	4.5 ± 1.4	−44 ± 16 (P = .011)	23.5 ± 4.9	12.3 ± 3.5	−48 ± 20 (P = .017)

*For patients with measurements at two sites, percent difference is the average of the percent differences. IT indicates inferotemporal; ST, superotemporal.
†Significance was determined by using a two-tailed one-sample *t* test that compared the percent difference with zero.

then calculated by means of

$$O_2 \text{ Delivery} = 0.201 \cdot F \cdot \Delta O_2 \text{ Saturation}/100, \quad (7)$$

where blood flow (F) was expressed in microliters per minute and ΔO_2 saturation in percent O_2 saturation, and where the constant 0.201 μL of O_2 per microliters of blood was the O_2 capacity of arterial blood.[7]

Diameter of the Central Retinal Artery.—The diameter of the central retinal artery was estimated using a method and algorithm developed by Parr and Spears.[9] Measurements of the vessel diameters of the five to seven largest arteries that emerged from the optic disc were made using projection micrometry.[3] The diameters of the invisible parent vessels for each bifurcation were computed using the algorithm,[9] and progressive calculations yielded a prediction for the diameter of the central retinal artery.

Data Analysis

To compare the measured or derived parameters (ΔO_2 saturation, vessel diameter, blood speed, blood flow, O_2 delivery, and central retinal artery diameter) obtained for the affected and fellow eyes, we calculated a percent difference defined as

$$\% \text{ Difference (Parameter)} = 100 \cdot \{\text{Parameter (Affected Eye)} - \text{Parameter (Fellow Eye)}\}/\text{Parameter (Fellow Eye)}, \quad (8)$$

for each pair of data at corresponding sites. When results were obtained from more than one set of corresponding sites in a patient, then the percent differences were averaged to yield a single percent difference. Statistical significance of this percent difference was evaluated by using a two-tailed one-sample *t* test that compared the percent difference with zero. Performing the analysis in this way eliminated the effect of any correlations that may have existed between measurements obtained at different sites in the same eye.

Table 4.—Oxygen (O_2) Delivery in Affected and Fellow Eyes*

Patient	Site	Retinal O_2 Delivery, μL O_2/min: Fellow Eye	Affected Eye	% Difference
1	IT	2.6	1.5	−28
	ST	2.2	1.8	
2	IT	3.0	0.9	−53
	ST	1.2	0.8	
3	IT	1.7	1.9	−5
	ST	2.4	1.8	
4	IT	2.8	0.8	−72
Mean ± SD significance†				
...	...	2.3 ± 0.6	1.4 ± 0.5	−40 ± 29 (P = .073)

*For patients with measurements at two sites, the percent difference is the average of the percent differences. IT indicates inferotemporal; ST, superotemporal.
†Significance was determined using a two-tailed one-sample *t* test that compared the percent difference with zero.

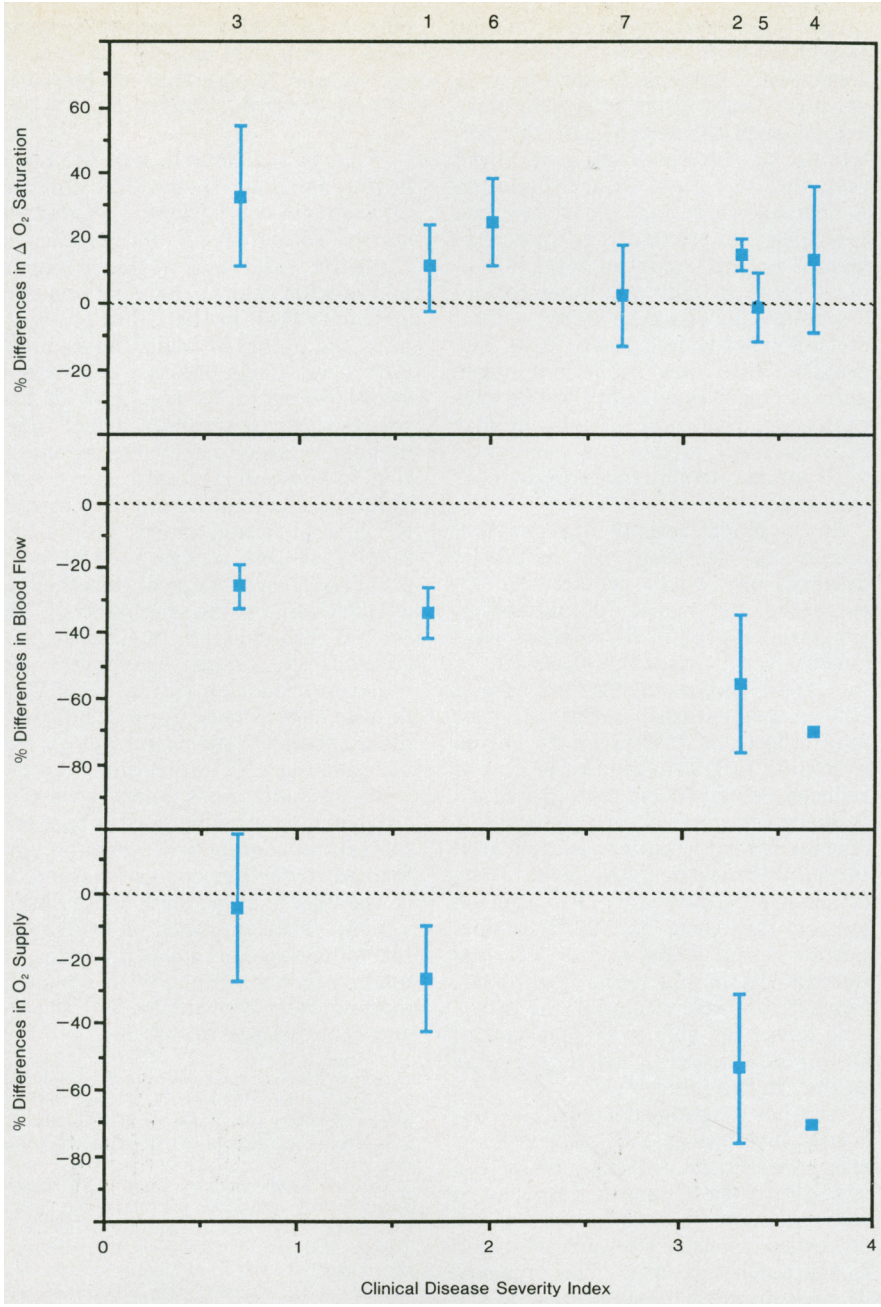
Table 5.—Comparison of Central Retinal Artery Diameter in Affected and Fellow Eyes

Patient	Central Retinal Artery Diameter, μm: Fellow Eye	Affected Eye	% Difference
1	207	188	−9
2	182	163	−11
3	151	144	−5
4	195	183	−6
5	148	152	2
6	172	147	−14
7	142*	131*	−7
Mean ± SD significance†	171 ± 25	158 ± 21	−7 ± 5 (P = .011)

*Derived from vessel diameter measurements performed on color slides (Kodachrome), not on 575-nm monochromatic photographs.
†Significance was determined using a two-tailed one-sample *t* test that compared the percent difference with zero.

RESULTS

Oxygen saturation and vessel diameter measurements were obtained for 21 preselected pairs of retinal veins (14 temporal and seven nasal) in the seven patients. Results for venous diameter and for the arteriovenous O_2 saturation difference ΔO_2 saturation (calculated using equation 3) for both affected and fellow eyes, are given in Table 2. For the temporal segments (14 vessel pairs), ΔO_2 saturation was, on average, 49% and 54% O_2 satura-



Average percent differences in Δ oxygen (O_2) saturation, blood flow, and oxygen delivery for temporal vessels displayed as a function of clinical severity index (0, normal, to >4, most severe). Error bars are ± 1 SD of mean associated with two determinations of percent differences in each patient. Patient numbers are indicated at top.

tion for the fellow and affected eyes, respectively. The average percent difference was +12%, reflecting a significant increase in Δ O_2 saturation in the affected eyes ($P = .028$). For the nasal segments (seven vessel pairs), Δ O_2 saturation was, on average, 58% and 65% O_2 saturation for the fellow and affected eyes, respectively. In this case, the average increase in Δ O_2 saturation was 11% ($P = .001$). The nasal Δ O_2 saturation was significantly higher than the temporal Δ O_2 saturation in both affected ($P = .00013$) and fellow ($P = .0014$) eyes. When the temporal and nasal data were pooled, then the average percent difference in Δ O_2 saturation was +12% ± 9% ($P = .010$).

Blood speed measurements were obtained in seven of the preselected pairs of retinal arteries. These seven pairs, from four patients, were all temporally located. Data obtained from the remaining preselected vessel pairs did not, for one or both vessels, satisfy previously established objective data acceptability criteria.[2] In most cases, eye movements did not permit the incident laser beam to be centered on the vessel for a sufficient length of time (at least one cardiac cycle, see "Patients and Methods" section). The results of these measurements, together with the corresponding arterial diameters, are given in Table 3. These data correspond to the first seven rows of Table 2. Arterial blood speeds were, on average, 7.6 and 4.5 cm/s for the fellow and affected eyes, respectively. The average percent difference was −44%, reflecting a significant reduction in blood speed in the affected eyes ($P = .011$).

Retinal artery diameters were, on average, 6% narrower in the affected than in the fellow eyes (Table 3), but the difference was not statistically significant for the seven vessel pairs in Table 3. However, the difference became significant when all 14 pairs of temporal branch arteries were considered (additional data not shown); the average percent difference in diameter was then −6% ± 6% ($P = .024$).

Table 3 also gives the results for segmental blood flow for the seven pairs of temporal retinal arteries derived from the blood speeds and the diameters (equation 6). The average segmental blood flow rates were 23.5 and 12.3 μL/min for fellow and affected eyes, respectively. The average percent difference was −48%, corresponding to a significant reduction in blood flow in the affected eyes ($P = .017$).

The results for O_2 delivery rates for seven temporal segments are given in Table 4. The O_2 deliveries were calculated (equation 7) from the Δ O_2 saturation data of Table 2 (first seven rows) and the blood flow data of Table 3. The average O_2 delivery rates were 2.3 and 1.4 μL of O_2 per minute for fellow and affected eyes, respectively. The average percent difference in O_2 delivery was −40%. This decrease in the O_2 delivery rate, however, was not statistically significant ($P = .073$).

The Figure illustrates the relationships between the clinical severity indexes determined for each affected eye (Table 1) and the averaged percent differences in Δ O_2 saturation, blood flow, and O_2 delivery determined for temporal vessels. The percent differences in Δ O_2 saturation did not show a significant variation with disease severity (Spearman's $\rho = -0.43$, $P = .30$). It should be noted, however, that the largest percent difference was observed at the lowest disease severity. The percent differences in blood flow decreased with disease

severity, reflecting a decrease with disease severity of the blood flow in the affected eyes, compared with that in the fellow eyes. Although the percent differences in blood flow ranked perfectly with disease severity ($\rho = -1$), that correlation was not statistically significant ($P = .10$). The percent differences in O_2 delivery also ranked perfectly with disease severity ($\rho = -1$), but the correlation is not statistically significant ($P = .10$).

Vessels in the affected eyes were narrowed as compared with the fellow eyes. This was documented for both retinal veins (Table 2) and arteries (Table 3). Results of the computations of the diameter of the central retinal artery are given in Table 5. The average diameters were 171 and 158 μm for fellow and affected eyes, respectively. The average percent difference was -7%, corresponding to a significant constriction of the central retinal artery ($P = .011$). There was no significant correlation between the calculated reduction in the central retinal artery diameter and the clinical index of disease severity.

COMMENT

This study demonstrates that in unilateral retrograde inner retinal degeneration due to neurogenic optic atrophy, there is an average decrease of 40% in O_2 delivery from the retinal circulation in the affected eyes compared with the fellow eyes. This reduction in O_2 delivery results from an average decrease of 48% in retinal blood flow and an opposing average increase of 12% in the arteriovenous O_2 saturation difference (ΔO_2 saturation). With increasing disease severity in the affected eyes, the reduction in blood flow and O_2 delivery becomes more pronounced. The increase in ΔO_2 saturation is largest at low disease severity.

The observed progressive reduction in retinal blood flow is most likely due to the decreased metabolic demand associated with inner retinal degeneration. This decreased demand may produce constriction of precapillary arterioles of the retina and may contribute to the observed generalized reduction in retinal artery diameter. A decrease in retinal blood flow had been observed previously in an experimental animal model of total neurogenic optic atrophy and inner retinal degeneration.[10] In that study, retinal blood flow was decreased by 63%. The greater blood flow reduction in the animal model may relate to the fact that there was total atrophy in that experimental model, as compared with partial atrophy in the patients of this study.

Since inner retinal degeneration causes a decrease in metabolic demand, one would predict that O_2 extraction and, hence, ΔO_2 saturation would be reduced in the affected eyes. However, this was not observed. In fact, there was an average increase of 12% in ΔO_2 saturation. This increase may reflect an attempt by the retina to maintain O_2 delivery in the face of reduced retinal blood flow. Indeed, O_2 delivery for the eye with the mildest disease severity (patient 3) appeared to maintain itself at the level of the fellow eye ($\%d = -5\%$). The affected eye, in this case, had 20/20 vision, normal visual fields, and no discernible defects in the nerve fiber layer. Since the disease was mild, the retina may have been able to extract enough O_2 to maintain an O_2 delivery similar to that in the fellow eye.

Another explanation for the observed increase in ΔO_2 saturation is that more O_2 may diffuse out of the vasculature as a passive response to the reduction in blood speeds and a consequent longer exposure of blood to metabolizing tissue. The presence of such an effect is supported by the observed nasal-temporal differences in ΔO_2 saturation. In nasal vessels, where blood flow is generally lower than in temporal vessels,[11] ΔO_2 saturation was higher than in temporal vessels in both affected and fellow eyes.

What is not clear is why the blood flow was reduced by 28% in the affected eye of patient 3 (Table 3), which, as described above, had no clinically observable retinal changes and in which the O_2 delivery was only 5% lower than in the fellow eye. Perhaps the observed reduction in blood flow is not solely due to a decrease in vessel diameter at the level of the precapillary arterioles. Local phenomena related to neuronal degeneration in the anterior optic nerve may induce a decrease in the diameter of the central retinal artery. Indeed, the results of this study, as well as a previous report,[12] suggest that there is a reduction in the diameter of the central retinal artery in cases of neurogenic optic atrophy. This might contribute to reducing retinal blood flow in mild cases where there is sufficient metabolizing tissue to extract O_2 and increase the ΔO_2 saturation.

Additional studies using these sensitive noninvasive techniques to monitor retinal metabolism must be performed to further our understanding of the events underlying these observations. This approach of evaluating retinal metabolism holds promise as a noninvasive technique with which to monitor retinal physiology in disease and the response to therapy.

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References

1. Riva CE, Feke GT: Laser Doppler velocimetry in the measurement of retinal blood flow, In Goldman L (ed): *The Biomedical Laser: Technology and Clinical Applications.* New York, Springer-Verlag NY Inc, 1981, pp 135-161.

2. Feke GT, Goger DG, Tagawa H, et al: Laser Doppler technique for absolute measurement of blood speed in retinal vessels. *IEEE Trans Biomed Eng* 1987;34:673-680.

3. Delori FC, Fitch KA, Feke GT, et al: Evaluation of micrometric and microdensitometric methods for measuring the width of retinal vessel images on fundus photographs. *Graefes Arch Clin Exp Ophthalmol* 1988;226:393-399.

4. Delori FC, Rogers FJ, Bursell SE, et al: A system for noninvasive oximetry of retinal vessels, in Potvin AR, Potvin JH (eds): *Frontiers of Engineering in Health Care-1982: Proceedings of the Fourth Annual Conference of the IEEE Engineering in Medicine and Biology Society, Philadelphia, 1982.* New York, Institute of Electrical and Electronics Engineers, 1982, pp 296-299.

5. Delori FC: Noninvasive technique for oximetry of blood in retinal vessels. *Appl Optics* 1988;27:1113-1125.

6. Sebag J, Delori FC, Feke GT, et al: Anterior optic nerve blood flow decreases in clinical neurogenic optic atrophy. *Ophthalmology* 1986; 93:858-865.

7. Comroe JH: *Physiology of Respiration,* ed 2. Chicago, Year Book Medical Publishers Inc, 1974, pp 186-187.

8. Albritton EC (ed): *Standard Values in Blood,* Air Force technical report 6039, Dayton, Ohio, Wright-Patterson AFB. Wakefield, Mass, McGregor & Werner, Inc, 1952.

9. Parr JC, Spears GFS: General caliber of the retinal arteries expressed as the equivalent width of the central retinal artery. *Am J Ophthalmol* 1974;77:472-477.

10. Sebag J, Feke GT, Delori FC, et al: Anterior optic nerve blood flow in experimental optic atrophy. *Invest Ophthalmol Vis Sci* 1985;26:1415-1422.

11. Feke GT, Tagawa H, Deupree DM, et al: Laser Doppler measurement of regional blood flow in the normal human retina. *Invest Ophthalmol Vis Sci* 1985;26(ARVO suppl):244.

12. Frisen L, Claesson M: Narrowing of retinal arterioles in descending optic atrophy: A quantitative clinical study. *Ophthalmology* 1984; 91:1342.