Investigative Ophthalmology & Visual Science, Vol. 32, No. 13, December 1991

Optic Nerve Head Blood Speed as a Function of Age in Normal Human Subjects

Joseph F. Rizzo, III,* Gilbert T. Feke,† Douglas G. Goger,† Hironobu Ogasawara,† and John J. Weiter†

We used the laser Doppler technique to determine the relation between age and the speed of blood cells moving through the capillaries of the optic nerve head. We studied 22 normal human volunteers ranging in age from 16–76 years. The results were best described by a statistically significant quadratic relationship between capillary blood speed and age. Blood speeds were lowest in the youngest and oldest subjects and highest in subjects between 27 and 35 years old. A two-phase linear model showed a statistically significant 20% decrease in blood speed in volunteers between the ages of 31 and 76. The results were not affected by gender, degree of refractive error, systemic blood pressure, intraocular pressure, cup/disc ratio of the optic nerve head, or by site-to-site differences in the light scattering properties of the optic nerve head tissue. Capillary blood speed was, on average, 15% greater from temporal sites than from nasal sites, corresponding to the equally greater distribution of ganglion cell axons within the same area. The results provide a baseline of normal age-controlled data that can be compared to measurements obtained from patients with disorders of the optic nerve head thought to have a vascular etiology. Invest Ophthalmol Vis Sci 32:3263–3272, 1991

Anatomical changes of the human optic nerve associated with aging have been previously described.[1–4] However, no studies have examined age-related physiological changes specifically related to the optic nerve head.

The optic nerve head is hypothesized to be an important site of damage in a number of diseases. In particular, for chronic open angle glaucoma[5–10] and ischemic optic neuropathy,[10–17] there is compelling evidence that the neural damage is at least partially related to the anatomy of the optic nerve head. Evaluating the circulatory physiology of the normal optic nerve head—which receives its blood supply primarily from the posterior ciliary circulation, with a small contribution from retinal arterioles to the superficial nerve fiber layer[10,12,18–24]—should be useful for understanding diseases related to this area.

From the *Neuro-Ophthalmology Service, Massachusetts Eye and Ear Infirmary, and the Department of Ophthalmology, Harvard Medical School, and the †Eye Research Institute, Boston, Massachusetts.

Supported in part by National Eye Institute grant R01EY01303 (Dr. Feke) and the Massachusetts Lions Eye Research Fund, Stoneham, Massachusetts.

Presented in part at the Annual Meeting of the Association of Research in Vision and Ophthalmology, Sarasota, Florida, May 2, 1989.

Submitted for publication: May 24, 1991; accepted July 16, 1991.

Correspondence: Gilbert T. Feke, Eye Research Institute, 20 Staniford Street, Boston, MA 02114.

Reprint requests: Joseph F. Rizzo III, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114.

The application of laser Doppler velocimetry to studies of the optic nerve head circulation was first proposed by Riva et al.[25] In conjunction with the theoretical method of Stern and Lappe,[26] this technique has been used to characterize the speed of red blood cells flowing in the capillaries of the optic nerve head in response to acute increases of intraocular pressure[27] and in studies of experimental[28] and clinical[29] optic atrophy. In this study, we sought to determine the effect of age on the circulation within the optic nerve head in normal human volunteers using the laser Doppler technique. This data could be useful in understanding the dynamics that underlie vascular disorders of the optic nerve head.

Materials and Methods

Subjects

Volunteers without a known history of ocular problems, other than refractive error, were solicited for the study. Those with a history of systemic hypertension, diabetes, glaucoma, amblyopia, stroke, transient cerebral attack, or transient visual loss were excluded. Informed consent was obtained from each subject. Each subject underwent a neuro-ophthalmological screening examination performed by one of us (JFR). The examination included a measurement of Snellen acuity at distance, color vision (Ishihara), intraocular pressure by applanation tonometry, systemic blood pressure, refractive error of each eye, as well as visual field testing with the Goldmann perimeter, assess-

ment of pupillary function, and auscultation of the carotid arteries. Each subject also received a dilated funduscopic examination, and high magnification color photographs were taken of both optic nerves to determine cup/disc ratios. Subjects were subsequently excluded if there were findings of carotid bruit, macular degeneration or other retinopathy, optic neuropathy, or greater than minimal cataract.

Laser Doppler measurements were obtained from 22 of 29 subjects who met the inclusion criteria. The seven subjects from whom measurements could not be obtained (ranging in age from 24 to 73 years) were unable to maintain adequate target fixation.

Six males and sixteen females between the ages of 16 and 76 years were studied. Females and males were distributed across age groups as follows: 16–22 years: 5 females/1 male; 27–35 years: 4/2; 50–59 years: 3/0; 67–76 years: 4/3). Blood pressures ranged from 100/60 to 155/88 mmHg. The remaining subject characteristics are summarized in Table 1.

Laser Doppler Technique

Our method of applying the laser Doppler technique to the measurement of red blood cell speed in the capillaries of the optic nerve head has been previously published.[28,29] When a region of optic nerve head tissue is illuminated by laser light, the frequency shift spectrum, $S(\Delta f)$, of the scattered light is broadened in direct proportion to the speed of the red blood cells flowing through the capillaries. Because the volume fraction of blood in the tissue of the optic nerve head is small, approximately 2%,[30] most of the light collected from the point of the illumination is scattered by nonvascular tissue. With our method, $S(\Delta f)$ is detected by heterodyne mixing of the Doppler-shifted light scattered by red blood cells with the light scattered by tissue.

It should be noted that there are a number of important differences between our method and the method that has become known as laser Doppler blood flowmetry.[31] In laser Doppler blood flowmetry, scattered light is collected from a region adjacent to the point of illumination so all of the collected light has been Doppler-shifted by red blood cells. Under these conditions, the scattered light contains information on the number and speed of red blood cells. Thus, in principle, a measure of blood flow is obtained. However, site-to-site variations in the light scattering properties of the tissue may affect the flowmeter output, preventing measurements from different tissues or different sites within a tissue from being reliably compared.[32] With our heterodyne detection scheme, we cannot extract information on the number of red blood cells in the illuminated tissue. However, we can, as described below, reliably compare measurements of Doppler broadening, which is directly proportional to red blood cell speed, from one site to another and from one subject to another.

Table 1. Subject characteristics

	OD	*OS*
Intraocular pressure* (mmHg)	17 ± 4	17 ± 4
Cup/disc ratio*	0.32 ± 0.13	0.29 ± 0.15
Refractive error* (diopters)	−0.05 ± 1.2	−0.05 ± 1.3

* Mean ± standard deviation.

A theory predicting the shape of $S(\Delta f)$ under our heterodyne detection conditions was developed by Stern and Lappe.[26] In their model, incident laser light diffuses through the tissue, becoming randomly scattered by nonvascular elements. Scattering by nonvascular tissue does not produce frequency shifts. Frequency shifts are produced only by red blood cell motion with respect to the tissue. Under these conditions, $S(\Delta f)$ is composed of a series of spectral components. The first-order component arising from single scattering dominates the total spectrum at low frequencies. This first-order single scattering component varies as the negative logarithm of Δf: $-\log(\Delta f)$. Furthermore, this logarithmic variation occurs for any speed distribution that may exist. Higher order components arising from multiple scattering merge into a low amplitude, high frequency "tail" that gradually approaches zero amplitude.

The low frequency portion of $S(\Delta f)$ can be expressed as:

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

where K is a measure of the spectrum's amplitude, and the frequency α is a measure of the spectrum's broadening.

Our data acquisition and analysis procedures were designed to minimize the effects of tissue scattering and tissue motion on our Doppler broadening measurements. During data acquisition, volunteers were positioned in front of a fundus camera apparatus equipped with a helium-neon laser light source (λ = 633 nm) and a photomultiplier (PMT) detector assembly that collected light scattered from the optic nerve head in a region free of surface vessels. Examination under red-free light enabled identification of vessels on the nerve head surface. Such vessels were avoided to ensure that measurements were obtained exclusively from regions of nerve head perfused by capillaries. Measurement sites were approximately 180 μm in diameter and were generally located midway between the periphery and center of the nerve (Fig. 1).

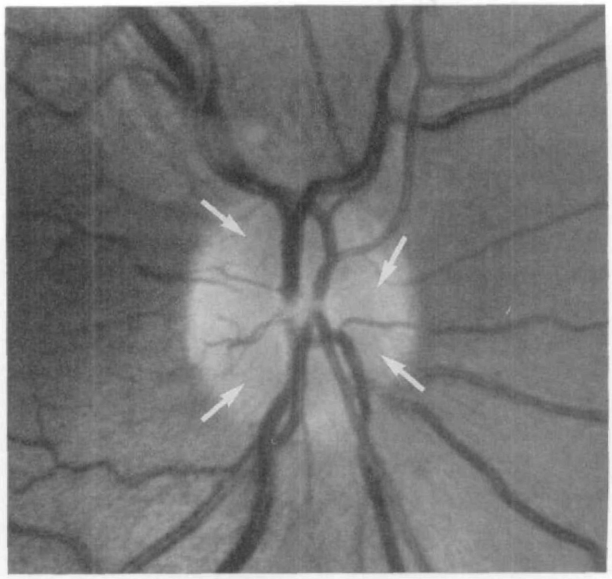

Fig. 1. Photograph of optic nerve head. Arrows depict representative sites from which laser Doppler measurements were obtained.

The PMT signal was recorded on a Honeywell 5600 C Recorder/Reproducer (Honeywell Test Instruments Division, Denver, CO) for approximately 1 minute at each measurement site. The signal also was channeled through a loudspeaker. The audio signal generated by nerve head tissue was easily distinguished from that generated by an individual vessel, and therefore helped maintain the position of the incident beam on optic nerve tissue free of surface vessels.

For data analysis, the portion of the 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, which is a measure of the tissue scattering intensity. The frequency spectrum [$S(\Delta f)$] of the photocurrent then was obtained using a Wavetek 5809 digital spectrum analyzer (Wavetek Rockland Scientific, Inc., Rockleigh, NJ). Spectra were obtained using a 5 kHz full-scale range with an averaging time of 5.12 seconds and were displayed on an Electrohome video monitor (Electrohome Limited, Kitchener, Ontario, Canada). The spectrum analyzer was interfaced to a Hewlett-Packard HP 9816S computer (Hewlett-Packard, San Diego, CA) programmed with an algorithm that determined the optimal logarithmic fit to the low frequency portion of the measured spectrum. Data between 100 and 500 Hz were used for this fitting procedure. The computer then determined the Doppler broadening parameter, α, which was defined as the frequency at which the logarithmic fit intersected the abscissa. The spectrum and the logarithmic fit were then plotted by a Hewlett Packard HP 7470a digital graphics plotter (Fig. 2).

Examination of the frequency shift spectrum shown in Figure 2 reveals the characteristics predicted by the model described above. In particular, the first-order component obeys the predicted logarithmic variation indicative of single scattering. The spectrum deviates from the predicted logarithmic shape at frequencies above approximately 800 Hz. This deviation is due to the effects of multiple scattering. An increase in tissue scattering would increase the probability of multiple scattering, thus broadening the high frequency "tail." However, such an increase in tissue scattering would not affect the width of the first-order, single scattering component of the spectrum, but would increase only the amplitude of the spectrum.

Restricting the data window for curve fitting to the interval 100 to 500 Hz, as we have done, minimized the effects of tissue scattering on the Doppler broadening parameter, allowing reliable site-to-site and subject-to-subject comparison. As shown below, the Doppler broadenings measured in this study were independent of the tissue scattering intensities that varied considerably from site to site. A similar finding was previously described by us in an experimental study of the effects of optic atrophy on optic nerve head circulation.[28] In that study, the laser Doppler findings were substantiated by histologic evaluation of microsphere distribution.

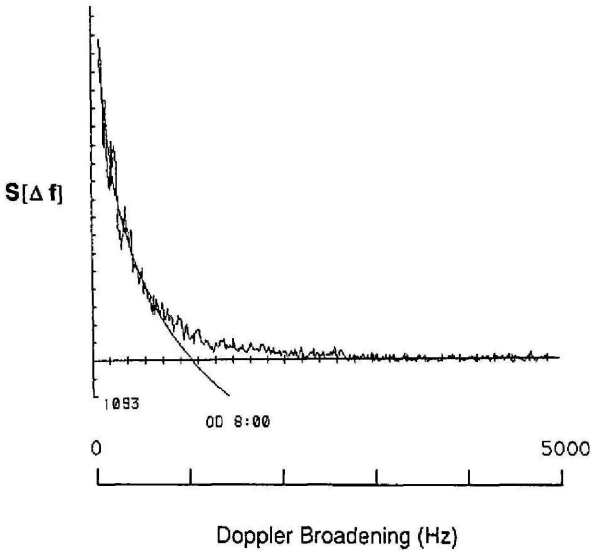

Fig. 2. A Doppler broadened frequency shift spectrum measured from the infero-temporal region of the optic nerve head of a 59-year-old female subject. The smooth curve is the computer fit to the low frequency portion of the spectrum. In this example, the Doppler broadening parameter, α, which is directly proportional to the capillary blood speed, is 1093 Hz.

The effects of tissue motion on our Doppler broadening measurements also were minimized by restricting the data window for curve fitting to the interval 100 to 500 Hz. As described by Riva et al,[27,33] eye movements produce marked increases in spectral power at frequencies below approximately 50 Hz. By conservatively beginning our curve fitting at 100 Hz, we expect that artifacts related to eye movement were minimized.

Laser Doppler measurements were obtained from up to four sites on the optic nerve head in both eyes of each subject. Five separate Doppler broadened frequency spectra were obtained from the signals recorded at each site. The Doppler broadening parameter α for a particular site was obtained by averaging the five separate α values.

Statistical Methods

While the primary goal of the study was to determine the relationship between Doppler broadening and age, the relationship between Doppler broadening and other characteristics of the subjects also was examined. These included subject-level characteristics (sex and mean blood pressure); eye-level characteristics (OD or OS, intraocular pressure, cup/disc ratio, and refractive error); and measurement site-level characteristics (temporal or nasal, and superior or inferior regions of the nerve head).

The relationship of Doppler broadening to the various subject, eye, and site-level characteristics initially was examined separately for each characteristic. Subject-level characteristics were evaluated by computing mean Doppler broadening by averaging all measurement sites from both eyes of the 22 subjects. A two-sample t-test was used to compare the mean Doppler broadenings for males and females. A scatterplot was examined and a correlation coefficient was computed to explore the relationship between mean Doppler broadening and mean blood pressure. To study the eye-level characteristics, mean Doppler broadening taken by averaging the measurements in each eye of each volunteer was computed. Mean Doppler broadening for OD and OS were compared using a paired t-test. The relationship between Doppler broadening and intraocular pressure, cup/disc ratio, and refractive error was examined separately for OD and OS using scatterplots and correlation coefficients. To examine the relationship between measurement site-level characteristics and Doppler broadening, the mean Doppler broadenings obtained from the same region of the optic nerve head from both eyes (temporal vs. nasal, superior vs. inferior) were compared using paired t-tests.

To examine the relationship between Doppler broadening and age, we computed the mean Doppler broadening per subject separately for temporal and nasal sites by averaging the results from all temporal and all nasal sites from both eyes of each subject. In the subsequent correlation analysis, each mean was weighted by the square root of the total number of measurement sites per subject. A weighted quadratic regression analysis and a weighted two-phase linear regression analysis were used.

To confirm the findings of the univariate analyses described above, we also examined the relationship between Doppler broadening and aging with a multiple regression model. We employed a model developed by Rosner[34] for use with correlated data. This was necessary because of the likelihood that multiple measurements of Doppler broadening from the various sites in a particular subject were correlated. If this correlation had been ignored, and the data treated as independent observations, there would have been an artificial reduction in the standard errors of the parameter estimates in the model. This would have led to the possibility of erroneously concluding significance of variables that were not significant. Rosner's model accounts for the correlation between measurements obtained from different sites in each subject by incorporating these correlations into the calculation of the standard errors of the regression coefficients. Using this model, we computed regression coefficients for each variable. We then simplified the model by removing variables that did not appear significantly related to Doppler broadening. We verified that groups of variables could be removed by examining the likelihoods of the original and simplified models (likelihoods are measures of the difference between the observed data and the values predicted by the model). A quadratic regression model and a two-phase linear regression model were used.

Results

Doppler broadening was measured at 77 sites in 22 volunteers. The majority (64) were temporal sites. Measurements were obtained from 46 sites in right eyes and from 31 sites in left eyes. The average coefficient of variation of the 5 measurements at each of the 77 measurement sites was 8 ± 5% (mean ± standard deviation).

Figure 3 shows the Doppler broadening measured at each site plotted as a function of the tissue scattering intensity. As described above, the mean photocurrent measured at each site was used as a measure of the scattering intensity. While there were substantial differences in scattering intensity from site to site, no

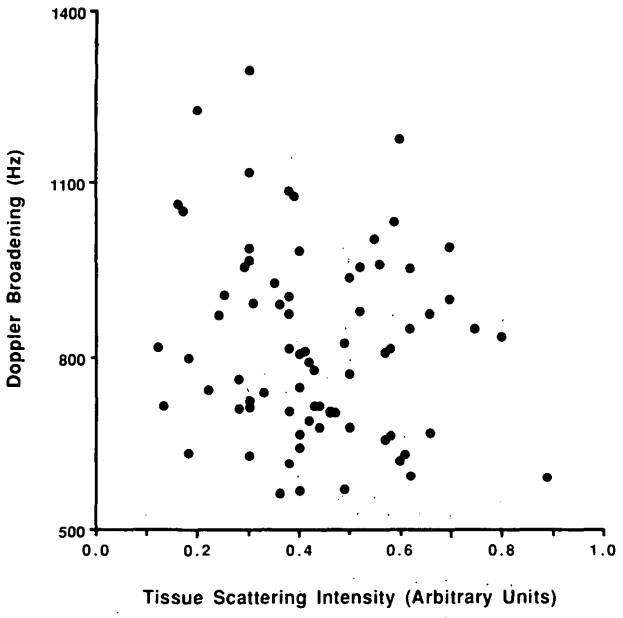

Fig. 3. Doppler broadening plotted as a function of tissue scattering intensity. No significant correlation was observed.

statistically significant correlation existed between Doppler broadening and scattering intensity (r^2 = 0.03). As discussed above, our measured Doppler broadenings were not dependent on tissue scattering intensities, permitting reliable site-to-site and subject-to-subject comparisons.

Subject-level Characteristics

The mean Doppler broadening was computed for each subject by averaging all measurement sites from each eye. For the six males, the average mean Doppler-broadening was 778 Hz (SD, 131 Hz). For the 16 females, the average was 837 Hz (SD, 111 Hz). The two-sample t-test for the difference between males and females was not significant.

Mean blood pressure was computed as diastolic blood pressure +⅓[(systolic − diastolic blood pressure)]. This information was available for 17 of the 22 subjects. A scatterplot of mean blood pressure versus mean Doppler broadening for these 17 subjects showed no discernible pattern, and the correlation coefficient (r = 0.26) was not significant.

Eye-level Characteristics

The mean Doppler broadening was computed for each eye of each subject by averaging all measurement sites. Twenty-one volunteers had OD sites measured; the average of the mean Doppler broadening was 829 Hz (SD, 133 Hz). Sixteen volunteers had OS sites measured; the average of the mean Doppler broadening was 815 Hz (SD, 130 Hz). Fifteen volunteers had measurements taken from OD and OS. A strong linear correlation existed between mean Doppler broadening in OD and OS (r = 0.55; P = 0.03) of the same subjects (Fig. 4). The paired t-test comparing mean OD and OS values in the same subjects did not show a significant difference. Based on these results, Doppler broadening in a given subject did not depend on whether measurements were obtained from OD or OS.

There were no statistically significant correlations between mean Doppler broadening and cup/disc ratio or refractive error in either eye. There was a statistically significant correlation between mean Doppler broadening and intraocular pressure in left eyes (r = −0.49, P = 0.05). However, this correlation was not present in right eyes (r = −0.08, P = 0.73). Scatterplots of mean Doppler broadening as a function of the cup/disc ratio are shown in Fig. 5.

Measurement of Site-level Characteristics

All 22 volunteers had Doppler broadening measurements from at least one temporal site, and nine had measurements from at least one nasal site. The average of the mean Doppler broadening from temporal sites in the 22 volunteers was 837 Hz (SD, 121 Hz), compared to an average of 731 Hz (SD, 114 Hz) measured at nasal sites. The paired t-test based on measurements from the nine volunteers having nasal and temporal measurements was highly significant (P

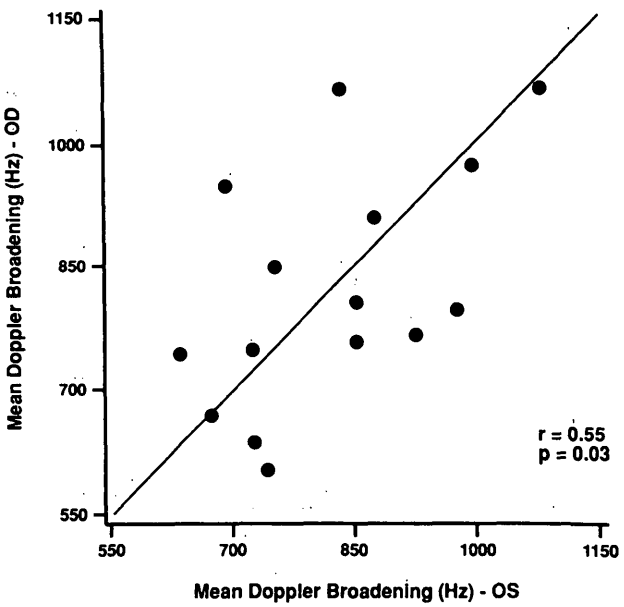

Fig. 4. Comparison of mean Doppler broadening measured in right and left eyes of the same subjects. Shown is the identity line representing measurements of equal magnitude in both eyes.

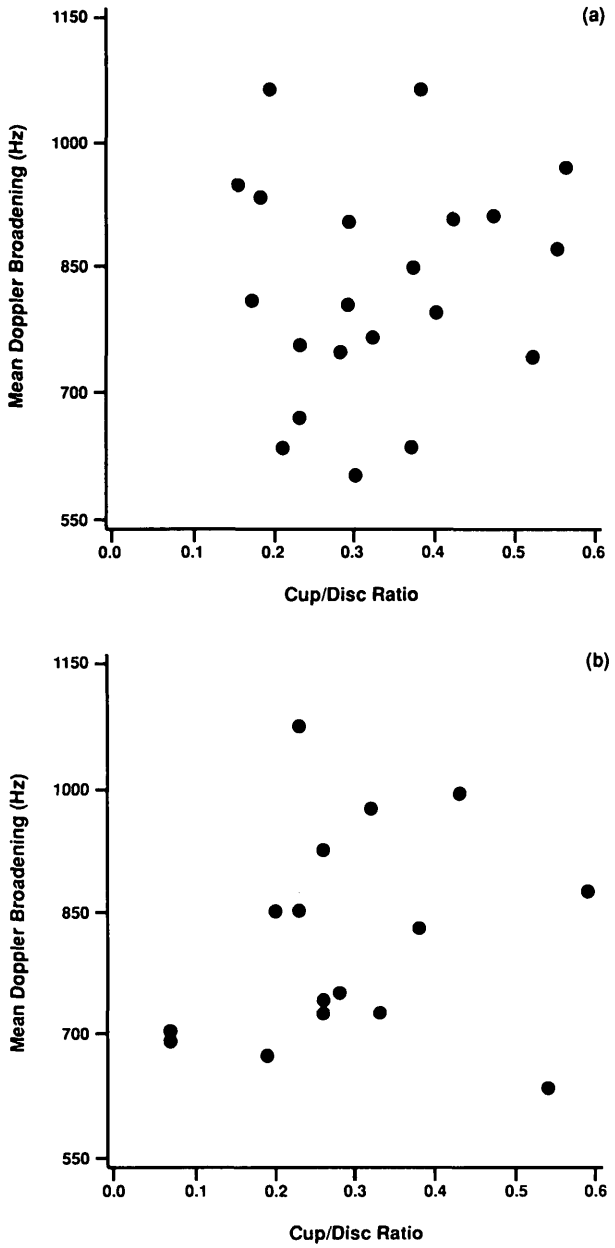

Fig. 5. Mean Doppler broadening plotted as a function of cup/disc ratio in right (**a**) and left (**b**) eyes. No significant correlation was observed.

= 0.0013). On average, Doppler broadening measured from temporal sites was 15 ± 10% greater than that measured from nasal sites in these subjects. Interestingly, in these subjects, the tissue scattering intensity was, on average, only 1% greater from temporal sites than from nasal sites, further demonstrating the independence of Doppler broadening and tissue scattering intensity.

Twenty-one volunteers had at least one superior, and 20 had at least one inferior site measured. The average mean Doppler broadening value for superior sites was 807 Hz (SD = 150 Hz) and the average for inferior sites was 835 Hz (SD = 141 Hz). The paired t-test based on the 19 volunteers having superior and inferior sites measured was not significant.

Effect of Age

The results presented so far indicated that the relationship between Doppler broadening and age might be influenced by whether the measurement sites were located temporally or nasally. Therefore, as described above, the mean Doppler broadening per subject was computed separately for temporal and nasal sites, and a weighted correlation analysis was performed to account for differences in the number of measurement sites per subject. Figure 6 shows the mean Doppler broadening for temporal sites for each subject plotted as a function of age. The data exhibited bimodal behavior, suggesting the use of a quadratic fit. The weighted quadratic regression fit shown in the figure was statistically significant ($R^2 = 0.36$, $P = 0.01$). The mean Doppler broadening for nasal sites for each subject, plotted as a function of age, exhibited similar behavior. However, the weighted quadratic regression fit was not statistically significant ($R^2 = 0.54$, $P = 0.10$) because only nine subjects had nasal sites measured.

To confirm the findings of the univariate analysis, we used a multivariate analysis to account for the possible influence of the subject-, eye-, and measurement site-level characteristics on the curve of Doppler broadening as a function of age. In this analysis, the Doppler broadenings at each of the 77 measurement sites were used, and correlations between measurements obtained from different sites in each subject were accounted for as described above.

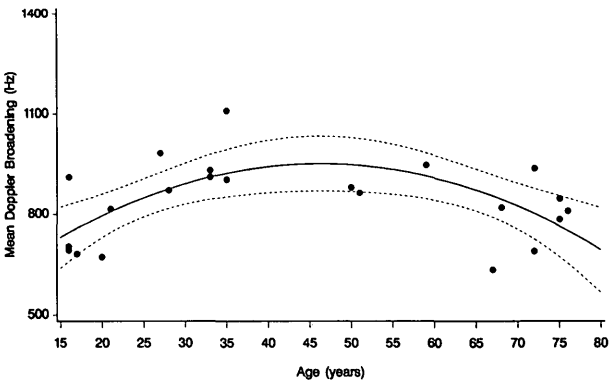

Fig. 6. Mean Doppler broadening for temporal sites for each subject plotted as a function of the subject's age. Solid line shows the statistically significant ($R^2 = 0.36$, $P = 0.01$) weighted quadratic regression fit to the data. Dashed lines represent the upper and lower 95% confidence interval bounds about the fit.

To simplify the multivariate analysis, intraocular pressure and cup/disc ratio were treated as subject-level characteristics by using the mean of the OD and OS values because these characteristics were highly correlated between the two eyes (the correlation coefficient for intraocular pressure in OD and OS of the same subjects was r = 0.87; $P = 0.0001$). The effect of mean blood pressure was excluded from the analysis because measurements were available only in 17 subjects. Furthermore, as presented above, Doppler broadening was not correlated with blood pressure. Similarly, the effect of refractive error was excluded from the analysis because measurements were available only in 19 subjects, and Doppler broadening was not correlated with refractive error.

The results of the multivariate quadratic regression model are presented in Table 2. The removal of sex, intraocular pressure, cup/disc ratio, and superior/inferior measurement site from this model resulted in a nonsignificant decrease in the likelihood. The simplified model is presented in Table 3 and shows the effect of the only two significant variables: age and whether the measurement site was temporal or nasal. In the multivariate analysis, the correlation between Doppler broadening and intraocular pressure suggested by the univariate analysis was no longer present. Clearly, from the multivariate and univariate analyses, the only information about a measurement site that was significantly related to Doppler broadening was whether the site was temporal or nasal. Whether the site was superior or inferior had little or no effect on Doppler broadening.

As an alternative to the quadratic regression model of Doppler broadening as a function of age, we modelled the measurements by a two-phase linear regression. The two-phase model was examined based on various cut-points between 21 and 35 years of age. The primary criterion for selecting the cut-point was to optimize the total likelihood. This was achieved using 30 years as a cut-point. The results of the optimal two-phase model are shown in Table 4. As with the quadratic model, there were only two significant variables: age and whether the measurement site was temporal or nasal. For ages ≤30 years, there were 32 measurement sites in eight subjects. For ages >30 years, there were 45 measurement sites in 14 subjects.

Table 2. Results of multivariate quadratic regression model (dependent variable: Doppler broadening)

Independent variable	*Regression coefficient*	*Standard error*	P
Constant	370.07	155.44	0.0173
Age	18.59	5.44	0.0006
Age-squared	−0.20	0.06	0.0008
Female/male	54.25	45.23	0.2304
Intraocular pressure	−3.39	5.35	0.5259
Cup/disc	188.15	154.87	0.2244
Superior/inferior	−22.20	27.96	0.4271
Temporal/nasal	107.58	38.98	0.0058

Table 3. Results of simplified multivariate quadratic regression model (dependent variable: Doppler broadening)

Independent variable	*Regression coefficient*	*Standard error*	P
Constant	361.06	106.80	0.0007
Age	20.87	4.67	0.0002
Age-squared	−0.23	0.06	0.0003
Temporal/nasal	107.63	39.49	0.0064

Figure 7 shows a plot of the mean Doppler broadening for temporal sites for ages >30 years. The weighted linear regression fit shown in the figure was statistically significant (r = 0.63, $P = 0.015$). In the age range 31 to 76 years, there was a 20% decrease in Doppler broadening. The weighted linear regression fit to the plot of the mean Doppler broadening for temporal sites for ages ≤30 years showed a 35% increase in the age range 16 to 30 years. However, because there were only eight subjects in this age range, the fit was not statistically significant (r = 0.67, $P = 0.07$).

Discussion

This study demonstrates that Doppler broadening, which is directly proportional to the speed of red blood cells flowing in the capillaries of the optic nerve head, varies significantly with age. The technique provided reproducible results with a coefficient of variation of 8 ± 5%, a percentage that is considerably less than the age-related variation found between the extremes of the results measured in the study. As described above, the method of application of the laser Doppler technique used in this study minimized the confounding effects of eye movements and differences in tissue scattering properties on the measured results. In particular, because the measured Doppler broadenings were independent of tissue scattering intensity over a wide range of intensities, reliable site-to-site and subject-to-subject comparisons could be made with some assurance that changes in Doppler broadening mirrored changes in capillary blood speed.

The primate optic nerve head blood supply is derived almost exclusively from the posterior ciliary arteries.[10,12,18–24] Retinal arterioles also contribute to the perfusion of the superficial nerve fiber layer of the

Table 4. Results of simplified multivariate two-phase linear regression model (dependent variable: Doppler broadening)

	Age ≤ 30 years			*Age > 30 years*		
Independent variable	*Regression coefficient*	*Standard error*	P	*Regression coefficient*	*Standard error*	P
Constant	331.56	123.59	0.007	1040.37	99.39	0.000
Age	18.29	6.30	0.007	−4.73	1.43	0.001
Temporal/nasal	88.61	43.25	0.042	107.70	63.26	0.089

optic nerve head. However, retinal arteriole perfusion is thought to be less significant over the temporal aspect of the nerve head because the capillaries in this region often are derived from the posterior ciliary circulation. The portion of nerve head sampled by our technique extends to a depth well below the surface nerve fiber layer. Studies in a variety of tissues[35] have indicated that the usual metric of penetration depth, the 1/e fraction of the incident intensity, is approximately one millimeter for the 633 nm wavelength used in this study. Therefore, the circulatory changes measured by our technique occur primarily in the portion of the nerve head supplied by the posterior ciliary arteries.

Disruption of the blood flow to the optic nerve head is thought to contribute to the onset of anterior ischemic optic neuropathy (AION),[10,11-13,18] a relatively common cause of visual loss in adults.[13,36-38] Unfortunately, the visual loss is usually permanent or shows only modest improvement. Approximately 33% of patients who experience AION in one eye will experience involvement in the second eye. Currently, there is no generally accepted treatment for this disease, and the lack of a good understanding of the etiology has hampered attempts to develop therapies.[39]

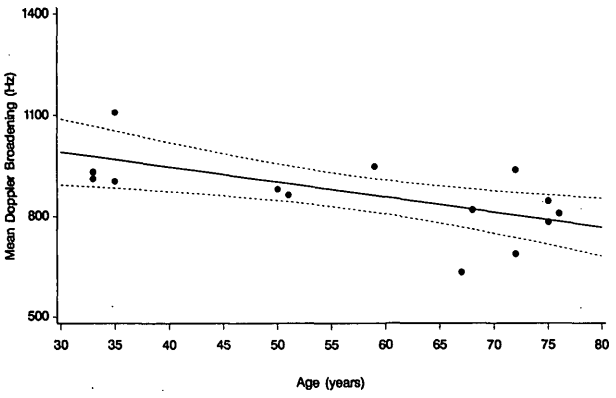

Fig. 7. Mean Doppler broadening for temporal sites for subjects > 30 years of age plotted as a function of the subject's age. Solid line shows the statistically significant (r = 0.63, P = 0.015) weighted linear regression fit to the data. Dashed lines represent the upper and lower 95% confidence interval bounds about the fit.

Chronic open-angle glaucoma and low-tension glaucoma are other diseases of the optic nerve head for which a vascular etiology has been proposed.[10,18,20,40,41]

The changes in capillary blood speed inferred from our measurements would indicate concomitant changes in capillary blood flow under certain circumstances. If it is assumed that optic nerve head capillaries do not dilate with age and that there is not an age-related increase in the number of capillaries, our results indicate a reduction in optic nerve head blood flow with age. In addition, if it is assumed there is narrowing or reduction in the number of optic nerve head capillaries with age, the decrease in optic nerve head blood flow would be even greater than the decrease in blood speed measured by our technique.

The reasons and mechanisms underlying the presumed reduction in blood flow to the optic nerve head with age are not known. Factors we have considered include: reduced metabolic requirements of the inner retina resulting from age-related attrition of ganglion cells, local alteration in the choroidal blood vessels, reduction concomitant with a decrease in cerebral blood flow, rheological changes, stenosis of carotid arteries, and reduced cardiac output.

Recent publications suggest the age-related loss of retinal ganglion cells is not dramatic and may not be significant given the variability in retinal neuronal numbers between normal individuals.[2-4,42] The amount of age-related depletion in the number of optic nerve axons is controversial, however. Balazsi et al[2] reported a much higher age-related attrition of axons, approximately 5600 fibers per year. Assuming Balazsi's mean counts of optic nerve axons and stated rate of attrition, there would be a 23% loss of axons from 31 to 75 years of age. This corresponds remarkably well to the 20% decline in blood speed we observed over the same age range. Interestingly, our results also are consistent with the age-related decrease in cerebral blood flow reported by other investigators, who found a 29% decline in cerebral gray matter blood flow between the third and eighth decades.[43]

Our study did not address the potential effect of carotid stenosis, other than to eliminate any volunteer

who had carotid bruits, a history of neurological events, or diseases that are highly associated with atherosclerosis. The potential confounding effect of carotid stenosis could only be conclusively determined by comparing the results of carotid angiography to the laser Doppler results. Change in resting cardiac output from the fourth to the eighth decade is only slight and is therefore not an important consideration.[44] It is likely that the age-related change in optic nerve blood flow we observed is the result of many interrelated factors that may be local and systemic.

The observed increase in optic nerve head blood speed from the second to the fourth decades was interesting and puzzling. This unexpected finding could be related to an unrecognized difference in the anatomy of the optic nerve head of younger persons. To this point, Morrison et al[4] recently described the age-effect upon axonal number and neural area in the optic nerve head of the rhesus monkey. The plot of age versus neural area in that report shows a remarkable similarity to our plots of age versus Doppler broadening. In particular, the increase in neural area in the younger monkeys (corresponding to a human age range of approximately 4 to 32 years) parallels our finding of an increase in capillary blood speed in our patients aged 16–30 years. The increase in neural area in the monkeys was thought to be the result of an increase in volume of myelin, glia, and connective tissue. If a similar timetable for maturational change occurs in humans,[1] the increase in blood speed we observed might be related to changes in the volume of myelin. In support of this, a 20% increase in white matter cerebral blood flow has been reported for normal humans between 18 and 29 years.[43] Intuitively, it might seem unlikely that maturational changes would still be occurring by the end of the second decade, but myelinogenesis within the afferent visual pathway is known to continue into adulthood in some mammals.[45–47]

A regional variation in optic nerve head blood speed was observed. On average, the temporal region displayed a 15% greater speed than the nasal region. This difference simply may be the result of the larger number of nerve fibers on the temporal side of the primate optic nerve head.[48] There was no statistically significant difference in blood speed between the superior and inferior regions of the nerve head. Indeed, there is little difference in the number of nerve fibers between these regions.[48]

We did not observe a consistent relationship between capillary blood speed and intraocular pressure, refractive error, systemic blood pressure, right/left eye, gender, or cup/disc ratio. This latter finding is especially interesting because a small cup/disc ratio is thought to be a predisposing factor for AION.[15–17]

In summary, we observed a statistically significant age-related change in Doppler broadening, which is directly proportional to optic nerve head capillary blood speed. Regional differences in Doppler broadening corresponded to regional differences in the density of axons across the optic nerve head. This study provides a baseline of normal age-controlled data that can be compared to similar measurements taken from patients with diseases of the optic nerve head that are thought to have a vascular etiology.

Key words: optic nerve, laser Doppler technique, aging, blood speed, blood flow, capillary perfusion

Acknowledgements

We thank Rebecca Rosenstein for her assistance in the statistical analysis of the data and for her helpful comments. We also thank Michael T. Milbocker for developing the computer algorithm used in data analysis.

References

1. Dohlman CL, McCormick AQ, and Drance SM: Aging of the optic nerve. Arch Ophthalmol 98:2053, 1980.
2. Balazsi AG, Rootman J, Drance SM, Schulzer M, and Douglas GR: The effect of age on the nerve fiber population of the human optic nerve. Am J Ophthalmol 97:760, 1984.
3. Repka MX and Quigley HA: The effect of age on normal human optic nerve fiber number and diameter. Ophthalmology 96:26, 1989.
4. Morrison JC, Cork LC, Dunkelberger GR, Brown A, and Quigley HA: Aging changes of the Rhesus monkey optic nerve. Invest Ophthalmol Vis Sci 31:1623, 1990.
5. Anderson DR: Pathology of the glaucomas. Br J Ophthalmol 56:146, 1972.
6. Quigley HA and Green WR: The histology of human glaucoma cupping and optic nerve damage: Clinicopathologic correlation in 21 eyes. Ophthalmology 86:1803, 1979.
7. Quigley HA and Addicks EM: Regional differences in the structure of the lamina cribrosa and their relation to glaucomatous optic nerve damage. Arch Ophthalmol 99:137, 1981.
8. Quigley HA, Hohman BA, Addicks BS, Massof RW, and Green WR: Morphologic changes in the lamina cribrosa correlated with neural loss in open-angle glaucoma. Am J Ophthalmol 95:673, 1983.
9. Quigley HA, Addicks EM, Green WR, and Maumenee AE: Optic nerve damage in human glaucoma: II. The site of injury and susceptibility to damage. Arch Ophthalmol 99:635, 1981.
10. Hayreh SS: Blood supply of the optic nerve head and its role in optic atrophy, glaucoma, and oedema of the optic disc. Br J Ophthalmol 53:721, 1969.
11. Hayreh SS: Anterior ischemic optic neuropathy. I. Terminology and pathogenesis. Br J Ophthalmol 58:955, 1974.
12. Hayreh SS: Anterior Ischemic Optic Neuropathy. New York, Springer-Verlag, 1975, pp. 3–23, 44–59, 72–73.
13. Hayreh SS: Anterior ischemic optic neuropathy. Arch Neurol 38:675, 1981.
14. Quigley HA, Miller NR, and Green WR: The pattern of optic nerve fiber loss in anterior ischemic optic neuropathy. Am J Ophthalmol 100:769, 1985.
15. Doro S and Lessell S: Cup-disc ratio and ischemic optic neuropathy. Arch Ophthalmol 103:1143, 1985.

16. Mansour AM, Shoch D, and Logani S: Optic disk size in ischemic optic neuropathy. Am J Ophthalmol 106:587, 1988.
17. Beck RW, Savino PJ, Repka MX, Schatz NJ, and Sergott RC: Optic disc structure in anterior ischemic optic neuropathy. Ophthalmology 91:1334, 1984.
18. Hayreh SS: Inter-individual variation in blood supply of the optic nerve head. Its importance in various ischemic disorders of the optic nerve head, glaucoma, low-tension glaucoma and allied disorders. Doc Ophthalmol 59:217, 1985.
19. Hayreh SS: Anatomy and physiology of the optic nerve head. Trans Am Acad Ophthalmol Otolaryngol 78:OP240, 1974.
20. Hayreh SS: Structure and blood supply of the optic nerve. *In* Glaucoma: Conceptions of a Disease, Heilman K and Richardson KT, editors. Stuttgart, Thieme, 1978, pp. 78–96.
21. Risco JM, Grimson BS, and Johnson PT: Angioarchitecture of the ciliary artery circulation of the posterior pole. Arch Ophthalmol 99:864, 1981.
22. Araki M and Honmura S: The collateral communications of the retinal circulation with the choroidal circulation at the optic nerve head. Nippon Ganka Gakkai Zasshi 77:1557, 1973.
23. Zhao Y and Li F: Microangioarchitecture of optic papilla. Jpn J Ophthalmol 31:147, 1987.
24. Hayreh SS: Letter to the editor. Jpn J Ophthalmol 33:519, 1989.
25. Riva CE, Feke GT, and Loebl M: Blood flow in the capillaries of the optic nerve. *In* Proceedings of the 5th Congress of the European Society of Ophthalmology, Francois J, editor. Stuttgart, Ferdinand Enke Verlag, 1978, pp. 414–416.
26. Stern MD and Lappe DL: Method and apparatus for measurement of blood flow using coherent light. U.S. Patent No. 4,109,647, 1978.
27. Riva CE, Grunwald JE, and Sinclair SH: Laser Doppler measurement of relative blood velocity in the human optic nerve head. Invest Ophthalmol Vis Sci 22:241, 1982.
28. Sebag J, Feke GT, Delori FC, and Weiter JJ: Anterior optic nerve blood flow in experimental optic atrophy. Invest Ophthalmol Vis Sci 26:1415, 1985.
29. Sebag J, Delori FC, Feke GT, Goger D, Fitch K, Tagawa H, Deupree D, Weiter JJ, and McMeel JW: Anterior optic nerve blood flow decreases in clinical neurogenic optic atrophy. Ophthalmology 93:858, 1986.
30. Quigley HA, Hohman RM, Addicks EM, Green WR: Blood vessels of the glaucomatous optic disc in experimental primate and human eyes. Invest Ophthalmol Vis Sci 25:918, 1984.
31. Laser-Doppler Blood Flowmetry, Shepherd AP and Öberg PA, editors. Boston, Kluwer Academic, 1990.
32. Tyml K, Roman RJ, and Lombard JH: Blood flow in skeletal muscle. *In* Laser-Doppler Blood Flowmetry, Shepherd AP and Öberg PA, editors. Boston, Kluwer Academic, 1990, pp. 219–222.
33. Riva CE, Petrig BL, and Grunwald JE: Retinal blood flow. *In* Laser-Doppler Blood Flowmetry, Shepherd AP and Öberg PA, editors. Boston, Kluwer Academic, 1990, pp. 374–375.
34. Rosner B: Multivariate methods in ophthalmology with application to other paired-data situations. Biometrics 40:1025, 1984.
35. Johnson JM: The cutaneous circulation. *In* Laser-Doppler Blood Flowmetry, Shepherd AP and Öberg PA, editors. Boston, Kluwer Academic, 1990, pp. 127–133.
36. Ellenberger C, Keltner JL, and Burde RM: Acute optic neuropathy in older patients. Arch Neurol 28:182, 1973.
37. Bogen DR and Glaser JS: Ischaemic optic neuropathy. The clinical profile and natural history. Brain 98:689, 1975.
38. Repka MX, Savino PJ, Schatz NJ, and Sergott RC: Clinical profile and long-term implications of anterior ischemic optic neuropathy. Am J Ophthalmol 96:478, 1983.
39. Shults WT: Ischemic optic neuropathy: Still the ophthalmologist's dilemma. Ophthalmology 91:1338, 1984.
40. Phelps CD and Corbett JJ: Migraine and low-tension glaucoma. Invest Ophthalmol Vis Sci 26:1105, 1985.
41. Carter CJ, Brooks DE, Doyle DL, and Drance SM: Investigations into a vascular etiology for low-tension glaucoma. Ophthalmology 97:49, 1990.
42. Rizzo JF, Sandell JH, and Masland RH: Genetic variation in the numbers of some retinal cells. Invest Ophthalmol Vis Sci 29(Suppl):205, 1988.
43. Davis SM, Ackerman RH, Correia JA, Alpert NM, Chang J, Buonanno F, Kelley RE, Rosner B, and Tavernas JM: Cerebral blood flow and cerebrovascular CO_2 reactivity in stroke-age normal controls. Neurol 33:391, 1983.
44. Gerstenblith G, Renlund DG, and Lakatta EG: Cardiovascular response to exercise in younger and older men. Fed Proc (United States) 46:1834, 1987.
45. Matheson DF: Some quantitative aspects of myelination of the optic nerve in rat. Brain Res 24:257, 1970.
46. Hirose G and Bass NH: Maturation of oligodendroglia and myelinogenesis in rat optic nerve: A quantitative study. J Comp Neurol 152:201, 1973.
47. Moore CL, Kalil R, and Richards W: Development of myelination in optic tract of the cat. J Comp Neurol 165:125, 1976.
48. Potts AM, Hodges D, Shelman CB, Fritz KJ, Levy NS, and Mangnall Y: Morphology of the primate optic nerve. II. Total fiber size distribution and fiber density distribution. Invest Ophthalmol Vis Sci 11:989, 1972.