Blood Flow in the Normal Human Retina

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The laser Doppler technique was used to measure the blood flow rate in 41 major vessels in ten eyes of healthy volunteer subjects. The specific relationship between blood flow rate, F, and vessel diameter, D, was determined for both retinal arteries and retinal veins. On average, F increased with increasing D at a power of 4.1, consistent with the presence of Poiseuille flow. In six eyes of six subjects, measurements on individual vessels were combined to yield the total retinal blood flow rate. The mean and standard deviation of the total retinal blood flow was $80 \pm 12 \,\mu$ l/min. The blood flow rate per unit mass of retinal tissue was calculated and found to be in good agreement with that reported for macaque monkeys. Blood flow to the temporal side of the retina was approximately three times larger than to the nasal side. There was no significant difference between blood flow to the superior and the inferior retina. Invest Ophthalmol Vis Sci 30:58–65, 1989

Even though the retinal circulation is directly observable, prior to the development of the laser Doppler technique^{1,2} there was no objective, quantitative means for noninvasive study of human retinal hemodynamics. Fluorescein angiography provides only qualitative information, and the assumptions inherent in the application of the fluorescein dye dilution technique to the estimation of retinal blood flow are often not valid, especially in cases of retinal vascular disease.3 Recently, we showed that, with appropriate modification, the laser Doppler technique provides accurate measurements of the absolute blood flow rate in individual retinal vessels.4 We now present measurements of blood flow in the normal human retina and demonstrate how measurements on individual retinal vessels are combined to yield a quantitative measure of the total retinal blood flow rate. We compare our measured total retinal blood flow rates to results reported for lower primates. From measurements on individual retinal vessels, we determine regional differences in retinal blood flow as well as the specific relationship between blood flow rate and vessel diameter for both retinal arteries and retinal veins. These relationships in the normal retina serve as standards against which altered retinal blood flow in disease states can be evaluated.

Materials and Methods

Laser Doppler Technique

Our laser Doppler system and technique of data analysis provides absolute measurements of the speed of red blood cells (RBCs) flowing at discrete, selected sites in the retinal vasculature; it has been described in detail elsewhere. Doppler-shifted frequency spectra of laser light scattered from RBCs flowing through individual retinal vessels exhibit large fluctuations in spectral power up to a clearly measurable 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 then calculated as

$$V_{\text{max}} = \kappa [\Delta f_{\text{max}_1} - \Delta f_{\text{max}_2}]/\cos \beta$$
 (1)

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, one must determine the time-averaged value of $V_{max}(t)$ during the cardiac cycle, \overline{V}_{max} . We have previously presented 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

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$$\overline{V_{max}} = V_{max}(diastole) + k[V_{max}(systole)]$$

- V_{max}(diastole)] (2)

where $k=0.48\pm0.04$. Blood flow in retinal veins does not exhibit systolic/diastolic variations, so that V_{max} measured at any phase of the cardiac cycle is identical to $\overline{V_{max}}$.

The blood flow rate is calculated as $F = \overline{V_{max}}$ S/2, where S is the cross-sectional area of the vessel at the measurement site. S is calculated from the measured blood column diameter, assuming a circular cross-section. The blood column diameter is measured from monochromatic (575 nm) retinal photographs, using an instrument calibrated to produce readings in micrometers from a magnified retinal image.⁵

The factor of 2 in the formula for F arises from the assumption of Poiseuille flow.^{1,2} In general, the presence of Poiseuille flow depends on flow rate, vessel diameter and blood hematocrit. Evidence from other studies^{6,7} indicates that Poiseuille flow is likely to be present in the major retinal vessels.

Study Population

The absolute retinal blood flow rate was measured in 19 major branch retinal arteries and 22 major branch retinal veins in ten eyes of seven healthy volunteer subjects (five females and two males). The mean age was 30.1 years (range 25-38 years). The mean brachial artery blood pressure was 86.6 mm Hg (range 80-93 mm Hg). The mean intraocular pressure as measured by applanation tonometry was 17.2 mm Hg (range 14-21 mm Hg). Total retinal blood flow was calculated for six eyes of six subjects. Five eyes were either emmetropic or slightly (<1D) hyperopic; the sixth was myopic (-3.5D). Mean axial length of the five essentially emmetropic eyes as measured by A-scan ultrasonography was 23.2 mm (range 22.6-23.9 mm). The axial length of the myopic eye was 25.9 mm. Written informed consent was obtained from all subjects.

Results

Figure 1 shows a pair of Doppler-shifted frequency spectra obtained from one subject during the diastolic phase of the cardiac cycle. The measurement site was along a 123 μ m diameter inferior temporal retinal artery of the right eye. For this example and for all the spectrum pairs used in this study, the maximum frequency shifts Δf_{max_1} and Δf_{max_2} were determined by experienced examiners using procedures previously described in detail. In essence, the examiner judges the location of the frequency at which there is an abrupt discontinuity in the fluctuations in spectral power. In practice, this is accomplished by moving

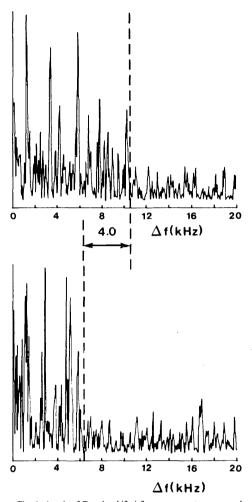


Fig. 1. A pair of Doppler-shifted frequency spectra measured simultaneously in two scattering directions from a site along the inferior temporal retinal artery of the right eye of a volunteer subject (see Fig. 2). The measurement was obtained during the diastolic phase of the cardiac cycle using an accumulation time of 100 msec. The dashed lines indicate the maximum frequency shifts at 10.5 and 6.5 kHz. The arrow indicates the frequency shift difference of 4.0 kHz.

the electronic cursor of the spectrum analyzer to the appropriate location in the spectrum. Δf_{max_1} and Δf_{max_2} are then read from the digital analyzer display. In this example, Δf_{max_1} was 10.5 kHz and Δf_{max_2} was 6.5 kHz. Using Eq. (1), with $\kappa = 0.33$ and $\beta = 66^\circ$, determined as described previously, we obtain V_{max} (diastole) = 3.2 cm/sec.



Fig. 2. A 575 nm monochromatic fundus photograph of the right eye of the same subject as in Figure 1. The blood flow rates (in μ l/min) measured at sites, indicated by arrows, along the inferior temporal retinal artery and the adjacent retinal vein are shown.

Recently, we have developed a computer algorithm for automated determination of the maximum frequency shift. As we have described, 8 Δf_{max} of 34 spectra were determined independently by an experienced examiner and by the computer algorithm. On average, the maximum frequency shifts determined by the algorithm were $3.9 \pm 6.6\%$ lower than those determined by the examiner. Application of the algorithm to the spectra shown in Figure 1 gives Δf_{max}. = 10.8 kHz and Δf_{max_2} = 6.1 kHz. The frequency shift difference of 4.7 kHz obtained using the computer algorithm is 18% higher than the difference obtained by the examiner. This difference can be used as a realistic estimate of the uncertainty associated with individual measurements of V_{max} . A recent study of the reproducibility of our measurements9 indicates that an uncertainty of ±18% on individual measurements is indeed a reasonable estimate. In that study, laser Doppler measurements at a designated site along a temporal retinal artery were performed on each of five subjects weekly for 5 successive weeks. The coefficients of variation (100 [standard deviation/mean]) were $3 \pm 1\%$ for arterial diameters, 12 \pm 3% for centerline red blood cell speed, and 12 \pm 6% for blood flow rate.

In the example shown in Figure 1 we can thus write V_{max} (diastole) = 3.2 ± 0.6 cm/sec. From spectra obtained during the systolic phase of the cardiac cycle, \underline{V}_{max} (systole) = 10.9 ± 2.0 cm/sec. Using Eq. (2), \overline{V}_{max} = 6.9 ± 1.2 cm/sec. The calculated blood flow

rate, F, is $25 \pm 4 \mu l/min$. The measurement site and arterial blood flow rate are shown in the fundus photograph Figure 2.

Measurements were also obtained from a site along the adjacent 179 μ m diameter retinal vein (see Fig. 2). $\overline{V}_{max} = 3.2 \pm 0.6$ cm/sec, and $F = 24 \pm 4$ μ l/min. Within the precision of the measurements, the arterial and venous flow rates are essentially the same, suggesting that the inferior temporal vascular segment in this eye approximates a closed loop.

Figure 3 shows the sites of blood flow measurements along retinal arteries and veins in the superior temporal quadrant of the right eye of another subject. F measured in the superior temporal artery proximal to the branching point was $40 \pm 7 \mu l/min$, and in the two branches, 25 ± 4 and $12 \pm 2 \mu l/min$. The mean of the sum of the measured branch flows differs by 8% from the flow measured before the branching, indicating, within the precision of the measurements, the expected balance of flow rates at the vascular branching. The flow rates measured in the two veins draining the superior temporal quadrant were 31 ± 6 and 3± 1 μl/min. The mean total measured venous flow differs by 8% from the mean of the sum of the measured branch arterial flows and by 15% from the arterial flow measured before the branching.

Figure 4 shows the measurement sites in the right eye of another subject, along all four major veins draining the retina and both major temporal arteries. The total retinal blood flow rate, calculated by summing the rates measured in the major veins, is $81 \pm 9 \mu$ l/min.

Relationship between Blood Flow Rate and Vessel Diameter

As noted above, evidence from other studies^{6,7} has indicated that Poiseuille flow is likely to be present in our measured retinal vessels. According to the Poiseuille formula¹⁰:

$$F = \frac{\pi}{128} \times \frac{\Delta P}{\Delta L} \times \frac{1}{n} \times D^4$$
 (3)

where $\Delta P/\Delta L$ is the pressure drop per unit length of blood vessel, η is the blood viscosity, and D is the blood column diameter. If Poiseuille flow is present, the measured blood flow, F, should vary as D⁴ provided that $\Delta P/\Delta L$ is independent of the diameter of the measured vessel.

To determine experimentally the relationship between our measured values of F and D, we constructed separate log-log plots of F as a function of D for the data obtained on each subject. For the six subjects (#2-7) on whom measurements on retinal arteries were obtained, the average slope of the six linear regression fits to the data was 4.34. The coefficient of variation was 58%. For the six subjects (#1-6) on whom measurements on retinal veins were obtained, the average slope of the six linear regression fits to the data was 3.91. The coefficient of variation was 37%. The average slope of the 12 sets of arterial and venous data is 4.12, so that, on average, F varies as D.4,12 Our data thus indicate that, to a close approximation, the Poiseuille formula [Eq. (3)] describes blood flow in the major retinal vessels.

Figure 5A shows the combined data from retinal arteries. Similarly, Figure 5B shows the combined data from retinal veins. We also constructed log-log plots of V_{max} as a function of D for the combined data. For retinal arteries, the linear regression fit was log $\overline{V}_{\text{max}} = [1.95 \pm 0.54] \times \log D - [3.31 \pm 1.13]$. For retinal veins, the linear regression fit was log $V_{\text{max}} = [1.93 \pm 0.35] \times \log D - [3.66 \pm 0.77]$. The retinal blood speed thus varies, to a close approximation, as D^2 . We note, of course, that since the blood flow rate, F, is proportional to the product of V_{max} and D^2 , then the exponent of the relationship between V_{max} and D is exactly 2 units less than the exponent of the relationship between F and D.

The equations of the linear regression fits to the data, along with appropriately transformed 95% confidence interval limits, ¹¹ can be used to predict blood flow rates in retinal arteries and veins if the vessel diameter is known. As described below, blood flow rates were predicted in four vessels in order to supple-

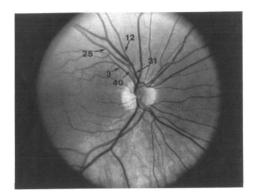
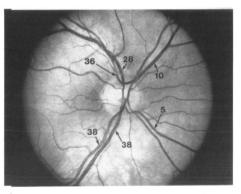


Fig. 3. A 575 nm monochromatic fundus photograph of the right eye of a volunteer subject. The blood flow rates (in $\mu l/min$) measured in the superior temporal retinal artery proximal to the branching point and in the two branches are shown, as well as the rates measured in the major superior temporal retinal vein and a small superior temporal retinal vein.

ment the directly measured flow rates in the six eyes in which total retinal blood flow was calculated.

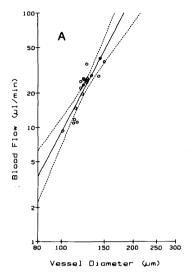
Total Retinal Blood Flow Rate

Table 1 summarizes the data on total retinal blood flow. For each eye the number of vessels in which flow rates were directly measured, as well as the number in which flow rates were predicted from the measured vessel diameter, are indicated. The data from Subject 2 are shown in Figure 4. Subject 4 was myopic. In Subjects 5 and 6, the total flow was calculated



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Fig. 4. A 575 nm monochromatic fundus photograph of the right eye of a volunteer (Subject 2, Table 1). The blood flow rates (in $\mu l/lmin$) measured at sites indicated by the arrows along all four major veins draining the retina and both major temporal retinal arteries are shown.



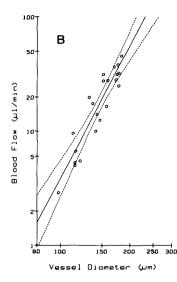


Fig. 5. The blood flow rate measured in retinal arteries (A) and retinal veins (B) of volunteer subjects plotted as a function of vessel diameter on a log-log scale. For arteries, the equation of the linear regression fit to the data (solid line) is $log F = [3.95 \pm 0.54] \times log$ $D - [6.93 \pm 1.14]$. For veins, the equation of the linear regression fit to the data (solid line) is log F $= [3.93 \pm 0.35] \times \log D$ $-[7.30 \pm 0.77]$. The dashed lines indicate the 95% confidence interval limits.

separately from measurements on arteries and on veins. In these two eyes, the total retinal blood flow rates calculated from arterial and from venous data differed by 9% and 6%, respectively, indicating, within the precision of the measurements, the expected balance of total arterial and venous flow rates.

The average and standard deviation of the total retinal blood flow rates shown in Table 1 is 80 ± 12 μ l/min.

Regional Differences in Retinal Blood Flow

To determine regional differences in retinal blood flow, we examined the data from eyes in which there were no discernible vascular branches crossing the

Table 1. Total retinal blood flow

Subject	Eye	Vessel type	No. of vessels		
			Flow measured	Flow predicted	Total flow (µl/min)
1	OD	v	3	1	89 ± 12
2	OD	v	4	0	81 ± 9
3	OS	V	4	0	56 ± 6
4	OS	Α	3	ı	79 ± 13
5	OD	Α	4	1	86 ± 10
5	OD	V	4	0	95 ± 9
6	OS	Α	2	0	78 ± 10*
6	os	V	2	1	74 ± 12*

A = artery; V = vein.

imaginary line separating the retina temporal and nasal to the optic disc. Only the eyes of Subjects 3 and 5 satisfied this criterion. In Subject 3, the total temporal venous blood flow was $44 \pm 6 \mu l/min$, and the total nasal venous blood flow was $12 \pm 2 \mu l/min$. In Subject 5, the total temporal arterial blood flow was $63 \pm 10 \mu l/min$, and the total nasal arterial blood flow was $23 \pm 3 \mu l/min$. Also in Subject 5, the total temporal venous blood flow was $68 \pm 9 \mu l/min$, and the total nasal venous blood flow was $27 \pm 4 \mu l/min$. On average, therefore, blood flow to the temporal side of the retina was approximately three times larger than to the nasal side.

In the five eyes in which the total retinal blood flow rate was calculated from measurements on both superior and inferior vessels, the blood flow to the inferior retina was, on average, 6% greater than the flow to the superior retina. This difference, however, is not statistically significant.

Discussion

The average retinal blood flow rate of $80 \,\mu\text{l/min/}$ whole tissue measured in our subjects can be compared to that measured in macaque monkeys by Alm and Bill¹² (25 ± 9 mg/min/whole tissue) and Alm et al¹³ (34 ± 8 mg/min/whole tissue), who used microsults (29.5 mg/min/whole tissue) and noting that the specific gravity of whole blood is approximately $1.06,^{14}$ the total retinal blood flow rate in the ma-

^{*} Measurements obtained only on vessels in the inferior half-retina; total flow obtained by doubling the measured flow rate.

caque monkey is found to be approximately $28 \mu l/min/whole$ tissue. For the same species, Caprioli et al¹⁵ reported a blood flow rate per unit mass of retinal tissue of 23 ± 4 g blood/min/100 g tissue. From these measurements we deduce a value of 128 mg for the wet weight of the macaque monkey retina. We determined the average wet weight of two human retinas obtained from autopsy eyes as 326 mg. Thus, the human/monkey retinal weight ratio is approximately 2.5. The human/monkey retinal blood flow ratio using our data and that of Alm and Bill^{12,13} is approximately 80/28 = 2.9. The blood flow data thus appear to scale approximately according to the retinal weight.

Alternatively, we may express our human results as blood flow rate per unit mass of retinal tissue. We obtain 26 ± 4 g blood/min/100 g tissue, in good agreement with the macaque monkey result of Caprioli et al. ¹⁵ In the only other laser Doppler study of blood flow in the normal human retina, Riva et al ¹⁶ reported total arterial and venous blood flow rates of 33 and 34 μ l/min, respectively, well below our average value of 80 μ l/min, and, on a per retinal mass basis, well below the macaque monkey results. The differences that exist between our experimental methodology and that of Riva et al ^{16,17} are most likely responsible for the difference in the results on total human retinal blood flow. These differences in methodology have been detailed elsewhere. ⁴

In calculating the blood flow rate in individual retinal vessels, we and Riva et al16 have assumed that the vessel cross-section is circular. Histologic evidence¹⁸ indicates that retinal arteries do indeed have circular cross-sections. Relatively high retinal arterial blood pressures would be expected to maintain circular cross-sections. Histologic evidence also indicates that whereas retinal veins sometimes appear to have circular cross-sections, they often do not, rather exhibiting a tendency toward flattening. This would lead to an overestimate of the vascular cross-section and, thus, an overestimate of retinal venous blood flow. However, the good agreement we found between the total retinal blood flow calculated by summing the flows measured in each of the major branch retinal arteries and the total retinal blood flow calculated by summing the flows measured in each of the major branch retinal veins suggests that errors introduced by the assumption of circularity are small. Similarly, when comparing flow rates measured in retinal arteries and veins of the same vascular segment, we have no indication that the retinal venous flow is overestimated.

The presence of the large regional differences in retinal blood flow that we measured had been indicated by microsphere infusion experiments on macaque monkeys.¹² In those studies, Alm and Bill found that the blood flow to the peripapillary and foveal regions of the retina was approximately four times larger than the blood flow to the intermediary and peripheral retina.

Although the blood flow rate in temporal retinal vessels is generally much greater than in nasal vessels, the relationship between flow rate and vessel diameter applies to both. Figures 5A and 5B, which illustrate the flow-diameter relationships, were constructed using data from both temporal and nasal vessels, and serve to verify that, to a close approximation, there is Poiseuille flow in the major retinal vessels.

Figures 5A and 5B also show that for a fixed vessel diameter, the blood flow rate in a retinal artery is greater than in a retinal vein. Using the equations of the linear regression fits to the data, we find that the expected blood flow rate as well as the expected average centerline blood speed in a retinal artery are approximately 2.5 times larger than the flow rate and blood speed expected in a retinal vein of the same diameter. From the Poiseuille formula [Eq. (3)], we see that this phenomenon must be due to the fact that $\Delta P/\Delta L$, the pressure drop per unit length of blood vessel, is 2.5 times greater in the major retinal arteries than in the major retinal veins.

The equations of the linear regression fits to the data can also be used to predict the ratio of venous to arterial diameter in closed arteriovenous vascular loops, where arterial and venous flow are equal. In this case we find that the ratio of venous to arterial diameter should be approximately 1.25.

Whereas we found that F varies approximately as D^4 and \overline{V}_{max} varies approximately as D^2 , Riva et al 16 reported that F varies approximately as $D^{2.8}$ and therefore that \overline{V}_{max} varies approximately as $D^{0.8}$. However, their data include measurements on vessels with diameters smaller than ours. Under these conditions there may be a blunting of the spatial profile of RBC velocities within the vessel. Furthermore, $\Delta P/\Delta L$ may become dependent on vessel diameter in these vessels.

In our determinations of blood flow rates, we have used the formula: $F = \overline{V_{max}}$ S/2. This formula assumes a parabolic spatial profile of velocities within the blood vessel consistent with Poiseuille flow. On the other hand, Riva et al¹⁶ used a different constant in the formula for F. They used $F = \overline{V_{max}}$ S/1.6. This factor of 1.6 is the ratio of the centerline RBC velocity to the spatially averaged RBC velocity found by several investigators ^{6.19,20} using the so-called dual-slit correlation method to measure flow rates in vitro as

well as in exposed arterioles and venules in the microvasculature of experimental animals. Baker and Wayland⁶ measured actual RBC velocity profiles using high-speed cinematography as well as dual-slit velocity profiles in the same blood samples. They found that even though the profiles were parabolic, the dual-slit technique provided a consistent 20% underestimate of the true centerline velocity. Harper and Bohlen²⁰ showed that the error in the dual-slit technique is associated with the illumination geometry typically used in the experiments. They compared the dual-slit results obtained using two types of illumination and found the artifactual 1.6 factor using standard transillumination. With nonstandard epiillumination, they found the theoretically expected factor of 2.0. Furthermore, Kiesewetter et al21 measured flow rates in vitro using the dual-slit technique, high-speed cinematography, the laser Doppler technique, and a so-called prism grating technique. Only high-speed cinematography and the laser Doppler technique gave the true relationship between the centerline velocity and the spatially averaged velocity. Thus, these reports^{6,20,21} clearly suggest that the 1.6 factor should be used only in interpreting the results of dual-slit experiments, whereas a factor of 2 should be used in the blood flow rate formula when the laser Doppler technique is applied to vessels in which there is Poiseuille flow. It should be noted that if Riva et al16 had used a factor of 2 in their blood flow rate calculations, their reported values of total retinal blood flow would have been 20% lower, and the difference between our results and theirs would have been even larger.

Inaccuracies in our blood flow rate measurements can arise from errors in interpreting our Dopplershifted frequency spectra, in measuring the angle β , and in measuring the blood column diameter at the laser Doppler measurement sites. We have previously described4 our approaches to minimize errors. The magnitude of our inaccuracies are best assessed by consistency checks. As described above, when measurements at a vascular branching point were compared, the sum of the flows in the branches differed by 8% from the flow measured before the branching. When the total retinal blood flow measured from arteries and from veins in the same eyes was compared, the differences did not exceed 9%. These data thus provide a realistic estimate of the inaccuracies inherent in our measurement technique.

In applying our technique to studies of altered retinal blood flow in patients with retinal vascular disease, it is conceptually most desirable to measure total retinal blood flow rates. However, at the current stage of instrument development, this procedure is

lengthy. The patient must cooperate while data are acquired from all the major vessels. Data analysis time, taken up mainly by the need to extract measurements from signals not degraded by eye movements, becomes multiplied by the number of measurement sites. For some clinical studies it may be feasible to measure the flow rate in only one major retinal vessel of each patient. Then, to determine whether the measured blood flow rate in a patient or group of patients is abnormal, comparison could be made with the flow rate-vessel diameter relationships that we found for normal subjects. Such a determination is likely to be valid in cases where there is no vasodilation or vasoconstriction in the major retinal vessels, but where there is altered microvascular resistance to flow in the retinal capillary network. Alternatively, the ratio of blood flow in a vessel to the area of retina supplied by that vessel could be used as a means of assessing the abnormality of blood flow rates in patients.

Key words: retinal blood flow, laser Doppler technique, retinal vessel diameter, Poiseuille flow, regional blood flow

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