

Retinal Circulatory Abnormalities in Type 1 Diabetes

Gilbert T. Feke,*† Sheldon M. Buzney,*† Hironobu Ogasawara,* Naoki Fujio,*
Douglas G. Goger,* Norman P. Spack,† and Kenneth H. Gabbay‡

Purpose. To quantify retinal circulatory abnormalities in patients with type 1 diabetes; to compare blood speed and blood flow in major temporal retinal arteries as well as total retinal arterial cross-section measured in patients to that measured in controls without diabetes; to determine which factors are related to the measured abnormalities within the patient group.

Methods. The laser Doppler technique and monochromatic fundus photography were used to measure retinal circulatory parameters in 39 patients with type 1 diabetes with duration of diabetes between 7 and 20 years and 13 age-matched controls without diabetes. Blood pressure, intraocular pressure, and heart rate were measured in all subjects. Glycosylated hemoglobin was measured in the patients. Retinopathy was assessed using standardized color fundus photography and fluorescein angiography.

Results. Total retinal arterial cross-section was, on average, 17% higher ($P = 0.007$) in the patients than in the controls, and it increased with increasing duration of diabetes ($P = 0.006$). Arterial blood speed was, on average, 33% lower ($P = 0.0001$) in the patients than in the controls, and it decreased with increasing duration of diabetes ($P = 0.03$).

Conclusions. The retinal circulation of patients with type 1 diabetes with no retinopathy or background retinopathy is characterized by dilated major arteries with reduced blood speeds. Dilation of the larger retinal arteries, with the accompanying decrease in vascular resistance to flow in those vessels, appears to counteract an increase in resistance to flow at the level of the smaller retinal vessels. *Invest Ophthalmol Vis Sci.* 1994;35:2968–2975.

Circulatory abnormalities in the diabetic retina are primarily influenced by changes in the resistance to flow through the retinal vascular network. Changes in resistance occur when vessels are either dilated or obstructed, or when blood rheologic properties are altered. There is evidence that each of these abnormalities occurs both before and during the development of clinically observable diabetic retinopathy.¹ Nonperfusion and obliteration of small blood vessels is a clinically observable feature of diabetic retinopathy that begins at an early stage. It is seen histologically as an increased prevalence of acellular capillaries. These acellular capillaries, which initially occur singly or in small groups, subsequently occur in larger clusters and are associated with atrophic arterioles.² As areas of nonperfusion become more extensive, they are traversed by a few tortuous, enlarged capillaries that act

as shunts between arterioles and venules.^{3,4} The retinal circulation appears to become progressively short-circuited as remaining functioning capillaries are bypassed by these shunts.

The time course of retinal circulatory changes in diabetes is, thus, likely to be complex. This inherent complexity, along with the differences that occur when a variety of measurement techniques are applied to dissimilar patient groups or to different animal species, is likely responsible for the variety of results reported in the literature on retinal circulatory alterations in diabetes.^{5–19}

In this study, we used the laser Doppler technique and monochromatic fundus photography to measure blood speed and blood flow in major temporal retinal arteries, as well as total retinal arterial cross-section in patients with type 1 diabetes and in controls without diabetes. We compared the results obtained in both groups and determined which factors were related to differences in the measured circulatory parameters within the group with diabetes.

METHODS

Subjects for the study included 39 patients with type 1 diabetes (22 men and 17 women), ranging in age from

From the *Schepens Eye Research Institute and the †Harvard Medical School, Boston, Massachusetts, and the ‡Baylor College of Medicine, Houston, Texas. Supported in part by United States Public Health grants EY01303 (GTF) and DK39044 (KHC). Submitted for publication May 26, 1993; revised December 6, 1993; accepted January 19, 1994. Proprietary interest category: N. Reprint requests: Gilbert T. Feke, PhD, the Schepens Eye Research Institute, 20 Staniford Street, Boston, MA 02114.

19 to 41 years, and 13 controls without diabetes (5 men and 8 women), ranging in age from 23 to 31 years. All were free of ocular or systemic disease. The patients with type 1 diabetes had no history or evidence of systemic hypertension, no other ocular or systemic diseases, no previous eye surgery or photo-coagulation treatment, and they had adequate pupillary dilatation and clear ocular media. The procedures performed in the study followed the tenets of the Declaration of Helsinki and were approved by the Scheepens Eye Research Institute Human Studies Committee. Written informed consent was obtained from all subjects.

Each patient underwent a complete ophthalmologic examination that included standardized color fundus photography²⁰ and fluorescein angiography.²¹ Photographs and angiograms were evaluated in a masked fashion by an examiner (SMB) who had no knowledge of retinal circulatory results. Nine patients had no observable retinopathy; 14 patients had microaneurysms only, with only 1 to 10 observable microaneurysms present; 16 patients had background retinopathy that consisted of varying combinations of microaneurysms, hemorrhages, exudates, capillary dilation, and macular leakage; clinically observable capillary nonperfusion was found in only one of these patients.

Age at onset of diabetes ranged from 1 to 30 years, mean 10.7 years; duration of diabetes ranged from 7 to 20 years, mean 13.5 years. Glycosylated hemoglobin, measured according to the method of Gabbay et al,²² ranged from 8.7% to 18.6%, mean 12.4% (upper limit of normal range, 6%). Daily insulin dosage ranged from 25 to 104 IU, mean 55 IU.

Before laser Doppler testing, subjects' pupils were dilated with 1% tropicamide. Monochromatic (575 nm) fundus photographs were taken of each eye. Intraocular pressure was measured by applanation tonometry, and brachial artery blood pressure was measured by sphygmomanometry. Retinal circulatory measurements were obtained without knowledge of the retinopathy evaluation of the patients.

Table 1 shows the comparison between the subjects with diabetes and the control subjects in terms of age, mean blood pressure, intraocular pressure, and heart rate. There were no statistically significant differences between the groups.

The methodology of our application of the laser Doppler technique to measurement of centerline blood speed in retinal arteries has been described in detail.²³ Modifications to the methodology have also been described.²⁴ Our projection micrometry technique for measurement of arterial diameters using monochromatic photographs has also been described.²⁵

Blood flow rate in an individual retinal artery was calculated as $\text{Flow} = \bar{V} \times \text{Area}/2$, where \bar{V} is the time average of the centerline blood speed during the car-

TABLE 1. Study Subjects

| Characteristics | Diabetic Group (n = 39) | Control Group (n = 13) | P Value* |
|------------------------------|----------------------------|---------------------------|----------|
| Age (years) | 24.2 ± 4.8 | 26.5 ± 2.5 | NS |
| Mean blood pressure† (mm Hg) | 85.9 ± 8.6 | 85.4 ± 5.2 | NS |
| Intraocular pressure (mm Hg) | 17.0 ± 3.2 | 16.3 ± 3.3 | NS |
| Heart rate (beats/min) | 74.3 ± 11.9 | 74.2 ± 9.7 | NS |

Values are mean ± SD.

* Comparison between control and diabetic groups (two-tailed unpaired *t*-test).

† Mean blood pressure = $0.33(\text{BP}_s + 2\text{BP}_d)$, where BP_s and BP_d are the systolic and diastolic pressures, respectively.

diac cycle, and Area is the cross-sectional area of the retinal artery at the laser Doppler measurement site.²⁶ The area was calculated from the arterial diameter assuming a circular cross-section. The ratio of the centerline blood speed measured during peak systole to that measured during minimum diastole was also determined. This ratio is known as the arterial velocity pulsatility.^{7,23}

Laser Doppler measurements were obtained from a temporal retinal artery in one eye of each subject. The arteries chosen for measurement had relatively straight segments that were sufficiently distant from adjacent vessels. Measurement sites were generally between the disc margin and the first bifurcation. In the group with diabetes, 32 right eyes and 7 left eyes were studied. Measurements were obtained from 21 superior temporal arteries and 18 inferior temporal arteries. In the control group, 8 right eyes and 5 left eyes were studied. Measurements were obtained from 6 superior temporal arteries and 7 inferior temporal arteries. The variability of repeated measurements at the same site was assessed in five of the patients. In this subgroup, laser Doppler measurements were obtained at approximately the same time of day and on the same day of the week each week for 5 successive weeks. Finger capillary blood glucose was measured immediately before the laser Doppler measurements using a Glucoscan (Lifescan, Mountain View, CA) blood glucose monitor.

In addition to the laser Doppler measurements at a single site in each subject, we also measured the cross-sectional area of each of the major quadrant arteries in the measured eye. The sum of these areas represents a measure of the total retinal arterial cross-section.

The central retinal artery blood flow in each eye was estimated using an iterative procedure. In this procedure, the flow measured at the single site and the diameters of the measured artery, its parent artery, and the fellow daughter artery were used to estimate

the flow in the parent artery. It was assumed²⁷ that the blood flow varies as [Diameter].³ Having estimated flow in the parent artery, the procedure was repeated with the original parent artery, its fellow artery, and a new parent artery until flow in the central retinal artery was estimated.

The statistical significance of differences in age, mean blood pressure, intraocular pressure, heart rate, arterial diameter, centerline blood speed, velocity pulsatility, blood flow rate, total arterial cross-section, and estimated total arterial blood flow between the group with diabetes and the control group was determined using two-sample *t*-tests. A Bonferroni adjustment was applied to the comparisons between subgroups with diabetes and the control group. Multiple linear regression analysis was used to study the relationship between centerline blood speed and duration of diabetes, glycosylated hemoglobin level, insulin dosage, age, mean blood pressure, intraocular pressure, heart rate, and arterial diameter within the group with diabetes. A similar analysis was applied to the measurements of total arterial cross-section. A *P* value of 0.05 or less was considered statistically significant.

RESULTS

In the five patients with diabetes who were studied weekly for 5 successive weeks, the coefficients of variation (100 [standard deviation/mean]) for the retinal blood flow rate ranged from 6% to 21%, with a mean of 12%. This variability in the retinal blood flow rate arose primarily from variability in the centerline blood

speed. Coefficients of variation for the blood speed ranged from 9% to 16%, with a mean of 12%. Variations in arterial diameter were much smaller. Coefficients of variation for the diameter ranged from 1% to 4%, with a mean of 3%. Variations in blood glucose were large; coefficients of variation for blood glucose ranged from 24% to 59%, with a mean of 43%. Linear regression fits to plots of centerline blood speed as a function of blood glucose for each patient gave an average slope of 0.5 cm/sec speed per 100 mg/dl blood glucose. In this subgroup, mean centerline blood speed was 5.1 cm/sec and mean blood glucose was 199 mg/dl. Thus, on average, $\pm 50\%$ changes in blood glucose were related to $\pm 10\%$ changes in centerline blood speed.

Group Comparisons

Figure 1 shows the arterial diameters, centerline blood speeds, and blood flow rates measured in a major temporal artery in the patients with diabetes and in the controls without diabetes. The controls are designated as group A, the patients with no clinically observable retinopathy as group B, the patients with retinopathy consisting only of 1 to 10 microaneurysms as group C, and the patients with additional background retinopathy as group D. Similarly, Figure 2 shows the total arterial cross-sections measured in the patients and in the controls. The results are summarized in Table 2. Arterial diameters at the laser Doppler measurement sites were $132 \pm 17 \mu\text{m}$ (mean \pm SD) in the 39 patients with diabetes and $132 \pm 15 \mu\text{m}$ in the 13 controls without diabetes. Centerline blood speed was $4.1 \pm$

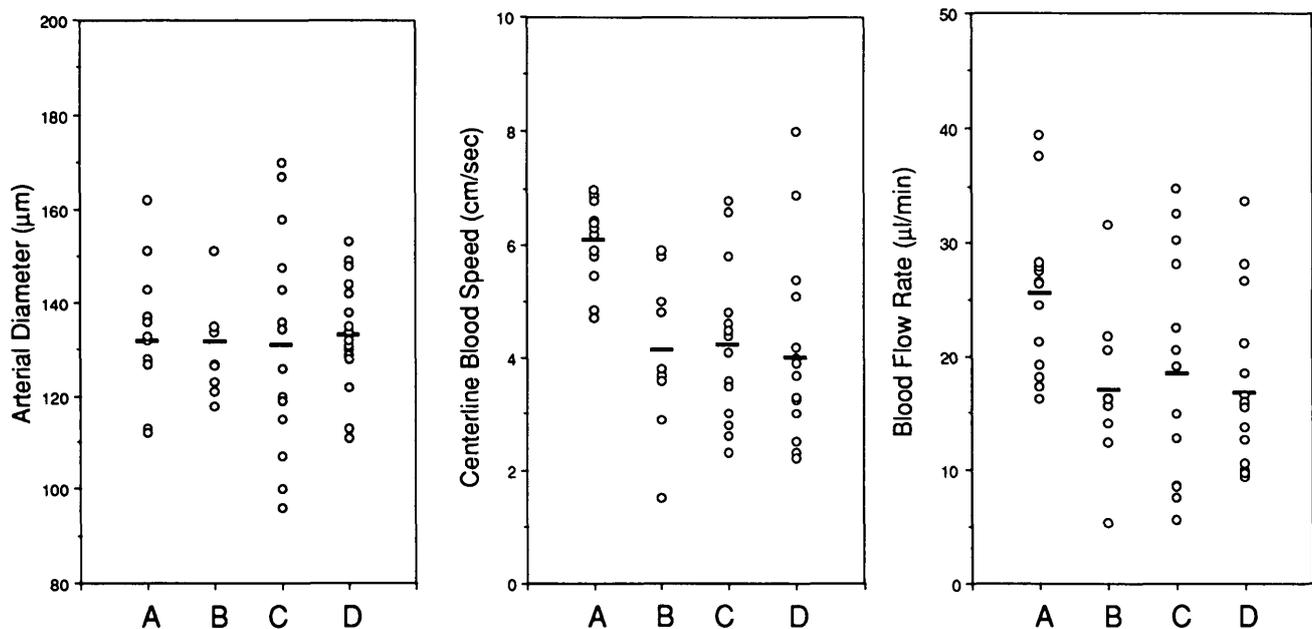


FIGURE 1. Arterial diameter, centerline blood speed, and blood flow rate measured in a major temporal retinal artery in (A) controls without diabetes, (B) patients with no retinopathy, (C) patients with 1 to 10 microaneurysms only, and (D) patients with additional background retinopathy. Lines indicate mean values.

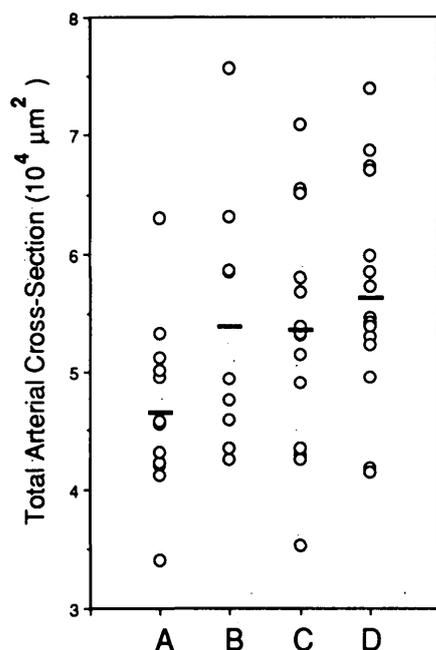


FIGURE 2. Total retinal arterial cross-section measured in (A) controls without diabetes, (B) patients with no retinopathy, (C) patients with 1 to 10 microaneurysms only, and (D) patients with additional background retinopathy. Lines indicate mean values.

1.5 cm/sec in the patients and 6.1 ± 0.7 cm/sec in the controls, a statistically significant 33% difference. The corresponding blood flow rate in the measured artery was 17.5 ± 8.2 μl/min in the patients and 25.5 ± 7.2 μl/min in the controls, a statistically significant 31% difference. Arterial velocity pulsatility was 2.88 ± 0.36 in the patients and 3.29 ± 0.15 in the controls, a statistically significant (*P* = 0.0002) 12% difference. Total arterial cross-section was [5.5 ± 1.0] × 10⁴ μm² in the patients and [4.7 ± 0.7] × 10⁴ μm² in the controls, a

statistically significant 17% difference. Estimated central retinal artery blood flow was 70 ± 30 μl/min in the patients and 81 ± 16 μl/min in the controls; the difference between patients and controls was not statistically significant.

Subgroup Comparisons

Centerline blood speed was significantly (31% to 34%) lower in each subgroup with diabetes than in controls. The corresponding blood flow rate in the measured artery in group B was 33% lower than in the controls (*P* = 0.045). In group D, it was 35% lower than in the controls (*P* = 0.009). Total arterial cross-section in group D, however, was 19% higher than in the controls (*P* = 0.007). Arterial velocity pulsatility was significantly lower in each subgroup with diabetes than in controls. In group B, pulsatility was 2.84 ± 0.27; in group C, it was 2.85 ± 0.40; and in group D, it was 2.92 ± 0.39. There were no significant differences in estimated central retinal artery blood flow between any of the subgroups with diabetes and the controls. There were no significant differences in arterial diameter, centerline blood speed, measured blood flow rate, velocity pulsatility, total arterial cross-section, or estimated central retinal artery blood flow between the subgroups with diabetes. There were no statistically significant differences in blood flow rate related to sex, eye studied, or superior versus inferior vessels measured in the patients or in the controls.

Blood Speed, Cross-Section, and Duration of Diabetes

Multiple linear regression analysis was used to determine if the low centerline blood speeds and high total arterial cross-sections measured in the patients with diabetes were related to patient age, mean blood pres-

TABLE 2. Laser Doppler and Arterial Cross-Section Measurements

| | Control Group (n = 13) | Diabetic Group (n = 39) | Diabetic Subgroups | | |
|--|---------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| | | | B (n = 9) | C (n = 14) | D (n = 16) |
| Arterial diameter (μm) | 132 ± 15 | 132 ± 17 (NS)* | 132 ± 12 (NS)† | 131 ± 24 (NS)† | 134 ± 12 (NS)† |
| Centerline blood speed (cm/sec) | 6.1 ± 0.7 | 4.1 ± 1.5 (<i>P</i> = 0.0001)* | 4.1 ± 1.4 (<i>P</i> = 0.0009)† | 4.2 ± 1.4 (<i>P</i> = 0.0009)† | 4.0 ± 1.7 (<i>P</i> = 0.0006)† |
| Blood flow rate (μl/min) | 25.5 ± 7.2 | 17.5 ± 8.2 (<i>P</i> = 0.003)* | 17.1 ± 7.3 (<i>P</i> = 0.045)† | 18.5 ± 9.9 (NS)† | 16.7 ± 7.4 (<i>P</i> = 0.009)† |
| Total arterial cross-section (10 ⁴ μm ²) | 4.7 ± 0.7 | 5.5 ± 1.0 (<i>P</i> = 0.007)* | 5.4 ± 1.1 (NS)† | 5.4 ± 1.1 (NS)† | 5.6 ± 0.9 (<i>P</i> = 0.007)† |

Values are mean ± SD.

B = no retinopathy; C = microaneurysms only (1-10); D = microaneurysms + additional background retinopathy.

* Comparison with control group (two-tailed unpaired *t*-test).

† Comparison with control group (two-tailed unpaired *t*-test with Bonferroni adjustment).

sure, duration of diabetes, glycosylated hemoglobin level, heart rate, daily insulin dosage, intraocular pressure or, in the case of blood speed, the arterial diameter at the laser Doppler measurement site. Table 3 shows the results with centerline blood speed as the dependent variable. With all the independent variables in the model, only duration of diabetes was significant. The regression coefficient was negative, indicating that blood speed decreases with increasing duration of diabetes. The regression coefficient for mean blood pressure was also negative, but the correlation was highly nonsignificant. Stepwise elimination of nonsignificant variables led to an optimum model ($R^2 = 0.15$, $P = 0.05$) that included only duration of diabetes (coefficient = -0.152 ± 0.065 , mean \pm SE, $P = 0.03$) and arterial diameter (coefficient = 0.027 ± 0.015 , $P = 0.08$). Figure 3 shows the centerline blood speeds plotted as a function of only the duration of diabetes.

Table 4 shows the results of multiple linear regression analysis with total arterial cross-section as the dependent variable. Arterial diameter at the laser Doppler measurement site is not, of course, an independent variable in this case. Once again, with all the independent variables in the model, only duration of diabetes was significant. In this case, however, the regression coefficient is positive, indicating that total arterial cross-section increases with increasing duration of diabetes. Stepwise elimination of nonsignificant variables led to an optimum model ($R^2 = 0.19$, $P = 0.006$) that included only duration of diabetes (coefficient = 1128 ± 390 , $P = 0.006$). Figure 4 shows the total arterial cross-section plotted as a function of the duration of diabetes.

DISCUSSION

There are two main findings of this study: Total retinal arterial cross-section was, on average, 17% larger in the patients with diabetes than in the controls without diabetes, and centerline blood speed was, on average, 33% lower in the patients than in the controls in retinal arteries of the same diameter.

TABLE 3. Results of Multiple Linear Regression Analysis—Dependent Variable: Centerline Blood Speed

| Independent Variable | Regression Coefficient | Standard Error | P Value |
|----------------------|------------------------|----------------|---------|
| Age | -0.006 | 0.061 | 0.92 |
| Blood pressure | -0.011 | 0.034 | 0.75 |
| Diameter | 0.026 | 0.018 | 0.16 |
| Duration | -0.175 | 0.077 | 0.03 |
| HbA1c | 0.011 | 0.116 | 0.93 |
| Heart rate | 0.017 | 0.025 | 0.52 |
| Insulin | -0.004 | 0.016 | 0.81 |
| Intraocular pressure | 0.069 | 0.09 | 0.45 |

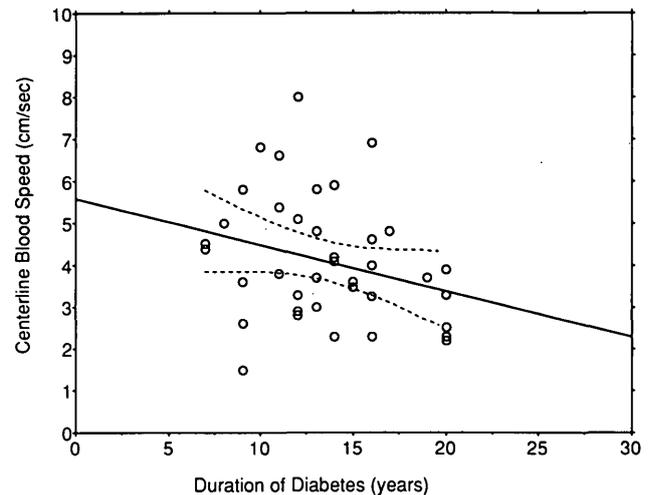


FIGURE 3. Centerline blood speed measured in major temporal retinal arteries plotted as a function of the duration of diabetes. Solid line represents the linear regression fit to the data. Dashed lines represent the upper and lower 95% confidence interval bounds about the fit.

The results on arterial cross-section are consistent with the findings of Skovborg et al.,²⁸ who reported that both retinal arteries and retinal veins in people with diabetes were dilated compared to those in controls. More recently, Grunwald et al.^{9,17} also reported that retinal vein diameters and total venous cross-sections were larger in patients with diabetes than in normals, and that these increases were already present in patients with the mildest form of retinopathy. Our arterial diameter measurements were obtained by projection micrometry²⁵ from monochromatic fundus photographs taken without synchronization to the cardiac cycle. Nevertheless, the coefficient of variation of arterial diameter measurements in the subgroup of patients in whom reproducibility was studied was small (mean = 3%). The cyclic variation of retinal arterial diameter with the cardiac cycle is small. Delori and Fitch²⁹ have shown that arterial diameter varies, on average, by $2.3\% \pm 0.7\%$ between maximum and minimum during the cardiac cycle.

The positive correlation between total arterial

TABLE 4. Results of Multiple Linear Regression Analysis—Dependent Variable: Total Arterial Cross-Section

| Independent Variable | Regression Coefficient | Standard Error | P Value |
|----------------------|------------------------|----------------|---------|
| Age | 76 | 362 | 0.83 |
| Blood pressure | -153 | 198 | 0.45 |
| Duration | 935 | 419 | 0.03 |
| HbA1c | 546 | 670 | 0.42 |
| Heart rate | -196 | 151 | 0.20 |
| Insulin | -72 | 94 | 0.45 |
| Intraocular pressure | 539 | 536 | 0.32 |

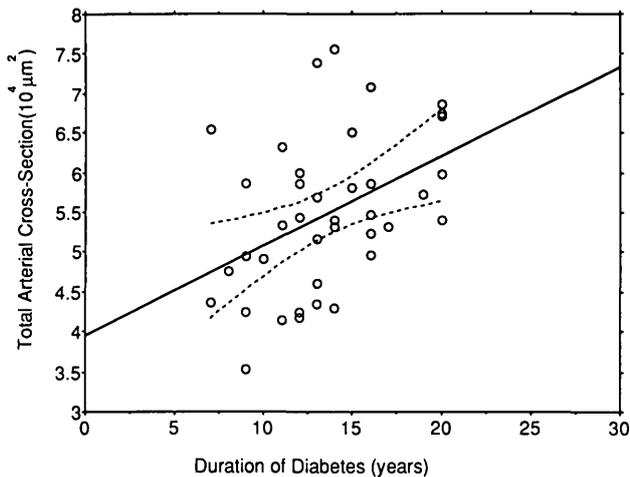


FIGURE 4. Total retinal arterial cross-section plotted as a function of the duration of diabetes. Solid line represents the linear regression fit to the data. Dashed lines represent the upper and lower 95% confidence interval bounds about the fit.

cross-section and duration of diabetes is also consistent with the findings of Skovborg et al,²⁸ who reported a correlation between duration of diabetes and retinal vein diameter. There were large patient-to-patient differences in arterial cross-section, however, and our correlation analysis, though statistically significant, showed that only approximately 20% ($R^2 = 0.19$) of the variability was related to duration of diabetes.

The arterial diameters at the laser Doppler measurement sites were, on average, the same in the patients with diabetes as in the controls. As described above, these arteries were chosen to facilitate the laser Doppler measurement. Clearly, these chosen arteries represented a smaller fraction of the total cross-section in the patients with diabetes than in the controls.

The reduction in centerline blood speed, 33% on average, was substantial and occurred in each subgroup of patients with diabetes. In the subgroup of patients in whom reproducibility was studied, $\pm 50\%$ changes in blood glucose in a given patient were related to $\pm 10\%$ changes in blood speed. Thus, blood glucose changes appear to modify the retinal arterial blood speed: Higher blood glucose yields slightly higher blood speed. A similar relationship between retinal blood speed and blood glucose was reported by Grunwald et al³⁰ and by Sullivan et al³¹ using laser Doppler techniques. Our basic finding, however, is that even in the presence of elevated blood glucose, retinal arterial blood speed is lower in the patients with diabetes than in the controls with diabetes.

As is the case of total arterial cross-section, there were large patient-to-patient differences in centerline blood speed. Although our correlation analysis showed a statistically significant result, only 15% ($R^2 = 0.15$) of the variability was related to duration of diabetes. It is likely that correction for blood glucose dif-

ferences may have increased the correlation coefficient between blood speed and duration of diabetes.

Arterial velocity pulsatility was significantly lower in each subgroup with diabetes than in the controls. The value measured in the control group (3.29 ± 0.15) agrees with our previous result (3.23 ± 0.17) measured in a similar group.⁷ We had also previously shown that pulsatility was significantly lower than normal in patients with diabetes who had mild background retinopathy.⁷

The blood flow rate in the major retinal arteries in the patients with diabetes is determined by the competing effects of dilated arteries and reduced blood speeds. The blood flows shown in Figure 1 and summarized in Table 2 were measured in arteries that represented a smaller fraction of the total cross-section in the patients with diabetes than in the controls. Therefore, the reduced blood flows in the measured arteries are not directly indicative of differences in total retinal blood flow. As described above, the central retinal artery blood flow was estimated in each eye using an iterative procedure. The value estimated in the control group ($81 \pm 16 \mu\text{l}/\text{min}$) agrees with our previously reported value of directly measured total retinal blood flow ($80 \pm 12 \mu\text{l}/\text{min}$) in a similar group. There was no significant difference in estimated central retinal artery blood flow between the patients with diabetes and the controls. Dilation of the larger retinal vessels with the accompanying decrease in vascular resistance to flow in these vessels appears to balance an increase in resistance to flow at the level of the smaller retinal vessels.

The likely sites of increased resistance are the retinal capillaries and the pre-capillary arterioles. Capillary or arteriolar obstruction is likely due to abnormalities of the endothelial cells lining the vessel wall, or to blood rheologic abnormalities, or to a combination of both of these factors.¹

Blood rheologic abnormalities—including decreased red cell deformability,³² increased red cell³³ and platelet³⁴ aggregation—and increased plasma viscosity³⁵ have been widely reported in patients with diabetes. A more intrinsic abnormality, however, appears to be endothelial cell dysfunction. Abnormal levels of prostacyclin,³⁶ von Willebrand factor,¹ and plasmin activator³⁷ have been measured in patients with diabetes. These abnormalities would tend to compromise the antithrombotic and fibrinolytic activity of the vascular endothelium, leading to the obstruction of retinal capillaries.

When comparing the results of our study to findings previously reported by other investigators, it is important to consider the species studied, the stage of diabetes, the techniques used for measurement, and the sites of measurement in the retina. Several investigators have studied the retinal circulation in diabetic animal models. Tilton et al¹² and Pugliese et al¹³ found

increased retinal blood flow in rats that were diabetic for 6 weeks based on microsphere impaction measurements. More recently, Cringle et al¹⁹ studied the same animal model at 5 weeks of diabetes using the hydrogen clearance technique and also found an average increase in retinal blood flow. In addition, they found that site-to-site differences in blood flow in the same eye were much larger in the group with diabetes than in the control group. Bursell et al¹⁶ used the fluorescein dye dilution technique to study the same animal model at 1 week of diabetes. They found that the mean arteriovenous circulation time was increased in the diabetic animals. Small et al¹⁰ used the microsphere impaction technique to study retinal blood flow in dogs at 5 months of diabetes. They found decreased blood flow. The differences in species and in the duration of diabetes may explain the difference between this result and the results on diabetic rats also measured with the microsphere technique.

The retinal circulation in patients with diabetes was originally studied using fluorescein dye dilution techniques.^{5,6} However, as noted by Fallon et al⁸ and by Grunwald et al,⁹ the conditions required for the proper application of the technique are not likely to be present in the diabetic retinal vasculature. Other investigators have used the blue field entoptic simulation technique to study the speed of leukocytes flowing in macular capillaries. Fallon et al⁸ found increased speeds in patients with background retinopathy. Follow-up studies by Rimmer et al¹¹ on the same patients showed a progressive slowing of the speeds over an interval of several years. More recently, Sinclair¹⁵ reported an increase in the leukocyte speed in patients with diabetes as well as a decrease in the density of the entoptically perceived leukocytes. He concluded that the findings were consistent with the concept that in diabetes, capillary obstruction may focally occur within the retina associated with vasodilation in the adjacent microvasculature. The findings of Cringle et al¹⁹ of large site-to-site differences, described above, support this conclusion. Arend et al¹⁴ used the scanning laser technique to measure the speed of red blood cell rouleaux flowing in perifoveal capillaries and to quantitate perifoveal intercapillary areas in patients with diabetes. They found reduced flow speeds and increased intercapillary areas in the patients. The finding of increased area is consistent with Sinclair's report of decreased leukocyte density. The differences between leukocyte speed and red cell rouleaux speed, however, have not been explained.

In contrast to the capillary-level measurements obtained using the blue field or scanning laser techniques, the laser Doppler technique measures the circulation in a large retinal sector. Thus, measurements on a large retinal artery or retinal vein represent the net effect of the phenomena occurring at the level of the smaller vessels. Using the laser Doppler technique,

Grunwald et al⁹ reported reduced retinal arterial and venous blood speeds as well as enlarged retinal veins in patients with diabetes with background retinopathy. Calculated blood flow did not differ from normal. Patel et al,¹⁸ also using the laser Doppler technique, reported no differences in venous blood speed in patients with background retinopathy compared to controls without diabetes, but they did report enlarged retinal veins in the patients. The calculated blood flow was higher than normal in the patients with diabetes. Grunwald et al¹⁷ have also recently reported abnormally elevated retinal blood flow in poorly controlled patients with diabetes. The results of our study are consistent with the original report of Grunwald et al.⁹ Both studies found that the major retinal vessels were enlarged in patients with diabetes and that the blood speed was abnormally low in these vessels.

In summary, retinal circulatory alterations appear to be sensitive indicators of microvascular pathology. Indeed, in the patients studied, arterial blood speeds were already low before the clinical appearance of retinopathy. The effectiveness of therapies aimed at forestalling the onset or retarding the development of retinopathy should be able to be assessed by measuring their effect on retinal circulation.

Key Words

retinal circulation, patients with type 1 diabetes, laser doppler technique, retinal arterial cross-section, retinal arterial blood speed

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