Retinal haemodynamics in patients with early diabetes mellitus

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Abstract

Aims/Background—The retinal circulation was investigated in a group of 19 patients with insulin dependent diabetes mellitus with less than 4 years of disease duration and no evidence of diabetic retinopathy. Results of these patients were compared with those of 16 age-matched normal controls.

Methods—Venous diameter (D) was measured from monochromatic fundus photographs. Maximum erythrocyte velocity (V_{max}) was assessed by bidirectional laser Doppler velocimetry in the major retinal veins of one eye of each subject. Total volumetric blood flow rate (Q_T) was calculated by adding the flow rates of the major retinal veins.

Results—Average Q_T was 12% larger than normal in diabetic patients (one tailed, non-paired Student's *t* test, $p < 0.05$). A statistically significant correlation was observed between Q_T and disease duration ($r = 0.35$, $p < 0.04$). Patients with longer disease duration tended to have somewhat larger Q_T . The average retinal vascular regulatory responses to hyperoxia were not significantly different from normal in diabetic patients. In these patients, however, higher blood glucose levels were associated with decreased regulatory responses to hyperoxia.

Conclusions—Patients with diabetes mellitus of relatively short duration have mildly increased Q_T , suggesting that increased blood flow may play an early role in the development of diabetic retinal microangiopathy.

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Although a number of studies have reported alterations of retinal haemodynamics and its regulation¹⁻¹⁶ in patients with long standing diabetes mellitus, relatively little is known about these changes in the earlier stages of the disease.

Information on these changes in the early stages of diabetes mellitus is important because

it may help us elucidate their role in the development of the morphological changes typical of diabetic retinopathy. Evidence of early haemodynamic abnormalities would support the hypothesis that such changes play an aetiological role in the development of diabetic retinopathy and are not just the result of these morphological changes.

The purpose of this paper was to study the retinal circulation and its regulation to hyperoxia in a group of patients who had diabetes mellitus for less than 4 years. Retinal volumetric blood flow rate was assessed by a combination of laser Doppler velocimetry and monochromatic fundus photography.

Materials and methods

Nineteen patients with insulin dependent (type I) diabetes mellitus (age range 15 to 37 years; mean (SD), 27 (7) years, 10 males and nine females) were included in this study. Duration of diabetes was 4 years or less in all subjects (range 4 months to 4 years; 2 (1) years). All patients had normal external, slit-lamp and dilated funduscopic eye examinations and no evidence of diabetic retinopathy. Excluded from the study were patients who had a history of systemic hypertension, substance abuse, or ocular disease. Average glycosylated haemoglobin (GHb) measured by affinity chromatography was 8.2% (2%). Blood glucose was determined from finger capillary blood samples using an Accu-Check blood glucose monitor (Boehringer Mannheim, IN, USA). The average blood glucose at the time of retinal volumetric blood flow determination was 167 (107) mg/dl (Table 1).

Findings in patients with diabetes mellitus were compared with those of 16 normal volunteers (age range 14 to 45 years, 29 (8) years, 10 males and six females) without systemic or ocular diseases. Characteristics of normal subjects and diabetic patients are provided in Table 1. All eyes studied has a best refracted visual acuity of 6/7.5 or better and an intraocular pressure < 21 mm Hg.

After a detailed explanation of the procedures, all subjects were asked to sign an appropriate consent form approved by the internal review board of our institution.

Only one eye, chosen at random, was investigated in each subject. After pupil dilatation with tropicamide 1% and phenylephrine hydrochloride 10%, a Polaroid (Cambridge, MA, USA) colour fundus photograph of the posterior fundus was obtained to localise the sites of bidirectional laser Doppler velocimetry (BLDV) measurements. These measurements of the maximum, centre line erythrocyte

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Table 1 Study characteristics

	Normal		Diabetes	
	Mean (SD)	Range	Mean (SD)	Range
Age (years)	29 (8)	14-45	27 (7)	15-37
Disease duration (years)	—	—	2 (1)	0-2-4
Glycosylated haemoglobin (%)	—	—	8.2 (2.0)	5.6-12.1
Blood glucose (mg/dl)	—	—	167 (107)	47-449
Mean brachial blood pressure (mm Hg)	87.9 (12.9)	56-109	92.3 (16.2)	70-132
Intraocular pressure (mm Hg)	14.0 (1.0)	12-17	14.3 (1.7)	12-18
Perfusion pressure (mm Hg)	45.6 (6.8)	36-59	47.5 (12.0)	33-73

Table 2 Total venous cross section (S_T), total measured volumetric blood flow (Q_M), and corrected total volumetric blood flow (Q_T) in normal subjects

Subject	No of veins Q measured	% S_T	S_T ($\text{cm}^2 \times 10^{-5}$)	Q_M ($\mu\text{l}/\text{min}$)	Q_T ($\mu\text{l}/\text{min}$)
1	6	100	105.9	49.5	49.5
2	4	100	62.5	35.1	35.1
3	5	100	79.3	36.7	36.7
4	4	100	88.3	35.7	35.7
5	5	100	91.5	42.2	42.2
6	4	100	86.1	37.3	37.3
7	6	100	101.2	40.6	40.6
8	5	100	66.8	31.6	31.6
9	5	100	93.9	42.5	42.5
10	5	100	87.7	43.0	43.0
11	3	89	63.5	32.3	36.3
12	3	76	59.4	23.9	31.4
13	5	100	82.6	37.4	37.4
14	4	100	85.0	42.2	42.2
15	4	100	96.0	40.0	40.0
16	4	100	88.4	35.0	35.0
Mean	4.5	98	83.6	37.8	38.5
SD	0.9	6	14.0	5.9	4.7

% S_T =Sum of cross section of all veins from which volumetric blood flow measurements were obtained expressed as a percentage of the cross section of all visible veins (S_T).

velocity ($V_{\max}$) were obtained in major retinal veins.

Velocity was measured on straight portions of veins at a distance of less than 2 disc diameters from the centre of the optic nerve head. We avoided sites close to venous junctions or arteriovenous crossings and those where two vessels lay close to each other. The location of the measurement site was marked on the Polaroid photograph for later reference. We used flow measurements from veins instead of arteries because the minimal flow pulsatility in these vessels permitted a more accurate determination of the average velocity.^{8,17}

During the BLDV measurements, an area of the posterior retina (30° in diameter) was illuminated at a wavelength of 570 nm with a retinal irradiance of about $0.30 \text{ mW}/\text{cm}^2$. The levels of laser light used during the experiments were within the maximum permissible levels for extended sources.¹⁸

Fundus photographs were taken in monochromatic light at 570 nm using a Zeiss (Oberkochen, Germany) fundus camera and

Plus-X pan film (Eastman Kodak, Rochester, NY, USA). Intraocular pressure was measured by applanation tonometry, and brachial artery blood pressure was obtained by sphygmomanometry.

Volumetric blood flow rate (Q) was calculated as described previously^{6,8} as $V_{\text{mean}} \pi D^2/4$, where mean blood velocity (V_{mean}) was calculated as $C V_{\max}$. A value for C equal to $1/1.6$ was used,¹⁹ and the relation between $V_{\max}$ and V_{mean} was assumed to be the same in normal and diabetic subjects. This assumption has been discussed previously.⁸ The venous diameter at the site of BLDV measurement, D (determined from projected photographic negatives using a calliper), was an average obtained from six photographs. Total venous cross section (S_T) was calculated by adding the cross section of all visible veins observed around the disc.

BLDV measurements of $V_{\max}$ and therefore, Q , were not obtained in all veins in all studied eyes. To include those vessels in which $V_{\max}$ and, therefore, Q was not determined, a total volumetric blood flow rate (Q_T) was calculated based on an estimation of flow rates for the vessels for which $V_{\max}$ was not obtained, using the formula: $Q_T = (Q_M/\%S_T) \times 100$ (Tables 2 and 3), where Q_M represents the sum of the blood flows of all vessels in which $V_{\max}$ measurements were obtained and the % S_T values represent the sum of the cross section of all veins from which $V_{\max}$ and, therefore, volumetric blood flow measurements were obtained, expressed as a percentage of the cross section of all visible veins present in each studied eye. We have previously demonstrated that this approach provides a close estimation of Q_T in normal and diabetic subjects.¹³

Measurements of $V_{\max}$ and D were done on a major retinal vein during room air breathing and during 4–6 minutes of breathing 100% oxygen at atmospheric pressure. Oxygen was provided through a Rudolph valve attached to a mouthpiece. Breathing through the nose was prevented with a nose clip. The retinal vascular regulatory response to hyperoxia (R_Q), defined as the percentage decrease in Q between air and 100% oxygen breathing, was calculated using the formula: $R_Q = 100 (Q_{\text{air}} - Q_{\text{ox}})/Q_{\text{air}}$. A similar formula was used to calculate the regulatory response to hyperoxia of D (R_D) and $V_{\max}$ ($R_{V_{\max}}$).

All measurements of D were done by one examiner, and all $V_{\max}$ determinations were done by another one. Both examiners were masked with regard to the results obtained by the other and the clinical status of the subject measured.

Mean brachial artery blood pressure (BP_m) was calculated as $BP_m = BP_d + 1/3 (BP_s - BP_d)$, where BP_s and BP_d are the brachial artery systolic and diastolic pressures. Perfusion pressure (PP) was calculated as $PP = 2/3 BP_m - IOP$, Where IOP was the intraocular pressure determined by applanation tonometry.

Unpaired one tailed Student's t tests and correlation analysis based on r^2 values obtained from regression fits of the data were used in the evaluation of the results. The Wilk-Shapiro

Table 3 Total venous cross section (S_T), total measured volumetric blood flow (Q_M), and corrected total volumetric blood flow (Q_T) in patients with diabetes mellitus

Subject	Disease duration (years)	No of veins measured	% S_T	S_T ($\text{cm}^2 \times 10^{-5}$)	Q_M ($\mu\text{l}/\text{min}$)	Q_T ($\mu\text{l}/\text{min}$)
1	1.5	6	100	118.4	56.0	56.0
2	1.0	4	100	100.9	48.1	48.8
3	3.0	7	100	143.4	67.1	67.1
4	4.0	4	87	61.2	31.3	36.0
5	3.0	4	85	83.8	40.1	47.1
6	1.5	4	100	76.7	30.4	30.4
7	2.5	4	100	72.6	43.1	43.1
8	2.0	5	100	109.4	45.2	45.2
9	4.0	4	92	125.3	47.7	51.8
10	3.0	4	100	93.1	36.6	36.6
11	0.5	2	55	70.5	21.0	38.2
12	2.5	2	44	91.1	19.6	44.4
13	2.5	5	100	101.6	44.6	44.6
14	0.3	5	100	78.7	37.0	37.0
15	3.0	6	100	93.3	45.8	45.8
16	2.0	5	100	80.4	28.6	28.6
17	3.0	4	100	99.5	39.1	39.1
18	0.2	4	100	83.5	40.4	40.4
19	4.0	5	100	93.9	41.6	41.6
Mean	2.3	4.4	92.8	93.5*	40.2	43.3*
SD	1.2	1.2	16	20.3	11.3	8.9

% S_T =Sum of cross section of all veins from which volumetric blood flow measurements were obtained expressed as a percentage of the cross section of all visible veins (S_T).

*Significantly different from normal by one paired Student's t test, $p < 0.05$.

Figure 1 Corrected total volumetric blood flow (Q_T) versus disease duration in all study subjects. A statistically significant correlation was observed ($r=0.35$, $p<0.04$; $Q_T=38.8+1.84$ disease duration).

test was used to assess the normal distribution of the data. We used $p<0.05$ for statistical significance. One tailed Student's t test was used because we had previously shown, in diabetic patients with longer disease duration and diabetic retinopathy, that blood flows were increased.¹³

Results

Table 1 shows a comparison of the characteristics of patients with diabetes and normal subjects. There were no statistically significant differences in age, BP_m , intraocular pressure, or perfusion pressure between diabetic patients and normal subjects.

Values of total measured Q (Q_m), obtained by adding the Q of two to six vessels in which BLDV determinations were done in each eye, are summarised in Table 2 for normal subjects and in Table 3 for diabetic patients.

Average estimated total retinal blood flow Q_T in our diabetic patients was 43.3 (SD 8.9) $\mu\text{l}/\text{min}$, a value that was significantly higher than normal (38.5 (4.7) $\mu\text{l}/\text{min}$) by about 12% (one tailed, non-paired Student's t test adjusted for unequal variance, $p<0.05$). Furthermore, a statistically significant positive correlation ($r=0.35$, $p<0.04$, Fig 1) was observed between Q_T and disease duration when all subjects were included in the analysis. In other words, although the correlation was not very strong, longer disease duration was associated with increased Q_T .

As can be seen in Tables 2 and 3, the variability of the Q_T data in diabetics was larger than that of normals. An F test indeed showed that the variance of Q_T in diabetics was significantly larger than normal (F test, $p<0.02$).

Average S_T was 93.5 (20.3) $\text{cm}^2 \times 10^{-5}$ in diabetic patients, a value that was larger than that of normal subjects (83.6 (14) $\text{cm}^2 \times 10^{-5}$) by about 12% (one tailed, non-paired Student's t test, $p<0.05$). A significant correlation was observed between S_T and duration of the disease when all subjects were included in the analysis ($r=0.34$, $p<0.05$, Fig 2). Subjects with longer disease duration tended to have a somewhat larger S_T , although the association was not strong.

Average V_{max} in the largest retinal vein of each eye was not significantly different from normal (1.79 (0.22) cm/s) in diabetic eyes (1.72 (0.39) cm/s). No significant correlation was detected between V_{max} in the largest retinal vein and disease duration ($r=0.05$, $p<0.1$).

Regarding the retinal vascular regulatory responses to hyperoxia, we found in diabetic patients average R_D of -11.6% (4.5%), $R_{V_{\text{max}}}$ of -35.2% (8.4%), and R_Q of -49.2% (7.8%), values which were not significantly different from those of normal subjects ($R_D=-12.6\%$ (4.1%), $R_{V_{\text{max}}}=-38.2\%$ (10%), and $R_Q=-53.0\%$ (8.8%)).

In diabetic patients, a statistically significant correlation was observed between R_Q and blood glucose measured at the time of the experiment ($r=0.53$, $p<0.03$). Higher blood glucose levels were associated with decreased regulatory responses to hyperoxia. No significant correlation was observed between blood glucose and Q_T .

No significant correlations were detected between any of the haemodynamic variables measured and age, glycosylated haemoglobin, systemic blood pressure, intraocular pressure, or perfusion pressure.

Discussion

Our results suggest that patients with early diabetes mellitus of less than 4 years' duration, have a small average increase in Q_T of about 12%. This increase is in the same direction as the changes reported previously by Kohner *et al*,² Grunwald *et al*,¹³ and Patel *et al*¹² in patients with more prolonged diabetes mellitus and diabetic retinopathy.

On the other hand, Fekete *et al*,¹⁵ using laser Doppler velocimetry, measured retinal blood flow in a single major retinal artery of diabetic patients and reported that the average blood flow was decreased from normal in diabetic patients with retinopathy. In this study, however, the average diameter of the single artery in which blood flow was measured in diabetic patients was very similar to that obtained in normals, whereas the average total arterial cross section of diabetic patients was 17% larger than the normal. These results raise a

Figure 2 Total venous cross section (S_T) versus disease duration in all study subjects. A statistically significant correlation was observed ($r=0.34$, $p<0.05$; $S_T=83.8+4.2$ disease duration).

question as to a possible bias in the selection of the single artery that was chosen for blood flow measurement in diabetic patients, a factor that would affect their blood flow measurement.

Data obtained in animal models of diabetes mellitus have shown diverging results. Tilton *et al*²⁰ reported increases in retinal blood flow in streptozotocin induced diabetic rats of 6 weeks' duration using the microsphere technique. Increases in retinal blood flow were also reported by Cringle *et al*²¹ in the same model using hydrogen clearance polarography. On the other hand, Small *et al*²² found in alloxan induced diabetic dogs of 6 months' duration a decreased retinal blood flow using the microsphere technique. Bursell *et al*,²³ using video fluorescein angiography in a streptozotocin induced diabetic rat model of 1 week's duration, found an increase in mean circulation time which suggested a decrease in retinal blood flow.

A direct comparison of our measurements in human diabetes of less than 4 years' duration and those of the above mentioned animal models cannot be easily made. It is not known how accurately these short term animal models may reflect the changes that occur in the retinal vasculature of human diabetics. Species differences may lead to differences in retinal haemodynamic changes. In addition, in these animal models, it is difficult to separate the effects of the diabetic state and those produced by very high blood glucose levels,²⁴ which are known to lead to increased retinal blood flow.^{9 25 26}

The mild increase in retinal volumetric flow rate observed in our study, which is present early in the disease and before the development of clinically detectable retinopathy, suggests that retinal haemodynamic changes may have a role in the development of retinal morphological abnormalities and may not be just the result of them. This early increase in blood flow lends support to the haemodynamic hypothesis^{27 28} which postulates that increased blood flow through a vascular bed may play a role in the development of diabetic microangiopathic features such as increased vascular permeability and capillary closure.

Although clinically detectable retinopathic changes were not present in these patients, it is possible that subtle changes in the vasculature such as basement membrane thickening²⁹ and/or endothelial functional changes could affect retinal blood flow. In addition, changes in the rheological properties of blood such as abnormalities in the fibrinolytic response,^{30 31} increases in blood thixotropy,³² erythrocyte aggregation,³³⁻³⁵ blood viscosity at low shear rates^{36 37} and plasma viscosity,³⁸ and decreases in erythrocyte and leucocyte deformability,³⁹⁻⁴¹ presumed to occur in diabetes mellitus, could also contribute to the changes in blood flow observed.

Diabetic patients had significantly larger variability in Q_T than normal subjects. This larger variability was due to the fact that the disease produced an increase in Q_T that was associated with increased disease duration.

Our patients with diabetes mellitus also showed an average increase in S_T of about 12%

above normal, a result that is similar to the retinal vasodilatation previously reported by Skovborg *et al*,⁴² Grunwald *et al*,⁸ Feke *et al*,¹⁵ Patel *et al*¹² in patients with diabetes of longer disease duration and diabetic retinopathy. Increased vascular diameters in the diabetic patients was the main factor that produced an increase in Q_T , since we found a very small and not statistically significant change in average V_{max} .

V_{max} in the largest retinal vein of each eye was slightly lower than normal. Although this change was not statistically significant, its direction was similar to the decrease in V_{max} previously reported in patients with longer disease duration.^{8 15 16}

Because we did not find in this study any significant correlations between blood glucose, glycosylated haemoglobin, blood pressure or perfusion pressures and Q_T , we cannot draw conclusions about any possible roles of any of these variables in the increase in Q_T in our diabetic patients.

R_D , $R_{V_{max}}$ and R_Q in diabetic patients were very similar to those of normals, strongly suggesting that at this early stage of the disease the regulatory responses to hyperoxia are not greatly affected by the disease process.

We have previously shown that R_Q decreases with the progression of diabetic retinopathy^{6 13} and improves following panretinal photocoagulation therapy,⁴³ in particular in those patients that show a positive response to treatment with disappearance of their neovascular proliferation.¹⁰ Based on these results, we have hypothesised that the decreased regulatory responses to hyperoxia may be related to the degree of retinal hypoxia.^{6 9 11} The lack of any significant abnormalities in R_Q in our diabetic subjects suggests that retinal hypoxia may not be an important factor at this stage of the disease.

The significant correlation present between the blood glucose and R_Q suggests that even at this early stage of the disease, elevated blood glucose levels are associated with decreased regulatory responses. These results support our previous report in patients with background diabetic retinopathy⁹ and that of Ernest *et al* in dogs⁴⁴ showing that hyperglycaemia reduces retinal regulatory responses. Decreased regulatory responses may render the retina more vulnerable to changes in blood pressure, intraocular pressure, or changes in levels of inspired gases, a mechanism that could play a role in the development of retinal diabetic microangiopathy.

In summary, our results show that retinal volumetric blood flow is mildly increased in diabetic patients with relatively short disease duration and no diabetic retinopathy. These findings suggest that early retinal haemodynamic alterations may have a role in the development of diabetic retinopathy.

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CER has financial interest in the equipment used in this study. Other authors have no proprietary interest in the development or marketing of this or a competing instrument.

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