Diabetic Glycemic Control and Retinal Blood Flow

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The effect of strict glycemic control on retinal volumetric blood flow rate ($\dot{Q}$) was investigated in 13 insulin-dependent diabetic patients with laser Doppler velocimetry and monochromatic fundus photography. Strict glycemic control was achieved by glucose monitoring and four daily insulin injections. $\dot{Q}$ was determined in a major retinal vein at baseline and then 5 days, 2 mo, and 6 mo after the institution of strict control. Level of retinopathy was assessed from stereocolor fundus photographs taken at baseline and 6 mo. After 6 mo of strict diabetic control, five eyes demonstrated progression (P) by one or more retinopathy levels, and eight eyes showed no progression (NP). At 5 days, there was a significant decrease in $\dot{Q}$ of 1.4 ± 0.9 μl/min ($P < 0.005$) in NP eyes and a nonsignificant increase in $\dot{Q}$ of 1.2 ± 1.7 μl/min in P eyes. Changes in $\dot{Q}$ from baseline observed at 5 days were strongly correlated with changes in retinopathy level at 6 mo ($r = 0.79$, $P < 0.005$). No significant changes in $\dot{Q}$ from baseline were observed at 2 and 6 mo. A lack of decrease in $\dot{Q}$ at 5 days was associated with the progression of retinopathy that occurs in some patients after the institution of strict glycemic control and may serve as a predictor for progression of retinopathy. *Diabetes* 39:602–607, 1990

One of the controversial issues in the treatment of diabetes mellitus is whether a regimen of strict diabetic control (SDC) of blood glucose will delay the development and progression of the vascular complications of this disease (1–15). Although several studies have shown improvements in retinal, renal, and nerve functions after the institution of SDC (7–9,12,16,17), other studies have suggested that SDC produces a transient worsening of diabetic retinopathy in some patients. This phenomenon has been characterized mainly by the appearance of nerve fiber layer infarcts and intraretinal microabnormalities (10–13,18–20).

In a previous study, we showed that an acute insulin-induced normalization in blood glucose is accompanied by a decrease in retinal blood flow (21). We suggested that this decrease in flow is related to the appearance of nerve fiber layer infarcts. In this study, we summarize preliminary results of an ongoing investigation designed to test whether retinal hemodynamic changes are also associated with a more chronic and long-term improvement of blood glucose such as that achieved in patients under a regimen of SDC.

RESEARCH DESIGN AND METHODS

Our study population consisted of 13 patients with insulin-dependent diabetes mellitus whose age ranged between 22 and 38 yr (mean ± SD 30 ± 5 yr). Duration of diagnosed diabetes ranged between 5 and 25 yr (mean ± SD 16 ± 12 yr).

Before the beginning of our study, all patients had glycosylated hemoglobin (GHb) values >3SD above the mean of nondiabetic subjects. Average GHb measured by affinity chromatography at the beginning of the study was 11.4 ± 2.4% (upper limit of the normal range 8%). Average HbA_{1c} level measured at the Diabetes Laboratory of the University of Missouri, Columbia, by high-performance liquid chromatography was 8.8 ± 1.2% at the beginning of the study (upper limit of normal range 6%). Average fasting C-peptide analyzed by radioimmunoassay was 0.15 ± 0.38 ng/ml. All patients had background diabetic retinopathy. The distribution of retinopathy levels in the study eyes is shown in Fig. 1.

Excluded from the study were patients who had *1*) previous treatment with three or more daily injections of insulin or an insulin pump, *2*) insulin resistance requiring a total of >2 U/kg body wt, *3*) three or more documented episodes

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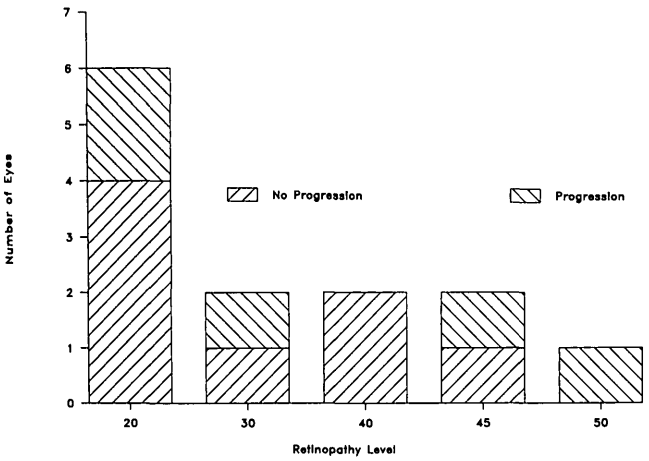

FIG. 1. Distribution of baseline retinopathy level according to Early Treatment of Diabetic Retinopathy Study (24) grading in eyes that showed progression or no progression of retinopathy at end of our 6-mo study.

of diabetic ketoacidosis requiring hospitalization, *4*) history of systematic hypertension, *5*) history of substance abuse, *6*) obesity defined as body weight >130% of ideal body weight, *7*) chronic disease requiring prescription medication that may be changed or discontinued during the study, *8*) severe and recurrent hypoglycemia, *9*) topical ocular medications, *10*) presence of intraocular pathology other than diabetic retinopathy, or *11*) previous laser photocoagulation treatment.

All eyes studied had a best refracted visual acuity of 6/7.5 or better, an intraocular pressure <21 mmHg, and a normal slit-lamp examination. A description of patient characteristics is presented in Table 1. After a detailed explanation of the study protocol, all subjects were asked to sign an appropriate consent form approved by the Internal Review Board of our institution.

Retinal volumetric blood-flow measurements. Only one eye, chosen at random at the beginning of the study, was investigated in each subject. After pupil dilation with a 1% solution of tropicamide and a 10% solution of phenylephrine hydrochloride, a Polaroid color fundus photograph of the posterior fundus was obtained for localization of the sites of bidirectional laser Doppler velocimetry (BLDV) measurements. BLDV measurements of the maximum or centerline erythrocyte velocity (V_{max}) in a main superior or inferior temporal retinal vein were obtained. Velocity was measured on straight portions of veins at a distance <2 disk diameters from the center of the optic nerve head. Sites close to venous junctions or arteriovenous crossings were avoided as were sites where two vessels lay close to each other. The location of the measurement site was marked on the Polaroid photograph for later reference. We chose to perform flow measurements from veins because the minimal flow pulsatility in these vessels permits a more accurate determination of the average velocity (22).

During the BLDV measurements, an area of the posterior retina (30° diam) was illuminated at a wavelength of 570 nm with a retinal irradiance of ~0.03 mW/cm². The levels of laser light used during the experiments were within the maximum permissible levels for extended sources.

Fundus photographs were taken in monochromatic light at 570 nm. Intraocular pressure was measured by applanation tonometry, and brachial artery blood pressure was obtained by sphygmomanometry.

Volumetric blood flow rate ($\dot{Q}$) was calculated as described previously (21,22) as $V_{mean} \cdot \pi D^2/4$, where mean blood velocity (V_{mean}) was calculated as $C \cdot V_{max}$. The constant C equal to 1/1.6 was used, and the relationship between V_{max} and V_{mean} was assumed to remain unchanged during the study. D represents the venous diameter at the site of BLDV measurement determined from projected photographic negatives. D corresponds to an average of the measurements obtained from six photographs.

All measurements of D were performed by one trained examiner, and all V_{max} determinations were done by another examiner. Each examiner was masked with regard to the results of the examiner, status of diabetic control, and status of diabetic retinopathy.

Study protocol. Patients who met our inclusionary criteria had a first session of baseline blood-flow measurement. A second session of baseline blood-flow measurement was performed 3–4 wk later. Immediately after this measurement, patients were hospitalized, and a regimen of SDC of blood glucose similar to that used in the Diabetes Control and Complications Trial (DCCT; 23) was instituted under careful monitoring. Patients were asked to monitor blood glucose levels (finger capillary blood samples determined by an Accu-Check blood glucose monitor, Boehringer Mannheim, Indianapolis, IN) four times daily before their meals and at bedtime. A fifth blood glucose check was performed at 0300 on selected days to safeguard against nocturnal hypoglycemia. Patients self-administered four daily insulin injections with the goal of achieving blood glucose levels that fall within the following guidelines: preprandial, 3.9–6.7 mM; 2 h postprandial, <8.4 mM. Regular insulin was administered before meals and at bedtime. NPH insulin was also given at bedtime in an adequate dose to keep blood glucose in the normal range overnight. Patients met several times with a diabetes dietitian who adjusted their diet and provided further in-depth dietary education.

After ~5 days of hospitalization, patients were released from the hospital, and on the same day, a third session of blood-flow measurement took place. Patients were asked to continue at home the regimen instituted during their hospitalization. Close regular telephone contact was maintained between patients, their treating physician, and the study nurse/coordinator.

The SDC regimen was maintained for 6 mo. During that time, patients were seen on a monthly basis by their treating physician. Changes in insulin doses were made according to records of four daily blood glucose measurements kept

TABLE 1
Patient characteristics

Characteristics	Mean ± SD	Range
Age (yr)	30 ± 5	22–38
Disease duration (yr)	16 ± 6	5–26
Glycosylated hemoglobin (%)	11.4 ± 2.4	9–15
Mean brachial blood pressure (mmHg)	86 ± 11	69–107
Intraocular pressure (mmHg)	16 ± 2	12–19
Perfusion pressure (mmHg)	42 ± 9	30–57

by the patients. GHb levels were also obtained at monthly intervals. Additional sessions of blood-flow measurement were held 2 and 6 mo after the institution of SDC.

Seven standard field stereocolor fundus photographs and fluorescein angiograms were obtained according to the Early Treatment of Diabetic Retinopathy Study (ETDRS; 24) protocol at baseline and at the end of the 6-mo study. Assessment of retinopathy was performed in a masked fashion at the Fundus Photographic Reading Center of the University of Wisconsin. An overall retinopathy level according to the ETDRS grading protocol was assigned to the study eye of each patient at baseline and at the end of the study.

Mean brachial artery blood pressure (BP_m) was calculated as $BP_d + \frac{1}{3}(BP_s - BP_d)$, where BP_s and BP_d are the brachial artery systolic and diastolic pressures. Perfusion pressure (PP) was calculated as $\frac{2}{3}BP_m - IOP$, where IOP is intraocular pressure.

One-way analysis of variance for repeated measures, paired and unpaired Student's *t* test, and correlation and rank correlation analysis was used in the evaluation of the results. The Wilk-Shapiro test was used to assess the normal distribution of the results. $P < 0.05$ was considered statistically significant.

RESULTS

After 6 mo of SDC, eight study eyes showed no progression (NP) and five showed progression (P) of retinopathy by one or more levels as defined in the ETDRS study. Of the eight NP eyes, two actually showed a regression of retinopathy by one level. Two eyes in the P group progressed to proliferative diabetic retinopathy at the end of the study and received panretinal photocoagulation therapy.

The degree of improved diabetic control achieved in our study is shown in Fig. 2, which depicts the average monthly GHb levels for the 13 patients studied. The decrease in GHb shown in this figure is similar to that achieved in the SDC group of the DCCT study (23). The mean largest drop in GHb (baseline GHb − lowest GHb) for the 13 subjects was 4.7 ± 2.6%.

No significant change in average $\dot{Q}$ was observed between the first (16.6 ± 4.1 μl/min) and second (16.6 ± 5.4 μl/min) baseline BLDV measurement. Average absolute value of the percent change in $\dot{Q}$ between these two measurements was 11%.

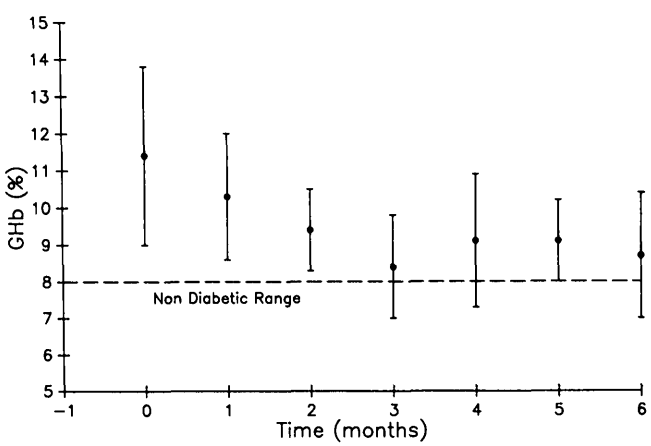

FIG. 2. Mean ± SD monthly glycosylated hemoglobin (GHb) levels measured by affinity chromatography in 13 patients. Upper limit of normal range is 8%.

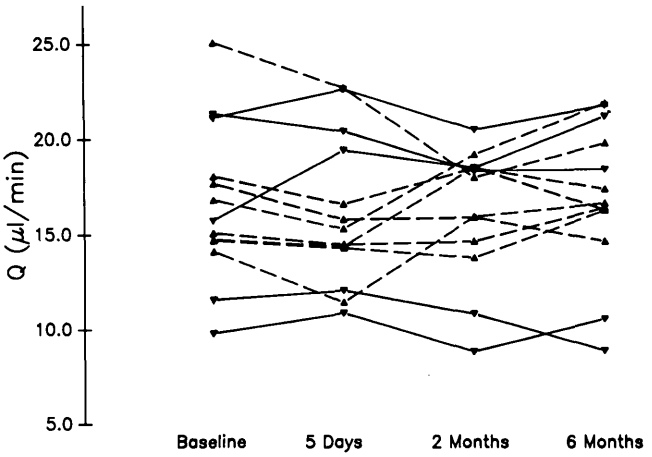

FIG. 3. Volumetric blood flow rate ($\dot{Q}$) measured in major temporal retinal vein at baseline and then 5 days, 2 mo, and 6 mo after institution of strict diabetic control. *Solid lines*, eyes that showed progression of retinopathy at end of study; *dashed lines*, eyes that showed no progression of retinopathy at end of study.

Figure 3 shows $\dot{Q}$ in a major retinal vein at the first baseline BLDV measurement and then 5 days, 2 mo, and 6 mo after the institution of SDC. A one-way analysis of variance, taking into consideration all measurements and grouped according to progression or no progression of retinopathy, did not show any statistically significant changes over time. The average absolute blood flows for eyes that did and did not show progression of retinopathy were also not significantly different at any point in time by unpaired Student's *t* test.

Relative changes in $\dot{Q}$ from baseline at 5 days, 2 mo, and 6 mo were calculated for each subject with the results of the first baseline BLDV measurement. Calculation with the second baseline BLDV measurement showed similar results. All eight NP eyes had decreased blood flow on the 5th day of the study (Fig. 4). Four of five P eyes showed increased blood flow. With the data shown in Fig. 4, a one-way analysis of variance for repeated measures with progression or no progression as a grouping factor showed a strong crossover effect between $\dot{Q}$ changes over time and the two groups of eyes ($P < 0.005$). In other words, on the 5th day of SDC, $\dot{Q}$ changes in P eyes were significantly different from those measured in NP eyes. NP eyes had a significant average decrease in $\dot{Q}$ of 1.4 ± 0.9 μl/min ($P < 0.005$ by paired *t* test). In P eyes, the average increase in $\dot{Q}$ of 1.2 ± 1.7 μl/min was not statistically significant ($P > 0.05$).

On the 5th day of SDC, changes in $\dot{Q}$ from baseline were significantly correlated with the change in retinopathy level observed at 6 mo (rank correlation 0.79, $P < 0.005$). In other words, eyes with the larger increases in blood flow had the greater increases in retinopathy and vice versa (Fig. 5).

No significant differences in the relative changes in $\dot{Q}$ from baseline obtained at 2 and 6 mo were detected between P and NP eyes.

No significant differences in duration of diabetes, baseline GHb, decreases in GHb achieved during the study, baseline blood glucose, largest decrease in blood glucose achieved in the study, or lowest GHb achieved under strict control were found between NP and P eyes by unpaired Student's

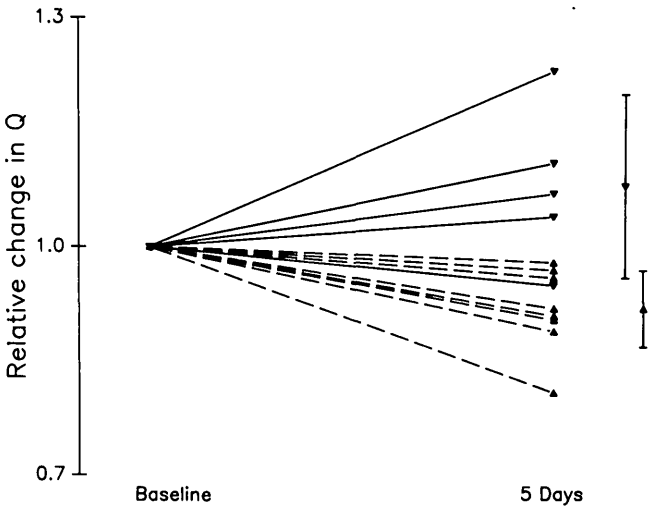

FIG. 4. Relative changes in volumetric blood flow rate ($\dot{Q}$) from baseline measured in each subject ~5 days after institution of strict diabetic control. *Solid lines*, eyes that showed progression of retinopathy at end of study; *dashed lines*, eyes that showed no progression of retinopathy at end of study. *Vertical lines*, mean ± 95% confidence limits for each group.

t test (Table 2). However, at baseline, mean brachial artery pressure and perfusion pressure were significantly higher in P than NP eyes ($P < 0.05$ and $P < 0.01$, respectively, by unpaired *t* test; Table 3).

A strong statistical association was present between the blood flow changes observed on the 5th day of SDC and progression of retinopathy detected at the end of the study ($F = 9.24$ by Fisher's exact test, $P < 0.01$). In eyes in which retinopathy progressed, $\dot{Q}$ increased in four eyes and decreased in one eye. In eyes in which retinopathy did not progress, $\dot{Q}$ decreased in eight eyes.

DISCUSSION

The results of this study show that a lack of decrease in $\dot{Q}$ on the 5th day of SDC is associated with progression of retinopathy. Moreover, the amount of change in $\dot{Q}$ on the 5th day of SDC correlates significantly with the degree of change in retinopathy level detected at 6 mo (Fig. 5). Patients with larger increases in $\dot{Q}$ show more progression of retinopathy and vice versa. These changes in $\dot{Q}$ were detected soon after the institution of SDC and were not observed 2 or 6 mo later. It is possible that the sudden lowering of blood glucose levels could produce a transient retinal metabolic imbalance and hemodynamic change lasting for only a few days or weeks. The fact that the transient progression of retinopathy seen in some patients also occurs soon after institution of SDC supports this hypothesis (18–20,25).

Progression of retinopathy after the institution of SDC is often characterized by the appearance of nerve fiber layer infarcts (18–20,25). Infarcts are usually associated with decreases in blood flow, and therefore, our results showing that a lack of decrease in $\dot{Q}$ is associated with progression of retinopathy and the appearance of nerve fiber layer infarcts may seem surprising.

However, in a previous study, we showed that an acute insulin-induced switch from hyperglycemia to normoglycemia resulted in a significant decrease in $\dot{Q}$ in diabetic patients (21). In other words, retinal blood flows that were significantly higher than normal during hyperglycemia returned toward normal once normoglycemia was achieved. In addition, in the same study, we found a significant correlation between the amount of decrease in $\dot{Q}$ toward normal and the duration of retinopathy. Patients with shorter disease duration showed larger decreases in $\dot{Q}$ toward normal, whereas patients with disease duration of 12–16 yr showed almost no decreases in $\dot{Q}$ after normalization of blood glucose.

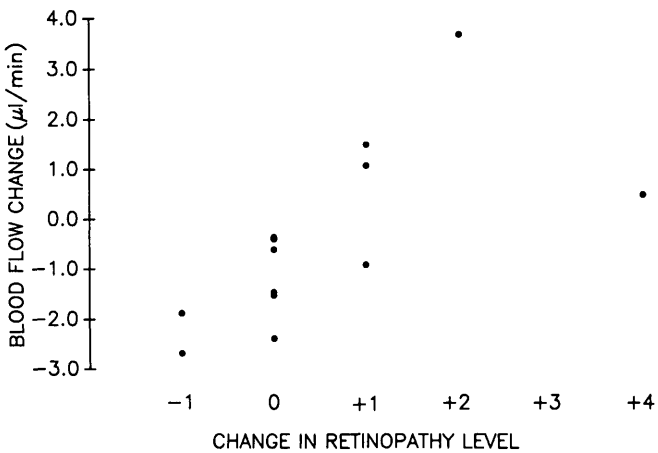

FIG. 5. Relationship between changes in volumetric blood flow rate from baseline observed on 5th day of strict diabetic control and change in retinopathy level observed in study eye 6 mo later. Rank correlation 0.79, $P < 0.005$.

TABLE 2
Characteristics of subjects with and without progression of retinopathy in the study eye

	No progression (n = 8)	Progression (n = 5)
Disease duration (yr)	18 ± 7	13 ± 3
Baseline GHb (%)	12.7 ± 3.4	12.4 ± 2.0
Baseline blood glucose (mM)	13.0 ± 5.9	10.6 ± 5.7
Largest decrease in GHb (%)	4.2 ± 2.3	4.4 ± 2.3
Lowest GHb during study (%)	7.8 ± 2.8	8.0 ± 2.8
Venous diameter (μm)	174 ± 15	182 ± 24

Values are means ± SD. GHb, glycosylated hemoglobin. Differences were not significant by 2-tailed unpaired *t* test.

TABLE 3
Mean blood pressure and perfusion pressure in subjects with and without progression of retinopathy in the study eye at the time of blood-flow measurements

	No progression (n = 8)	Progression (n = 5)
Mean blood pressure		
Baseline	81.7 ± 10.9	94.0 ± 7.2*
After 5 days	78.0 ± 8.0	88.0 ± 9.7
Perfusion pressure		
Baseline	37.0 ± 6.8	49.3 ± 4.7†
After 5 days	35.3 ± 6.4	44.9 ± 8.2

Values are means ± SD (mmHg).
*$P < 0.05$, †$P < 0.01$, by 2-tailed unpaired *t* test.

A decrease in $\dot{Q}$ toward normal appears to be a regulatory response present in early diabetes that seems to disappear in patients with longer disease duration. This decrease in $\dot{Q}$ is probably an important regulatory response needed to adjust to the metabolic changes that occur in the retina when blood glucose levels are suddenly normalized. Patients who do not show this decrease in $\dot{Q}$ could be at an increased risk of having their retinopathy progress. The fact that patients with longer disease duration more frequently show worsening of the disease after the institution of SDC lends support to this hypothesis (11).

In our previous study, we speculated that the decrease in $\dot{Q}$ that accompanies an insulin-induced normalization of blood glucose could lead to the development of nerve fiber layer infarcts (21). The results of our current study suggest that this decrease may not play a major role. A more important factor leading to the development of these infarcts may be a loss of the ability of the vasculature to regulate $\dot{Q}$ in response to the metabolic changes arising from fluctuating blood glucose levels. Indeed there is evidence that individuals with diabetes have decreased retinal regulatory responses to hyperoxia (26) and to acute increases in intraocular pressures (27). Furthermore, the regulatory response to hyperoxia also becomes more abnormal in patients with longer disease duration or more advanced retinopathy or during hyperglycemia (21,26).

Although we did not find a significant difference in $\dot{Q}$ between NP and P eyes in our study, the findings of Brinchmann-Hansen et al. (28) showing that patients whose retinopathy progressed after the institution of SDC have larger retinal vessel diameters than those who do not show progression suggest that increased $\dot{Q}$ may indeed be present in those eyes that show deterioration of retinopathy.

Previous studies on the effect of SDC on diabetic retinopathy have suggested that progression of retinopathy occurs more frequently in patients with more advanced retinopathy (11), longer disease duration (11,29), higher baseline GHb or blood glucose (29), larger decreases in GHb or blood glucose (29,30), lower blood glucose levels during the study (29), and dilated retinal vessels (28,30). We compared these parameters in the P and NP groups to investigate whether there were any significant differences and whether such differences could explain the different $\dot{Q}$ changes observed in our study in the two groups of eyes.

The distribution of baseline retinopathy levels was similar in both groups (Fig. 1). In addition, no statistically significant differences in any of the other above-mentioned parameters were found between the two groups of eyes (unpaired *t* test, $P > 0.05$; Table 2). The failure to find such differences may be due to the small sample size of our preliminary study, which does not allow us to investigate in-depth the presence of confounding factors. However, there were two parameters that were significantly different. Baseline mean brachial arterial pressure and perfusion pressure (which is derived from the mean brachial arterial pressure) were significantly higher ($P < 0.05$ and $P < 0.01$, respectively) in P than NP eyes (Table 3).

Systemic hypertension is known to be a risk factor for the development of diabetic retinopathy (31–33). However, all our patients had systemic blood pressures and intraocular pressures that were within the normal range. Our results show that within the range of normal blood pressures and intraocular pressures, higher normal blood pressures and higher normal perfusion pressures may be associated with an increased risk of retinopathy progression, and this could be a confounding factor. However, differences between the changes in pressures seen in NP and P eyes on the 5th day could not explain the differences in the $\dot{Q}$ changes observed, because mean blood pressure and perfusion pressure decreased in both NP and P eyes (although not statistically significantly).

The type of glycemic control achieved in our study is very similar to that reported for the experimental group of the DCCT (23). Mean HbA_{1c} levels measured with the method employed by the DCCT at the beginning (8.8 ± 1.2%) and the end (6.5 ± 0.7%) of our study are very similar to those reported for the experimental adult group of the DCCT.

Baseline glycemic control before the beginning of the study and the improvement in glycemic control during the study were not the same in all subjects. Therefore, we investigated whether there were any correlations between the baseline GHb level, the decrease in GHb achieved during the study, or GHb at the end of the study and $\dot{Q}$ or changes in $\dot{Q}$. We found no significant correlations between any of these parameters. Blood glucose levels determined at the time of measurements or the changes in blood glucose between two measurement sessions also did not correlate with $\dot{Q}$ or changes in $\dot{Q}$. Controlling for blood glucose changes between different sessions of blood-flow measurement with blood glucose as a covariate in the one-way analysis of covariance also did not make any difference in the statistical analysis. All of these findings suggest that, with the small sample size of our study, we cannot detect any relationships between changes in blood glucose levels or changes in GHb levels and the $\dot{Q}$ changes observed in this study. It is possible that future studies performed on larger numbers of patients may provide more information on these relationships.

There was a strong association between blood-flow changes on the 5th day and the progression or lack of progression of retinopathy at the end of the study. With our data, we calculated that within the sample size of our study, the changes in $\dot{Q}$ measured on the 5th day of SDC can predict nonprogression of retinopathy with a sensitivity of 100% and a specificity of 80%. A larger study needs to be done to assess the predictive value of these measurements in regard to the progression of retinopathy that occurs in some patients after the institution of SDC.

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