Purpose. Color Doppler imaging is a new noninvasive technique that enables measuring blood flow velocity in small orbital vessels, arteries as well as veins. Because hemodynamic changes are seen in patients with diabetic retinopathy by other techniques, the authors compared 61 eyes with proliferative, 59 eyes with nonproliferative, and 26 eyes with preproliferative diabetic fundus changes with a matched control group of 70 patients without diabetes (128 eyes).

Methods. The central retinal artery (CRA), short posterior ciliary artery (PCA), and ophthalmic artery (OA) of all patients were examined, and the systolic, diastolic, and mean velocities were measured for each vessel.

Results. Differences between the groups were most prominent in the CRA. The perfusion velocity was significantly lower \( (P < 0.001) \) in proliferative eyes \( (V_{\text{sys}}, 5.7 \pm 1.8 \text{ cm/sec}) \) than in the control group \( (V_{\text{sys}}, 9.4 \pm 1.2 \text{ cm/sec}) \) or in nonproliferative eyes \( (V_{\text{sys}}, 8.4 \pm 1.8 \text{ cm/sec}) \). In the preproliferative group, there was great variability in velocity distribution. Consequently, no statistically significant difference could be deduced, either in the group with background retinopathy or in the group with proliferative diabetes. In the OA and PCA, neither group showed significant differences from normal.

Conclusions. Measurements indicate a correlation between severity of diabetic retinopathy and decreased flow velocity in the CRA.

In this way, the circulation of the central retinal artery (CRA), central vein (CV), and posterior ciliary arteries (PCAs), as well as the ophthalmic artery (OA) and the superior ophthalmic vein (SOV), may be investigated. Even the different vortex veins can be identified under favorable conditions. The course of the central retinal and ophthalmic vessels is usually visible over a distance of at least 1 to 2 cm. However, only a short section of the long and short ciliary vessels may regularly be demonstrated because of their tortuous course (Fig. 1). In the past few years, several clinical applications of this new technique in the evaluation of ophthalmic disorders have been established. The vascularization of intraocular tumors has been demonstrated. Diagnostic imaging of orbital tumors, particularly vascularized lesions such as carotid-cavernous fistulas and orbital varices, has been greatly improved. In addition, color Doppler imaging is a useful adjunct in the evaluation and management of arteriolar and venous occlusive disease. It also may help to monitor pharmacologically induced changes in or-
FIGURE 1. (top left) Color Doppler imaging. Orbital vessels. PCA = posterior ciliary arteries; CA+CV = central retinal artery + vein.

FIGURE 2. (top right) Blood flow velocities. Systolic and diastolic velocities of the central retinal artery. Values are shown as mean ± standard error of the mean.

FIGURE 3. (middle) Color Doppler imaging. Spectrum mode. (A) Normal. CRA = central retinal artery; N = optic nerve. (B) Proliferative diabetic retinopathy.

TABLE 1. Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Background Retinopathy</th>
<th>Preproliferative Retinopathy</th>
<th>Proliferative Retinopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>70</td>
<td>31</td>
<td>14</td>
<td>32</td>
</tr>
<tr>
<td>Eyes</td>
<td>128</td>
<td>59</td>
<td>26</td>
<td>61</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.9 ± 19.2</td>
<td>51.3 ± 18.5</td>
<td>52.3 ± 17.7</td>
<td>55.4 ± 15.2</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>—</td>
<td>15.4 ± 7.3</td>
<td>15.1 ± 6.0</td>
<td>17.0 ± 6.9</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>—</td>
<td>140 ± 32</td>
<td>173 ± 53</td>
<td>173 ± 69</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>132 ± 15</td>
<td>141 ± 21</td>
<td>135 ± 16</td>
<td>142 ± 14</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>85 ± 8</td>
<td>77 ± 8</td>
<td>79 ± 13</td>
<td>85 ± 9</td>
</tr>
</tbody>
</table>

Values are shown as mean ± standard deviation.

bital hemodynamics. Further investigations addressing this subject are under way.

It was the aim of this study to determine whether color Doppler imaging is sensitive enough to detect hemodynamic changes in the orbital circulation in different stages of diabetic retinopathy.

PATIENTS AND METHODS

The study population consisted of a control group and three different sets of patients with diabetes, namely 59 eyes of 31 patients with background diabetic retinopathy, 26 eyes of 14 patients with preproliferative changes, and 61 eyes of 32 patients with proliferative diabetic retinopathy (Table 1). The study was approved by the internal review board of the Johannes Gutenberg University of Mainz, and informed consent was obtained from all patients according to the tenets of the Declaration of Helsinki. The control group was randomly selected from a data base of 188 patients without ocular pathology, systemic hypertension, diabetes mellitus, or vascular disease. To adjust the age distribution of the controls to the patients with diabetes, patients in the data base were divided into four age groups: younger than 20 years, 20 to 39 years, 40 to 59 years, older than 60 years. A random selection of control patients was then performed separately for each age group. The percentage of patients entered into each group matched the age distribution in the study population with proliferative diabetic retinopathy and was not significantly different from the other groups of patients with diabetes.

The classification of diabetic retinopathy was performed according to the modified Airlie House system on the basis of stereoscopic fundus examination with a 90-D lens. The level of retinopathy was judged by two examiners for each patient. If there was disagreement, the higher level of retinopathy was assigned. Background retinopathy was assumed when retinal hemorrhages, microaneurysms, or hard exudates were present, according to retinopathy level 2–3 in the Airlie House classification. Preproliferative retinopathy included cotton wool spots, intra retinal microvascular abnormalities, venous loops, or larger hemorrhages qualifying for retinopathy level 4–5. Proliferative diabetic retinopathy was assigned when new vessels and proliferations were present, according to level 6–7 in the Airlie House system. Patients with diabetes without retinopathy were not included.

The mean duration of diabetes mellitus was 15.4 ± 7.3 (SD) years for the background group, 15.1 ± 6.0 (SD) years for the preproliferative group and 17.0 ± 6.9 (SD) years for the proliferative group respectively. In our study, there was no statistically significant correlation between the level of retinopathy and the duration of diabetes mellitus, probably because usually only patients with long-standing diabetes mellitus are referred to our clinic. The mean fasting blood glucose level was elevated in all patients with diabetes, corresponding to the stage of diabetic retinopathy (Table 1). Eyes with a history of ocular, nondiabetic vascular disease (i.e., central retinal artery or vein occlusion, ocular ischemic syndrome), retinal detachment, panretinal laser treatment or surgical therapy were excluded. The intraocular pressure was in the normal range (<22 mm Hg). Twenty-five patients with diabetes and systemic hypertension were included in our study, 8 in the background group, 5 in the preproliferative group, and 12 in the proliferative group. However, at the time of the measurements, the systemic blood pressure was not elevated above systolic values of 170 mm Hg and diastolic values of 100 mm Hg. Furthermore, the mean systolic and diastolic blood pressures were not statistically different between controls and patients with diabetes (Table 1).

The color Doppler unit Quantum Q 2000 (Siemens-Quantum, Issaquah, WA) was used throughout our study. It was equipped with a 7.5-MHz linear array
transducer combined with a 5-MHz Doppler element (transducer 7L30). To our knowledge, color Doppler imaging is a safe technique as far as permanent disturbances of ocular structures are concerned. The energy used during color coding (5 to 59 mW/cm² SPTA) is only slightly higher than in conventional B-mode ultrasonography. When spectrum analysis is performed, the so-called "spatial peak temporal average" (SPTA) is in the range of 56 to 476 mW/cm². These values exceed Food and Drug Administration guidelines for prenatal diagnostic ultrasound of 17 mW/cm² SPTA as well as recommendations of 100 mW/cm² issued by the American Institute of Ultrasound in Medicine. However, there is still an extraordinary safety margin up to ultrasound energy levels that have led to cataract formation or retinal lesions in animal experiments (>100 W/cm²). The measurements were performed in a supine position by coupling the transducer to the closed eyelids with sterile ophthalmic methylcellulose gel. This technique has been described in detail by Lieb et al and Guthoff et al. The Doppler signal was registered on line after the cursor was positioned on the region of interest and the Doppler angle adjusted to the taper of the vessel under consideration. The peak systolic, diastolic, and mean blood flow velocities over the cardiac cycle were calculated by the built-in software. The mean velocity is computed by electronically integrating the flow velocity over one or more cardiac cycles. Misinterpretation of the Doppler spectrum by the software led to false results whenever the Doppler signal was noisy or included positive and negative frequencies. The CRA, one (usually a temporal) PCA, and the OA of all eyes enrolled in the study were examined. For each vessel, the systolic, diastolic, and mean velocities were measured. Because the Doppler signal from the CRA regularly contained a negative component from the corresponding vein, reliable values for the mean velocity of this vessel could rarely be obtained. When both eyes of one patient were measured, the mean velocity values of right and left eyes were entered into the statistical tests. Statistical comparison was performed by the two-tailed Student's t-test. Significant results (P < 0.01) were confirmed by a nonparametric statistical test (Wilcoxon–Mann–Whitney test). The mean flow velocity of the CRA was not evaluated for reasons mentioned above.

RESULTS

There is a highly significant correlation between velocity measurements in the right and the left eye of the same patient in all groups (correlation coefficient, r > 0.95). Therefore, we feel justified to calculate the average of both eyes for further evaluation.

Table 2 presents the mean values of the flow velocities for the different study groups. In the CRA, all patients with diabetes show a significant reduction in peak systolic and end diastolic flow velocity compared to the control group (Fig. 2). The differences from control (V_{systolic} 9.4 ± SD 1.2 cm/sec, P = 1.6 · 10^{-10}) are most prominent in those patients with proliferative fundus changes (V_{systolic} 5.7 ± SD 1.8 cm/sec). They are less marked but still significant in the background group (V_{systolic} 8.4 ± SD 1.8 cm/sec, P = 0.008) and in the preproliferative group (V_{systolic} 6.5 ± SD 2.6 cm/sec, P = 0.001). An original recording from the CRA of a patient with proliferative diabetic retinopathy and a control subject is given in Figure 3. Furthermore, the perfusion velocity in the proliferative group (5.7 ± 1.8 cm/sec) is significantly lower than in the nonproliferative group (8.4 ± 1.8 cm/sec, P = 1.1 · 10^{-7}). In the preproliferative group, the variability of the velocity distribution is relatively high. Therefore, no significant difference can be deduced in relation to the other patients with diabetes. In the PCA, neither group shows statistically significant differences from normal. However, there is a tendency toward higher blood flow velocities in patients with less severe diabetic retinopathy (background and preproliferative retinopathy) compared to control. The variability of the velocity distribution in the PCA is considerably higher than in the CRA. This may be attributed to the less accurate adjustment of the Doppler angle and varying perfusion velocities in different branches of the ciliary circulation. Also, the OA shows no significant differences in flow velocity between the study groups.

In the control group, the systolic and diastolic flow velocities of the CRA are inversely correlated with age, i.e., higher age is accompanied by decreased blood flow velocity (correlation coefficient, r = −0.42; P = 0.0002). This correlation, however, is present in none of the groups with diabetes. Furthermore, there is no significant correlation between our measurements and blood pressure, blood glucose level, and duration of diabetes.

DISCUSSION

Color Doppler imaging is a new technique for analyzing orbital perfusion in pathologic conditions affecting the vascular system. Velocity measurements in central retinal, ciliary, and orbital circulations are rendered possible.

In the current study, we demonstrate for the first time that color Doppler imaging is sensitive enough to assess hemodynamic changes in different stages of
TABLE 2. Blood Flow Velocity (cm/sec)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Background Retinopathy</th>
<th>Proliferative Retinopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central retinal artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{\text{sys}}$</td>
<td>9.4 ± 1.2</td>
<td>8.4 ± 1.8</td>
<td>6.5 ± 2.6</td>
</tr>
<tr>
<td>$V_{\text{dias}}$</td>
<td>2.4 ± 0.8</td>
<td>1.8 ± 0.9</td>
<td>1.4 ± 1.0</td>
</tr>
<tr>
<td>Posterior ciliary arteries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{\text{sys}}$</td>
<td>11.2 ± 1.9</td>
<td>12.8 ± 2.9</td>
<td>12.7 ± 4.2</td>
</tr>
<tr>
<td>$V_{\text{dias}}$</td>
<td>3.4 ± 1.2</td>
<td>3.2 ± 1.6</td>
<td>4.2 ± 3.3</td>
</tr>
<tr>
<td>$V_{\text{mean}}$</td>
<td>5.5 ± 1.3</td>
<td>6.2 ± 2.0</td>
<td>7.2 ± 3.0</td>
</tr>
<tr>
<td>Ophthalmic artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{\text{sys}}$</td>
<td>35.9 ± 5.1</td>
<td>35.2 ± 6.3</td>
<td>36.1 ± 7.3</td>
</tr>
<tr>
<td>$V_{\text{dias}}$</td>
<td>8.5 ± 2.5</td>
<td>7.0 ± 2.3</td>
<td>7.4 ± 2.5</td>
</tr>
<tr>
<td>$V_{\text{mean}}$</td>
<td>16.1 ± 3.2</td>
<td>14.4 ± 3.1</td>
<td>14.8 ± 3.4</td>
</tr>
</tbody>
</table>

$V_{\text{sys}}$ = peak systolic velocity; $V_{\text{dias}}$ = end diastolic velocity; $V_{\text{mean}}$ = mean velocity over the cardiac cycle.

Values are shown as mean ± standard deviation.

The reduction in blood flow velocity we observed in the CRA agrees with laser Doppler velocimetry measurements reported by Grunwald and coworkers.17 Those authors found a reduction of the center line velocity in the temporal branches of retinal vessels. As in our investigation, the decrease in flow velocity was most prominent in those subjects with proliferative fundus changes. Unlike Michelson and coworkers,18 who used a conventional 4-MHz Doppler device, we could not confirm an elevation of flow velocity in the OA. This discrepancy may be attributed to differences in the constitution of the study groups as well as to our placement of the sample volume closer to the globe. Thus, a different set of downstream daughter vessels may have influenced our measurements in the OA. So far, fluorescein angiography has been widely used to study perfusion in patients with diabetic retinopathy. Compared to angiographic studies, our findings have some common and some different features. Whereas some authors have reported prolonged perfusion times in proliferative diabetic retinopathy,19-22 others showed shortened or normal perfusion times in moderate diabetic retinopathy.23-25 Those discrepancies are primarily related to the measuring technique. Color Doppler imaging determines the velocity of moving cells, whereas fluorescein angiograms indicate plasma movement. In addition, the dye dilution technique requires a closed arteriovenous perfusion segment. Because of leakage from altered vessels in diabetic retinopathy, this prerequisite is not fulfilled. This problem has already been noted by Kohner26 and Grunwald et al.17

In contrast to fluorescein angiography, color Doppler imaging is a noninvasive technique that may be repeated in short intervals. Cataract or intraocular hemorrhages of any severity and localization do not hinder velocity measurements. Severe complications of diabetic retinopathy, such as tractional retinal detachments and neovascular membranes, may be diagnosed without using additional techniques (Fig. 4). Under favorable conditions, color Doppler imaging may help to differentiate between nonvascularized vitreous membranes and vascularized retinal or choroidal folds.26 Vessels inaccessible by fluorescein angiography or laser Doppler velocimetry, such as the OA or PCA, may be examined by color Doppler imaging. Thus, disorders affecting the eye that might otherwise have escaped notice, e.g., occlusive carotid artery disease, can be easily diagnosed by a significant reduction in the flow velocity or even a reversal of flow in the OA because of collaterals from the external carotid artery.8

The only disadvantage of this new technique is that close contact between the eyelids and the transducer must be established. In this way, some pressure may be applied to the globe, particularly when the examiner is not familiar with the method. Williamson and coworkers,27 however, have shown that this influence can be minimized with experience. Repeated measurements of the same subject by the same or different trained examiners have shown that the results of velocity measurements may be well reproduced. We conclude, therefore, that this influence may be neglected when considering differences in blood flow velocity of more than 15% to 20%.

Clinical applications of color Doppler imaging are under evaluation. Because the mean of the systolic and diastolic blood flow velocities in the CRA are considerably lower in proliferative diabetic retinopathy than in control and nonproliferative retinopathy, an inverse correlation between flow velocity in the CRA and the progression of diabetic retinopathy is suggested. In addition, we may suppose
that the great variability in the preproliferative group is due to a mixture of patients; in some, more severe stages of diabetic retinopathy develop, whereas in others the disease remains stable. However, such a relationship must be confirmed in a longitudinal series. Furthermore, it remains unknown whether there is a close correlation between a reduction in blood flow velocity and volumetric flow. The present models of the retinal circulation used to calculate volumetric flow from diameter and velocity measurements assume a constant cylindrical vessel geometry and velocity profile. Yet, changes in vessel shape in pathologic conditions such as diabetic retinopathy must be taken into account. Grunwald and coworkers have presented data from the evaluation of fundus photographs confirming a statistically significant enlargement of venous and arterial vessel diameters in patients with diabetes compared to normal controls.\(^7\) Vasodilation, however, leads to decreased blood flow velocity even without any change in volumetric flow. Therefore, a decreased flow velocity might still reflect unchanged volumetric flow when marked vasodilation is present. Nevertheless, reliable, noninvasive techniques to measure orbital volumetric flow directly are unavailable.

Despite its limitations, color Doppler imaging may become a valuable method to assess orbital blood flow in diabetic retinopathy and other ocular vascular disorders. As indicated, detailed longitudinal studies must be initiated to confirm a close association between decreased blood flow velocity and progression of diabetic retinopathy. This new technique may be used when standard diagnostic procedures, e.g., fundus examination or fluorescein angiography, are impossible because of cataract and vitreous hemorrhage or when they render equivocal results concerning the indication for panretinal photocoagulation.

**Key Words**

color Doppler imaging, ultrasound, blood flow, ocular perfusion, diabetic retinopathy

**References**

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