Contrast Sensitivity Loss Is Coupled With Capillary Dropout in Patients With Diabetes

Oliver Arend,* Andreas Remky,* David Evans,† Reinhard Stüber,* and Alon Harris‡

Purpose. To assess the relationship of foveal microcirculation to contrast sensitivity function in early diabetes mellitus.

Methods. Twenty patients with diabetes with visual acuity of 20/25 or better without clinically significant macular edema were evaluated. Measurements of contrast sensitivity at four spatial frequencies (3, 6, 12, and 18 cycles/degree [c/deg]), macular capillary blood velocity (CBV), capillary density (PIA: perifoveal intercapillary area), foveal avascular zone (FAZ), and microaneurysm count were performed. Contrast sensitivity data collected from age-matched normal subjects and previously published normal angiographic data were used for comparison with our cohort with diabetes.

Results. The CBV was significantly reduced \( (P < 0.0001) \) and PIA and FAZ were significantly enlarged \( (P < 0.0001) \) when compared with healthy subjects. Contrast sensitivity was significantly lower in the group with diabetes at 6 \( (P= 0.01) \) and 12 \( (P= 0.002) \) c/deg as compared with healthy control values. FAZ and PIA correlated significantly \( (FAZ; r = -0.60, P = 0.005; PIA; r = -0.54, P = 0.02) \) with contrast sensitivity at 12 c/deg.

Conclusions. The alterations of the perifoveal network are related to selective disturbances of central visual function as measured by contrast sensitivity. In patients with diabetes measurement of contrast sensitivity may provide a clinical adjunct in further identifying early ischemic diabetic maculopathy. Invest Ophthalmol Vis Sci. 1997;38:1819–1824.

To understand, define, and treat ischemic diabetic maculopathy further, clinical tools have to be developed for early identification of progressive ischemic damage. For example, treatment of macular edema with focal photocoagulation is less effective if the procedure is performed after macular capillary nonperfusion occurs.\(^1\) Although fluorescein angiography is effective for detection and quantification of early macular capillary changes, these changes are not reflected in visual acuity loss until the disease is well progressed.\(^5,6\) Data show that patients with diabetes with normal visual acuity (20/25 or better) exhibit abnormally enlarged foveal avascular zone (FAZ) compared with healthy subjects.\(^1\) A visual function measurement that reflected early changes in retinal circulation would potentially be useful for quantifying disease progression.

Contrast sensitivity has been widely studied in diabetic eye disease and the dissociation of visual acuity and contrast sensitivity in patients with diabetes with normal visual acuity is well established.\(^5,6\) A recent report noted that patients with diabetes with normal visual acuity, but depressed contrast sensitivity, exhibited an acute recovery of contrast sensitivity to normal levels while breathing pure oxygen, suggesting an association between contrast sensitivity and retinal tissue ischemia.\(^7\)

The purpose of this study was to determine in patients with diabetes with normal visual acuity and without clinically significant macular edema the association, if any, between retinal microcirculation and contrast sensitivity.

MATERIALS AND METHODS

Scanning laser video fluorescein angiograms (SLO, Rodenstock Institute, Ottobrunn, Germany) com-
bined with an image analysis system (IBAS, Kontron, Munich, Germany) allow the evaluation of mean capillary blood velocity (CBV), the perifoveal intercapillary area (PIA), the foveal avascular zone (FAZ), and microaneurysm counts.

The CBV was measured by observing the transit of hypofluorescent fronts through the perifoveal vasculature (rouleaux formations of red blood cells). PIA provides an estimate of capillary density in the network around the FAZ (5°). The perifoveal intercapillary areas were marked by interactively drawing around the surrounding capillaries with the cursor in the digital image. The area described by the cursor was calculated with the picture analyzing system. One hundred randomly selected areas surrounded by capillaries were marked in the 5° area of interest, and the mean area was calculated from these measurements for each patient. Coefficients of variation calculated among the subjects characterize the homogeneity of capillary blood velocity (CBV) (cv[CBV]) and PIA (cv[PIA]) presented in this study. In addition to these parameters, the number of microaneurysms was counted. This approach has shown a good correlation with stage of retinopathy.

In modification of existing methods, a 10° circle was centered over the FAZ. This area of interest was chosen because of the possibility that the number of microaneurysms might reflect the severity of diabetic maculopathy. In a standardized fashion only hyperfluorescent dots with a diameter of 20 μm or greater were considered as being microaneurysm formations. All angiographic analyses were performed in a masked fashion without prior knowledge of visual acuity or contrast sensitivity results.

Patients

Prospectively, 20 patients with diabetes mellitus and visual acuity of 20/25 or better were recruited for this study. The clinical and demographic data of the patient group with diabetes are presented in Table 1. Informed consent was obtained from each subject including detailed explanations of all procedures before participation in this study. The study protocol was approved by the human study institutional board of the technical university of Aachen and followed the tenets of the Declaration of Helsinki. Slit lamp examination of the anterior segment was normal in all subjects. The fundus photographs of all patients with diabetes were classified as having no clinically significant macular edema according to Early Treatment Diabetic Retinopathy Study Group (ETDRS) guidelines.

In all patients, no cystoid edema, which is easily detectable by scanning laser angiograms, was present, and review of the late-phase angiograms revealed no presence of vascular leakage.

Retinopathy level was estimated by means of fundus photography according to ETDRS criteria. The patient group consisted of 6 patients (30%) having no retinopathy (level 10), 8 patients (40%) with microaneurysm formation only (level 20), 4 patients with mild retinopathy (level 35), one with severe nonproliferative (level 53) and another with proliferative (level 61) diabetic retinopathy.

Reference values for comparison of the angiographic measures were taken from previous studies and derived from healthy subjects of similar age (47 ± 11 years).

An age- and sex-matched group of 20 healthy control subjects (age, 47 ± 10 years) with no evidence or history of any ocular or systemic disease was examined to compare the results of contrast sensitivity.

Best corrected visual acuity was determined by an ophthalmologist using objective refractometry (Rodenstock, Germany), the lighting conditions, and standardized charts as described by DIN 58220, followed by a complete ophthalmologic examination. Best corrected contrast sensitivity was assessed by an ophthalmologist with the CSV-1000 (Vector Vision; Dayton, OH) contrast sensitivity testing instrument. For the calculations in this study, contrast was defined by the following:

\[
\text{contrast} = \frac{\text{Luminance}_{\text{max}} - \text{Luminance}_{\text{min}}}{\text{Luminance}_{\text{max}} + \text{Luminance}_{\text{min}}}
\]

where Luminance_{max} is the highest luminance of the sinusoidal luminance gradient and Luminance_{min} is the lowest luminance of the sinusoidal luminance gradient.

The CSV-1000 instrument has recently been demonstrated to have adequate test reliability compared to treatment-related changes of ocular disease. The instrument provides a retroilluminated translucent chart at a standardized light level of 85 cd/m². Four spatial frequencies (3, 6, 12, and 18 cycles/degree [c/deg]) were tested using an orientation-free two-alternative quasi-forced choice procedure. The patients' eyes then underwent subsequent SLO fluorescein angiographic studies. Because the patients' refractive er-

---

**Table 1. Clinical and Demographic Data for the Patients With Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Number (male/female)</th>
<th>Age (years)</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Diastolic blood pressure (mm Hg)</th>
<th>Hb A1c (%)</th>
<th>Duration of diabetes (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 (14/6)</td>
<td>42 ± 12</td>
<td>133 ± 20</td>
<td>81 ± 8</td>
<td>7.6 ± 1.5</td>
<td>13 ± 9</td>
</tr>
<tr>
<td>Values are mean ± SD.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

1. Age (years) was calculated with the picture analyzing system. One study. In addition to these parameters, the number of microaneurysm counts.

2. The CBV was measured by observing the transit of hypofluorescent fronts through the perifoveal vasculature (rouleaux formations of red blood cells). PIA provides an estimate of capillary density in the network around the FAZ (5°). The perifoveal intercapillary areas were marked by interactively drawing around the surrounding capillaries with the cursor in the digital image. The area described by the cursor was calculated with the picture analyzing system. One hundred randomly selected areas surrounded by capillaries were marked in the 5° area of interest, and the mean area was calculated from these measurements for each patient. Coefficients of variation calculated among the subjects characterize the homogeneity of capillary blood velocity (CBV) (cv[CBV]) and PIA (cv[PIA]) presented in this study. In addition to these parameters, the number of microaneurysms was counted. This approach has shown a good correlation with stage of retinopathy.

3. In modification of existing methods, a 10° circle was centered over the FAZ. This area of interest was chosen because of the possibility that the number of microaneurysms might reflect the severity of diabetic maculopathy. In a standardized fashion only hyperfluorescent dots with a diameter of 20 μm or greater were considered as being microaneurysm formations. All angiographic analyses were performed in a masked fashion without prior knowledge of visual acuity or contrast sensitivity results.
TABLE 2. Hemodynamic Values for the Healthy Reference Group and the Group With Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>CBV (mm/second)</th>
<th>cv(CBV) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subjects</td>
<td>52</td>
<td>2.85 ± 0.25</td>
<td>12 ± 5</td>
</tr>
<tr>
<td>Group with diabetes</td>
<td>20</td>
<td>1.78 ± 0.2</td>
<td>16 ± 4</td>
</tr>
<tr>
<td>*</td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Unpaired Student’s t-test. Values are mean ± SD. CBV = mean capillary velocity; cv(CBV) = mean coefficient of variation of capillary blood velocity.

errors affect the dimensions of the dynamic and morphologic measurements, all data were corrected for the refractive error.17,18

Statistical Analysis

Mean value and standard deviation are given for all samples with normal distribution (Kolmogorov-Smirnov test) and nonnormal distribution median and percentiles (2.5% and 97%). The unpaired Student’s t-test was used to assess the significance of the differences between groups. Findings less than 0.05 were considered to be statistically significant. Pearson correlation coefficients were calculated to evaluate the relationship between the parameters. P values were obtained after performing Fisher’s r to z transformations. For statistical analysis of visual acuity, the logarithmic minimal arc of resolution (log MAR) values were used, and for contrast sensitivity, 1/contrast threshold was used.

RESULTS

Compared to the reference normal population, the patients with diabetes displayed significantly reduced CBV (P < 0.0001) (Table 2), significantly enlarged, more than doubled, PIA (P < 0.0001) (Table 3), and significantly enlarged FAZ (P < 0.0001). The coefficients of variation for CBV (cv(CBV), P = 0.0008) and PIA (cv[PIA], P < 0.0001) were also significantly greater in the population with diabetes compared with the normal reference population, indicating increased inhomogeneity of perifoveal hemodynamics and vascularity. The number of microaneurysms ranged from 0 to 8 in the patient group with diabetes, but this count failed to correlate with CBV, PIA, or FAZ.

Average static contrast sensitivity and standard deviations of patients with diabetes (3 c/deg, 1.64 ± 0.12; 6 c/deg, 1.84 ± 0.14; 12 c/deg, 1.45 ± 0.24; 18 c/deg, 1.07 ± 0.21) and age-matched healthy controls (3 c/deg, 1.68 ± 0.14; 6 c/deg, 1.96 ± 0.14; 12 c/deg, 1.67 ± 0.15; 18 c/deg, 1.17 ± 0.15) are shown in Figure 1. Comparing the subjects with diabetes with age-matched healthy controls, contrast sensitivity was decreased significantly at spatial frequencies of 6 and 12 c/deg (6 c/deg, P = 0.01; 12 c/deg, P = 0.002).

Contrast sensitivity at 12 c/deg was significantly correlated with PIA (P = 0.016, r = −0.54), the coefficient of variation cv(PIA) (P = 0.04, r = −0.46), and FAZ (P = 0.005, r = −0.6), indicating decreased contrast sensitivity with increased size of PIA and FAZ and increased inhomogeneity of PIA as expressed by cv(PIA). Figures 2 and 3 show the scatterplots with regression lines of contrast sensitivity at 12 c/deg with PIA and FAZ. Although abnormal CBV and microaneurysm count were significantly associated with the patients with diabetes, neither of these measures correlated significantly with reduced contrast sensitivity at any spatial frequency tested.

Figures 4 and 5 show the fluorescein angiograms

TABLE 3. Morphologic Parameters for Group With Diabetes and Healthy Reference Group

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>PIA (μm²)</th>
<th>cv(PIA) (%)</th>
<th>FAZ (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subjects</td>
<td>52</td>
<td>3686 ± 345</td>
<td>34 ± 8</td>
<td>0.205 ± 0.052</td>
</tr>
<tr>
<td>Group with diabetes</td>
<td>20</td>
<td>6301 ± 2375</td>
<td>64 ± 23</td>
<td>0.327 ± 0.207</td>
</tr>
<tr>
<td>*</td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

PIA = mean of the perifoveal intercapillary areas; cv(PIA) = mean coefficient of variation of PIA; FAZ = foveal avascular zone.

* Unpaired Student’s t-test. Values are mean ± SD.
FIGURE 2. Scatterplot with regression line of contrast sensitivity at 12 c/deg with the perifoveal intercapillary area (PIA) in the patients with diabetes. With increasing size of PIA, contrast sensitivity was significantly decreased ($P = 0.016; r = -0.54$).

FIGURE 3. Scatterplot with regression line of contrast sensitivity at 12 c/deg with the foveal avascular zone (FAZ). With increasing size of FAZ, contrast sensitivity was decreased significantly ($P = 0.005; r = -0.6$).

FIGURE 4. (A) Patient 1. The fluorescein angiograms of the perifoveal network (OS) of a 50-year-old man with diabetes (duration of diabetes, 1 year, no diabetic retinopathy) with normal visual acuity (20/20). The picture shows early capillary closure with slightly increased PIA (4752 $\mu m^2$) and normal size of the FAZ (0.207 mm$^2$). (B) Contrast sensitivity function of the patient (squares) shown in A in comparison to the matched healthy control population (mean $\pm$ 2 standard deviations [SD]). There are no significantly differing results at any of the spatial frequencies for the patient with diabetes.

DISCUSSION

In this study, we evaluated patients with diabetes with no clinically significant macular edema. Despite normal visual acuity, contrast sensitivity revealed abnormalities at spatial frequencies of 6 and 12 c/deg. The decrease of sensitivity was related to a marked increase of the perifoveal intercapillary area and size of the foveal avascular zone.

The angiographic measures performed in this study have proven to be of particular value in detecting early diabetic capillary nonperfusion even before microaneurysm formation occurs. The present study showed that CBV, PIA, and FAZ, as well as coefficients of variation of CBV and PIA, were significantly affected when compared with healthy subjects although visual acuity remains normal.

In a previous study in patients with advanced diabetic disease, measures of capillary density and FAZ are coupled with decreased visual acuity. In the present study the significant correlation of contrast sensitivity with PIA ($r = -0.54$) and FAZ ($r = -0.60$) indicates that even in patients with early disease and unaffected visual acuity, alterations in vasculature have an impact on visual function. Interestingly, macular CBV, although affected in early disease stages, and microaneurysm count had no predictive value for visual pathway integrity.
FIGURE 5. (A) Patient 2. Fluorescein angiography of the perifoveal network of a 40-year-old man with diabetes (duration of diabetes, 15 years, mild nonproliferative diabetic retinopathy) with best corrected visual acuity of 20/20. Moderate capillary closure around the FAZ resulting in a more than doubled size of PIA (7761 μm²) and normal FAZ size (0.286 mm²) were detected. (B) Contrast sensitivity function of the patient with diabetes (squares) shown in A in comparison to the normal reference population (mean ± 2 SD). Decreased sensitivity at 12 c/deg in the patient with diabetes is demonstrated.

Frisén found that visual acuity remains unaffected until about 55% of all neuroretinal channels are affected. Visual acuity does not possess sufficient sensitivity to provide clinical information as to the impact of altered retinal function in early stages of diabetic eye disease. Others have shown that contrast sensitivity and visual acuity are dissociated in early disease and, specifically, that contrast sensitivity is significantly reduced in patients with normal visual acuity. Our results showed that contrast sensitivity and not visual acuity correlates to angiographic measures, suggesting that contrast sensitivity is a more sensitive indicator of early visual impairment secondary to alterations in retinal vasculature.

The decrease in contrast sensitivity at spatial frequency of 12 c/deg, related to lower capillary density (expressed by increased PIA), is of particular interest. Sokol et al found that the largest loss in contrast sensitivity in the population with diabetes tested occurred at 11.4 c/deg. Harris et al found significant differences in contrast sensitivity at 12 and 18 c/deg between normal controls and patients with no or early diabetic retinopathy. Isocapnic hyperoxia improved contrast sensitivity significantly only at 12 c/deg in the patients with diabetes, suggesting that tissue hypoxia initiates both visual and vascular dysfunction in diabetic angiopathy. Whether this result suggests a direct link between tissue ischemia and selective contrast loss at high spatial frequency remains unclear. Ischemic or hypoxic mechanisms may have injured other spatial frequency contrast sensitivity mechanisms, but perhaps not permanently or not to a sufficient degree such that sensitivity could be improved with acute hypoxic perturbation.

The correlation of capillary dropout and sensitivity leads to the question about the site of damage. Considering the bilevel capillary arrangement model of the retina, capillaries in the foveal avascular arcade are localized as a single strata within the ganglionic layer. With further eccentricity, capillary planes are localized either within the nerve fiber layer/ganglionic layer or within the inner nuclear layer. Using the scanning laser technology with a confocal mode, little depth resolution (less than 30 μm) is possible. Capillary density measurements represent the monolayer at the edge of the FAZ and in the nerve fiber and ganglionic layers. Capillaries of the inner nuclear layer, most likely, are not reflected in this measurement. Therefore, capillary density measurement represents predominantly the innermost retinal capillary plexus, vasculature that would have a significant influence on the ganglion cell (parvocellular and magnocellular) components.

The magnocellular and parvocellular ganglion cells are characterized by different morphology and functionality. Specifically, the parvocellular system shows higher spatial resolution and is largely responsible for chromatic processing. Clinical studies have shown the existence of early color vision defects before diabetic retinopathy occurs. This finding, in combination with high spatial frequency loss of contrast sensitivity, points in the direction of an early involvement of parvocellular cells or cone-specific alterations in diabetic disease course.

It is unknown what level of vascular abnormality is required to result in an ischemic diabetic maculopathy. This, however, is of particular interest in the decision to perform focal laser coagulation. Ticho et al have shown that patients with macular capillary nonperfusion do not benefit from macular laser coagulation. Fluorescein angiography provides the most sensi-
tive and objective detection criteria for early capillary loss. However, this procedure is invasive. Contrast sensitivity evaluation may add strength to existing clinical criteria for evaluating disease progression in early diabetic ischemic maculopathy. Analysis of a loss at 12 c/deg may prove to be a useful screening criterion to select those patients who may require further angiographic study.

In summary, the presence of perifoveal ischemia is related to a subtle deterioration of visual function as measured by contrast sensitivity. In patients without clinically significant macular edema and normal visual acuity, contrast sensitivity could be a clinical adjunct in further identifying early ischemic diabetic maculopathy.

Key Words
contrast sensitivity, diabetic maculopathy, fluorescein angiography, retinal ischemia, scanning laser ophthalmoscope

References