Differences in Pulsatile Ocular Blood Flow among Three Classifications of Diabetic Retinopathy

Howard I. Savage,1 Jason W. Hendrix,2 David C. Peterson,2 Heather Young,2 and Charles P. Wilkinson1,3

PURPOSE. Choroidal blood flow may be determined by pulsatile ocular blood flow (POBF) measurements. In the present study, the POBF of diabetic patients with increasingly severe retinopathy was compared with that in nondiabetic control subjects.

METHODS. The study was a masked cross-sectional analysis. Seventy-seven diabetic subjects, including 13 with mild or no retinopathy, 36 with moderate to severe retinopathy, and 28 with proliferative diabetic retinopathy (PDR), previously treated with panretinal photocoagulation (PRP), Fifty-six nondiabetic control subjects served as the comparison group. All subjects underwent masked measurement of POBF in the right eye by Langham pneumotonometer. Analysis of variance (ANOVA) determined whether differences existed between groups. Pair-wise comparisons between groups were conducted by Student’s t-test.

RESULTS. The main outcome measures were ophthalmic pulse amplitudes, intraocular pressure (IOP), heart rate, and POBF. Patients with moderate to severe nonproliferative diabetic retinopathy (NPDR) had POBF 18% higher than the control (mean OBF, 943 μL/min). Among PRP-treated subjects with PDR, ocular blood flow was 22% below the control (mean OBF, 619 μL/min), and 34% less than moderate to severe nonproliferative diabetic retinopathy. Diabetic patients with no retinopathy or mild NPDR had OBF indistinguishable from the control (785 vs. 797 μL/min). Differences between the four groups were statistically significant by ANOVA (P < 0.0001).

CONCLUSIONS. POBF is unaffected early in diabetic retinopathy, but increases significantly in eyes with moderate to severe NPDR. POBF is decreased in eyes with laser-treated PDR. These experimental data represent the largest published assessment of POBF in NPDR. This is the first study to examine POBF in subjects with PRP-treated PDR. (Invest Ophthalmol Vis Sci. 2004;45:4504 – 4509) DOI:10.1167/iovs.04-0077

Diabetic retinopathy remains a major public health problem and a leading cause of blindness in the United States and throughout the world.1,2 The damaging effects of chronic hyperglycemia on the microvasculature and subsequent focal ischemia are primary pathogenetic factors in disease progression.3 The cellular and biochemical mechanisms behind diabetic vasoconstriction and vasodilation are beginning to be understood. Protein kinase C (PKC)4 may play a key role in the complex biochemical cascade causing local vasoconstriction and diabetic retinopathy. Anti-PKC treatment has recently been shown to reduce nonproliferative diabetic retinopathy in humans with nonproliferative diabetic retinopathy (NPDR).5 Endothelin-1 activation, another potent vasoconstrictor, is also elevated in diabetic patients with retinopathy.6,7 By contrast, vascular endothelial growth factor (VEGF) appears to stimulate retinal vasodilatation and neovascularization.3 Although basic science may lead to clinical treatments to reduce or prevent retinopathy by blocking the pathologic effects of ischemia-induced growth factors and deranged autoregulation, the precise mechanisms responsible for various stages of disease progression remain unclear.8,9 Furthermore, studies describing the role of altered overall blood flow in the diabetic eye appear contradictory, and some controversy remains.

Ophthalmic circulation can be measured noninvasively in two ways. One general approach estimates retinal blood flow (RBF) by measuring the speed of blood transiting the retinal capillary bed (video fluorescein angiography and entoptic phenomena) or of single retinal vessels (ultrasound and laser Doppler). The former techniques for RBF are dominated by the peripheral blood column, and retinal flow can be reduced by endothelial activation and leukostasis. The latter technique (Doppler velocimetry) detects center-line blood velocities and is dependent on accurate estimates of vessel diameter and area to obtain valid RBF estimates.

A second approach, termed pulsatile ocular blood flow (POBF), determines the summed volume of blood entering the retina, choroid, and remaining uveal tract by measuring increases in intraocular pressure (IOP), with each heartbeat. This approach involves real-time pneumotonometer and provides a volumetric measurement of the pulsatile component of blood flow. POBF reflects the choroidal circulation, which is responsible for 85% of the POBF.10

Contrary conclusions have been reached with different techniques. Our review of the literature found 18 studies using five different techniques to determine blood flow in diabetic patients. The results of these studies differed in which circulation was measured, retinal or choroidal, as did the techniques used to for the measurement. For example, three groups found decreased RBF,11-13 whereas three others found increased RBF14-16 in diabetic patients with no or mild retinopathy. A seventh study showed no difference in blood flow in diabetic patients with no or mild retinopathy.17 This controversy is not limited to differences across studies of RBF with different measurement techniques. Results in two recent pneumotonometer studies, both examining choroidal circulation, were in disagreement on the change in POBF in nondiabetic retinopathy (NDR) and NPDR. One showed that POBF increased, whereas another found decreased POBF in these two groups compared with the control.13,15 A third study in which pneumotonometer was used showed no significant change in POBF as diabetic retinopathy advanced.17

We conducted a cross-sectional analysis of the OBF in 77 diabetic patients compared with randomly selected control subjects. Our goal was to resolve controversy regarding the
CME, cystoid macular edema; ERM, epiretinal membrane.

direction and amplitude of the changes in choroidal blood flow that occur during the course of diabetic retinopathy. The validity and reproducibility of pneumotonometry has been demonstrated by several research groups.\textsuperscript{18}–\textsuperscript{21} Prior investigations have shown that diabetic patients do not differ from control subjects in the validity of this measurement.\textsuperscript{10,18,22}

**METHODS**

This study is a cross-sectional analysis of consecutive diabetic patients referred to a retina specialist at Greater Baltimore Medical Center, a tertiary care retinal referral practice in Baltimore, Maryland. Nondiabetic control subjects attended the clinic for a variety of nonvascular retinal disorders. All patients presenting between October 1994 and November 1995 who agreed to the informed consent were eligible for entry in the study. Data, collected by interview, included detailed oculocutaneous histories, with particular attention to diagnosis, duration, and treatment of diabetes; presence of hypertension; and current medications. The ophthalmic examination included best refractioned Snellen visual acuity, Amsler grid testing, pupil examination, Goldmann tonometry, biomicroscopic examination, and dilated funduscopic examination with Hruby and 20-D lens indirect ophthalmoscopy.

Diabetic patients were included if they reported current medical treatment for diabetes mellitus with either oral hypoglycemic agents, insulin, or a combination. Controls subjects were included if they had no history of diabetes treatment \textit{and} no evidence of diabetic retinopathy on ophthalmic examination. Patients were excluded from both groups if they had previous or coexisting vascular occlusion, glaucoma, uveitis, or endophthalmitis. Individual eyes were excluded for history of exudative ARMD, retinal detachment, or a scleral buckling procedure. Patients were not excluded for prior argon laser treatment, nonexudative ARMD, or vitrectomy.

Every patient who signed an informed consent underwent masked measurement of the POBF in the right eye by a trained ophthalmic technician, before dilation and evaluation by the ophthalmologist. The POBF was measured with a computerized pneumotonometer (Ocular Blood Flow Laboratories, Timonium, MD). This technique automatically measures the cyclic variation in IOP with each heartbeat. A microcomputer automatically selects five regular pulse waves without user influence. Then, based on data from the known pressure-volume relation of living human eyes, the computer calculates the volume of blood entering the globe responsible for the measured pressure increase at the given pressure.\textsuperscript{18,19} Each POBF data point is actually an average of five regular pulse waves.

Masked POBF data were recorded and sealed in consecutive patient records for each visit occurring between October 1994 and November 1995. For those subjects with POBF determinations at multiple visits, we arbitrarily used only the most recent POBF. No subjects or data were excluded on the basis of the measurement's standard deviation or apparent outlier status. Each eligible patient’s chart was reviewed retrospectively for inclusion and exclusion criteria to either the diabetic or control group. Every diabetic patient who gave consent was included. Fifty-six of 130 consecutive control nondiabetic patients were entered into the study, selected by convenience sample. We included patients whose last names began with A through M. The study was approved by the hospital’s Institutional Review Board, and all procedures conformed to standards outlined in the Declaration of Helsinki.

One of us (CPW), masked to POBF readings, divided the diabetic patients into three groups, based on the severity of diabetic retinopathy. The criteria for defining the groups were generally consistent with the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale\textsuperscript{23} (Table 1). \textit{No or mild retinopathy} was defined as a few microaneurysms, but no dot-blot hemorrhages, cotton wool spots, or clinically significant macular edema (CSME). The moderate to severe group included patients with the mild criteria plus CSME, intraretinal microvascular abnormality (IRMA), or capillary dropout. The PDR group consisted of patients with new, recurrent, or regressed neovascularization. All 28 patients with PDR had panretinal photocoagulation (PRP) laser treatment before enrollment.

**Statistical Analysis**

Differences between groups with respect to mean POBF were assessed by one-way analysis of variance (ANOVA). Pair-wise comparisons between individual groups were made with Tukey’s test. The effect of age on mean POBF differences between groups was determined by analysis of covariance (ANCOVA). Statistical analysis was performed on computer (SAS, ver. 8.2; SAS Institute, Inc., Cary, NC). Given that the overall ANOVA yielded significant results, a series of four two-tailed \textit{t}-tests were performed, comparing each diabetic subgroup with the control, and also comparing the moderate to severe group with the PDR groups. These tests were performed on right eyes of each subject. Because four essential intergroup comparisons would be made for each eye, the Bonferroni adjustment for multiple comparisons indicates that 0.01 rather than 0.05 should be used for the purpose of determining statistical significance of pair-wise comparisons. A sample size calculation was not performed prospectively.

**RESULTS**

**Patients’ Characteristics**

The number of subjects, number of eyes, and mean ages are presented in Table 1. Principal diagnoses of the control group are summarized in Table 2. Groups differed significantly in average age ($P < 0.0002$), but not in gender.

**Blood Flow Differences by Severity of Retinopathy**

POBF differed substantially among the four groups of patients studied (Fig. 1). ANOVA showed a statistically significant difference between means among all four groups ($P < 0.0001$).
The $R^2$ for the ANOVA model was 0.182, indicating that roughly 18% of the variation in OBF was explained by the severity of diabetic retinopathy. Pair-wise comparisons showed that the moderate to severe NPDR groups and the PDR-PRP group were significantly different, as were the moderate to severe NPDR and control groups.

The control group had a mean POBF of $797 \pm 245 \, \mu L/min$ (SD). Diabetic patients with no or mild retinopathy had POBF similar to the control ($785 \pm 797 \, \mu L/min$; $P = 0.71$). Diabetic subjects with moderate to severe NPDR had POBF 18.4% higher than the control ($943 \pm 797 \, \mu L/min$; $P < 0.0002$).

The 28 patients with PRP-treated PDR had POBF 22.3% lower than the control group (619 vs. $797 \, \mu L/min$; $P < 0.0001$). A still larger difference was observed between the moderate to severe NPDR group and the PDR group (decrease of 34%; 943 vs. 619 $\mu L/min$; $P < 0.0001$).

**DISCUSSION**

**POBF in Moderate to Severe Diabetic Retinopathy**

This cross-sectional analysis contains the largest group of diabetic patients with moderate to severe retinopathy published to date, as shown in Table 3. Our finding of increased POBF in moderate to severe NPDR is consistent with a report by MacKinnon et al.16 in which a group of 20 patients with background retinopathy had POBF increase by 58% ($P < 0.05$) over that in 20 nondiabetic control subjects. They used the same Langham pneumotonometry OBF system used in our study, and patients were studied in a seated position in both studies.

Two other cross-sectional POBF investigations in patients with moderate to severe NPDR found no change in POBF.27,24 Still, two other groups reported a decrease in POBF in NPDR.13–25 The first such study25 measured patients in a supine position, which has since been shown to reduce POBF.25 In this study, researchers also used an early Langham OBF system without automated waveform selection, which system requires operator input to select pulse waves that appeared regular. Therefore, masked observation, not included in the study by Langham et al.,25 may have reduced the opportunity for bias to affect such measurements. Geyer et al.15 divided the diabetic patients somewhat differently than we did in the current study. Their NPDR group contained patients with mild-moderate NPDR, and thus these patients were earlier in the course of retinopathy than our moderate to severe group. The present report adds to the evidence that choroidal circulation, measured by POBF is not decreased, but is elevated, just as Doppler-determined RBF is elevated in moderate to severe NPDR.15,26

Recent work has demonstrated that VEGF, released locally by the ischemic retina, may be responsible for vasodiolation and increased blood flow, as well as the progression to macular edema.28 VEGF production may underlie the observed elevation in choroidal blood flow shown by POBF in patients with moderate to severe retinopathy in the present study. It is possible that at this late stage of NPDR, The VEGF response would overwhelm the vasoconstrictive effects of PKC and endothelin-1.1–7

**POBF in Laser-Treated PDR**

This is the first study in which the Langham pneumotonometer has been used to compare POBF in PRP-treated patients with PDR with that in control subjects. Table 4 puts the present work in the context of prior investigations of blood flow in proliferative retinopathy that were identified through a search of MEDLINE (provided in the public domain at www.ncbi.nlm.nih.gov/PubMed by the National Library of Medicine, National Institutes of Health, Bethesda, MD). Our results suggest that POBF changes are consistent with three cross-sectional studies of RBF after PRP.26,29,30 The current investigation suggests that PRP treatment reduces the choroidal circulation similarly to ultrasound or laser Doppler flowmetry in the retinal vasculature.26,29,30 Most studies of diabetic patients with untreated PDR showed increased POBF13,16 and RBF.12,26 Some showed no change versus the control15,24 or showed decreases.25,30

**POBF in Diabetic Patients with No Retinopathy or Mild Retinopathy**

Eleven cross-sectional studies, reviewed in Table 5, have addressed the alterations of blood flow in diabetic patients with either no retinopathy or mild retinopathy. The results are almost evenly divided. Four reports, including the present study, showed no statistically significant variation from the control. None of these, however, including our own study, contains a power calculation that would allow for a definitive conclusion that no difference truly exists. Of the seven cross-sectional studies reporting a difference in blood flow in the earliest diabetic patients, four showed decreased11–13,25 and three showed increased14–16 OBF. It is interesting that, for each study technique used, one group identified an increase, whereas another showed a decrease in blood flow in early diabetic retinopathy versus the control.

**TABLE 2.** Diagnoses among the Nondiabetic Control Subjects

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>Diagnosis</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular degeneration</td>
<td>21</td>
<td>Dry eye</td>
<td>2</td>
</tr>
<tr>
<td>Epiretinal membrane</td>
<td>8</td>
<td>Angiod streaks</td>
<td>1</td>
</tr>
<tr>
<td>Cystoid macular edema</td>
<td>5</td>
<td>Macular hole</td>
<td>1</td>
</tr>
<tr>
<td>Focal retinal detachment</td>
<td>5</td>
<td>Migraine</td>
<td>1</td>
</tr>
<tr>
<td>Cataract or media opacity</td>
<td>5</td>
<td>Presumed ocular</td>
<td>1</td>
</tr>
<tr>
<td>Posterior vitreous detachment</td>
<td>3</td>
<td>Retinal hemorrhage</td>
<td>1</td>
</tr>
<tr>
<td>Central serous retinopathy</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 1.** Blood Flow and Percent Change as compared with the control.
Table 3. Studies Measuring Blood Flow in Moderate to Severe NPDR

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Classification</th>
<th>n</th>
<th>Change in OBF vs. Nondiabetic Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Choroidal blood flow studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present Study</td>
<td>POBF</td>
<td>Moderate to severe</td>
<td>36</td>
<td>+18% (P &lt; 0.001)</td>
</tr>
<tr>
<td>MacKinnon16</td>
<td>POBF</td>
<td>Background</td>
<td>20</td>
<td>+58% (P &lt; 0.05)</td>
</tr>
<tr>
<td>Findl7</td>
<td>OPA</td>
<td>Moderate</td>
<td>12</td>
<td>Increased (P = 0.049), POBF no change</td>
</tr>
<tr>
<td>Schmidt24</td>
<td>POBF</td>
<td>NPDR</td>
<td>24</td>
<td>No change</td>
</tr>
<tr>
<td>Langham*25</td>
<td>POBF</td>
<td>NPDR</td>
<td>11</td>
<td>−27%*</td>
</tr>
<tr>
<td>Geyer15</td>
<td>POBF</td>
<td>NPDR</td>
<td>20</td>
<td>−14.6% (P = 0.054)*</td>
</tr>
<tr>
<td>Retinal blood flow studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kohner*15</td>
<td>FARF</td>
<td>PPDR</td>
<td>10</td>
<td>+50%*</td>
</tr>
<tr>
<td>Patel26</td>
<td>LDV</td>
<td>BDR</td>
<td>27</td>
<td>+27%*</td>
</tr>
<tr>
<td>Patel26</td>
<td>LDV</td>
<td>PPDR</td>
<td>13</td>
<td>+65%*</td>
</tr>
<tr>
<td>Feke8</td>
<td>LDV</td>
<td>Moderate</td>
<td>6</td>
<td>No change</td>
</tr>
</tbody>
</table>

BDR, background diabetic retinopathy; FARF, fluorescein angiographic retinal flow; LDV, laser Doppler velocimetry; OPA, ocular pulse amplitude; PPDR, preproliferative diabetic retinopathy.

* P nonsignificant or not reported.

Given the biochemical evidence for increased activated PKC and endothelin from hyperglycemia, one might reasonably anticipate a reduction in POBF among diabetic patients with no or mild retinopathy, but we did not find such a reduction. Although the inclusion of patients with nonexudative ARMD may have masked a reduction in choroidal blood flow, only two of five studies in which choroidal blood flow in diabetic patients with early retinopathy was assessed showed reductions.

The demonstration of altered choroidal blood flow across various stages of diabetic retinopathy strongly suggests that PKC, endothelin, and VEGF biochemical and cellular pathways identified to date are part of a more complex autoregulatory system with other critical components yet unidentified. Our results also suggest that, although the focal vasoconstriction induced by PKC and endothelin may cause localized retinal ischemic damage or macular edema, the net increase in choroidal blood flow measured by POBF may be paradoxically increased by VEGF or other vasodilators.

Two potential limitations of the current investigation are the greater age of the control subjects and the inclusion of patients with nonexudative macular degeneration in the control group. However, the difference in POBF between groups was still significant after adjustment for age. Furthermore, in contrast to a study by Grunwald et al.31 the univariate analysis of the present study demonstrated that age was not a significant factor in POBF in our cohort. It is unlikely that age, which in one report was associated with a very slight reduction in choroidal flow,31 would affect the main findings of the present study, as the direction of the bias caused by age would have opposed the trends we found. In the current investigation, the highest POBF was seen in the oldest diabetic group with moderate to severe retinopathy. The other diabetic groups had identical mean age, but markedly reduced POBF among laser-treated diabetic patients with PDR.

Since our study concluded, several reports of studies in which a variety of techniques were used have suggested that choroidal blood flow is reduced below control values in exudative macular degeneration32,33 and some34–36 but not all studies of patients with nonexudative macular degeneration have reported similar findings. Since one third (21/66) of our control subjects had nonexudative ARMD, the control group may not be representative. However, the published magnitude of the reduction in choroidal blood flow in nonexudative ARMD is roughly 30%, and only one third of our control subjects had ARMD. Thus, the underestimate of control POBF may be at worst, roughly 10%. Given this small effect size, the only result that could be qualitatively altered by an improperly low POBF among the control group would be the comparison of POBF between diabetic patients with no or mild retinopathy.

Table 4. Studies Measuring Blood Flow in PDR

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Classification of PDR: Treated or Untreated</th>
<th>n</th>
<th>Change in OBF vs. Nondiabetic Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Choroidal blood flow studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>POBF</td>
<td>PRP-treated PDR</td>
<td>27</td>
<td>−22.3% (P &lt; 0.001)</td>
</tr>
<tr>
<td>Geyer13</td>
<td>POBF</td>
<td>Untreated PPDR/PDR</td>
<td>12</td>
<td>+33.6% (P = 0.003)</td>
</tr>
<tr>
<td>MacKinnon16</td>
<td>POBF</td>
<td>Untreated PPDR/PDR</td>
<td>20</td>
<td>+70% (P &lt; 0.05)</td>
</tr>
<tr>
<td>Schmidt24</td>
<td>POBF</td>
<td>Untreated PDR</td>
<td>13</td>
<td>−67.6%*</td>
</tr>
<tr>
<td>Schmidt24</td>
<td>OPA</td>
<td>Untreated PDR</td>
<td>18</td>
<td>No change*</td>
</tr>
<tr>
<td>Retinal blood flow studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patel26</td>
<td>LDV</td>
<td>PRP treated PDR</td>
<td>12</td>
<td>−5% (P = 0.01)</td>
</tr>
<tr>
<td>Grunwald29</td>
<td>LDV</td>
<td>PRP treated PDR</td>
<td>15</td>
<td>−27% (P &lt; 0.001)</td>
</tr>
<tr>
<td>Mendivil30</td>
<td>USDV</td>
<td>PRP treated PDR</td>
<td>25</td>
<td>−29.8% (P &lt; 0.01)</td>
</tr>
<tr>
<td>Feke12</td>
<td>LDV</td>
<td>Untreated PDR</td>
<td>12</td>
<td>+5% (P &lt; 0.001)</td>
</tr>
<tr>
<td>Patel26</td>
<td>LDV</td>
<td>Untreated PDR</td>
<td>12</td>
<td>−51.4%*</td>
</tr>
<tr>
<td>Mendivil30</td>
<td>USDV</td>
<td>Untreated PDR</td>
<td>25</td>
<td>−15.4% (P = 0.03)</td>
</tr>
<tr>
<td>Kohner15</td>
<td>FARF</td>
<td>Untreated PDR</td>
<td>12</td>
<td>No change*</td>
</tr>
</tbody>
</table>

Abbreviations are defined in Table 3 or the text, with the exception of USDV, ultrasound retinal Doppler velocimetry.

* P not significant or not reported.
versus the control, which we found equivalent. It is possible that inclusion of patients with ARMD in the control group masked a small reduction in POBF among diabetic patients with no or mild retinopathy. Such a reduction has been reported in some but not all POBF studies of choroidal blood flow in early diabetes. The 18% increase we found in POBF among patients with moderate to severe diabetes versus control and the 34% reduction in POBF among PRP-treated subjects with PDR versus control are too great to be affected by a small underestimate in control POBF. Finally, differences between the three diabetic groups could not possibly be affected by the control group.

One additional concern may involve scleral rigidity in diabetic patients and its impact on POBF. We have excluded conditions and therapies that we know alter scleral rigidity, including scleral buckling or uveitis. However, it is possible that, because of protein glycation, scleral collagen becomes stiffer and less elastic. Reduced elasticity would be expected to increase pulse amplitudes for a given change in volume, exaggerating the POBF. However, this effect was not demonstrated in a study of scleral rigidity among diabetic patients compared with age-matched control eyes.19

Conclusions

This cross-sectional analysis of choroidal blood flow employing POBF measurement is based on the largest group of diabetic patients with moderate to severe retinopathy published to date, and it is the first POBF study of argon laser PRP-treated patients with PDR. The results suggest that choroidal blood flow is increased 18% above control in diabetic subjects with moderate to severe diabetic retinopathy. Choroidal blood flow is 34% lower than preproliferative levels among patients with PDR after argon laser PRP. Because POBF is representative of choroidal blood flow, our results suggest that the choroidal circulation largely mirrors the increase in RBF demonstrated in moderate to severe NPDR,15,16,26 and the decrease in RBF among patients with laser-treated PDR reported by other investigators.20,29,50 One potential source of bias in our study was age, because the mean age varied significantly between subgroups. However, ANCOVA showed that age was not a significant predictor of POBF in our study group, and the intergroup differences remained significant after adjustment for age. The study population was gathered consecutively, with the control group selected at random from consecutively enrolled patients.

Thus, the sample is representative of a typical suburban academic retina practice, and should be generalizable to patients of similar age and setting. The inclusion of subjects with non-exudative ARMD in the control group may have slightly depressed the apparent POBF in the control subjects. This may have masked a slight reduction in POBF among diabetic patients with no or mild retinopathy.

We speculate that cellular and biochemical mechanisms involving early activation of PKC and endothelin-1 may cause the patchy vasoconstriction responsible for focal ischemia that is just too localized and subtle to affect the global choroidal circulation measured by POBF in diabetic patients with the earliest retinopathy. We further suspect that later ischemia-induced upregulation of VEGF may be responsible for the sharp increase in choroidal blood flow we observed in diabetic patients with moderate to severe retinopathy.

It is clear that the cross-sectional approach to determining changes in OBF in early diabetes has produced some contradictory data, particularly among diabetic patients with little to no retinopathy. One longitudinal study of RBF in diabetic patients may give some insight into the contradictions.37 Konno et al.37 tracked the changes in 24 individuals with type 1 diabetes with a variety of retinopathy levels for 2 to 6 years with annual Doppler and video fluorescein angiographic determination of blood flow. They found a bimodal progression of blood flow, increasing in some, decreasing in others. They found that patients with the shortest duration of diabetes have the least retinopathy, the highest RBF, and the steepest decline in RBF in the years that follow. Thus, depending where patients with early diabetes are on the curve when recruited into a cross-sectional study, they may show either high or low blood flow. Perhaps a longitudinal study design, although more resource-consuming, would be a more powerful technique for resolving the conflicting data reported regarding the precise changes in pulsatile and Doppler-assessed OBF.

References


