Orbital color Doppler imaging (CDI) results suggest that diabetic patients have significantly lower blood flow velocities in both the central retinal artery (CRA) and central retinal vein (CRV) than in the corresponding vessels of normal eyes, and this reduction in velocity may arise from an increase in the resistance induced by diabetic retinal microvascular obstructions.\textsuperscript{1,2}

However, we have identified a subgroup of diabetic patients who have unexpectedly higher blood flow velocities in both the CRA and CRV bilaterally.\textsuperscript{3} These patients have low serum albumin and diffuse optic disc staining in fluorescein angiography. We have suggested that the low serum albumin causes leakage of serum because of the low osmotic pressure of the blood. The induced tissue edema, in turn, causes the narrowing of the CRA and CRV in the optic nerve head, thus leading to higher velocities in both vessels. As might be expected, the velocities are higher in the thin-walled CRV.\textsuperscript{4}

\textbf{Correlation Between Higher Blood Flow Velocity in the Central Retinal Vein than in the Central Retinal Artery and Severity of Nonproliferative Diabetic Retinopathy}

Sayuri Fujioka\textsuperscript{1}, Kaoruko Karashima\textsuperscript{1}, Norikiyo Nishikawa\textsuperscript{2}, and Yoshihiro Saito\textsuperscript{3}

\textsuperscript{1}Department of Ophthalmology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan; \textsuperscript{2}Department of Ophthalmology, Osaka Police Hospital, Osaka, Japan; \textsuperscript{3}Department of Ophthalmology, Osaka National Hospital, Osaka, Japan

\textbf{Abstract}

\textbf{Purpose:} To assess the correlation between a higher blood flow velocity in the central retinal vein (CRV) than in the central retinal artery (CRA) and the severity of nonproliferative diabetic retinopathy (non-PDR).

\textbf{Methods:} We evaluated both eyes of 20 non-PDR patients with higher peak systolic velocity (PSV) in the CRV than in the CRA unilaterally as determined by color Doppler imaging (CDI). The eyes with higher PSV in the CRV were placed in group D2-H, and the fellow eyes were placed in group D2-L. The stage of non-PDR was determined by the guidelines of the Early Treatment Diabetic Retinopathy Study. Normal subjects and non-PDR patients without higher PSV in the CRV were evaluated as CDI controls.

\textbf{Results:} Advanced non-PDR ($P=0.001$) and cystoid macular edema ($P=0.02$) were statistically more frequent in group D2-H. The velocities in the ophthalmic artery and the short posterior ciliary artery were not statistically different among all groups. The velocities in the CRA were similar in all non-PDR groups and significantly lower than in the normal subjects ($P<0.05$). The velocities in the CRV were significantly higher only in group D2-H ($P<0.001$).

\textbf{Conclusion:} Higher PSV in the CRV than in the CRA was significantly correlated with the severity of non-PDR, especially in the presence of cystoid macular edema. \textit{Jpn J Ophthalmol} 2006;50:312–317 © Japanese Ophthalmological Society 2006

\textbf{Key Words:} color Doppler imaging, cystoid macular edema, Early Treatment Diabetic Retinopathy Study, higher blood flow velocity, nonproliferative diabetic retinopathy

\textbf{Introduction}

Orbital color Doppler imaging (CDI) results suggest that diabetic patients have significantly lower blood flow velocities in both the central retinal artery (CRA) and central retinal vein (CRV) than in the corresponding vessels of normal eyes, and this reduction in velocity may arise from an increase in the resistance induced by diabetic retinal microvascular obstructions.\textsuperscript{1,2}

However, we have identified a subgroup of diabetic patients who have unexpectedly higher blood flow velocities in both the CRA and CRV bilaterally.\textsuperscript{3} These patients have low serum albumin and diffuse optic disc staining in fluorescein angiography. We have suggested that the low serum albumin causes leakage of serum because of the low osmotic pressure of the blood. The induced tissue edema, in turn, causes the narrowing of the CRA and CRV in the optic nerve head, thus leading to higher velocities in both vessels. As might be expected, the velocities are higher in the thin-walled CRV.\textsuperscript{4}
The narrowing of the CRV in the optic nerve head should increase the venous blood flow pressure in the retina. It is impossible to measure the diameter of the CRV by CDI, but we can assume that the outflow volume through the CRV is the same as the inflow volume through the CRA. Additionally, because the product of the cross-sectional area and the velocity is the blood flow volume, we suggest that the higher velocity in the CRV than in the CRA is due to greater narrowing of the CRV than the CRA. This hypothesis is supported by the fact that the CRV usually does not have any collateral pathway to the superior ophthalmic vein.

Thus, we hypothesize that the higher velocity in the CRV than in the CRA, which we attribute to the CRV being narrower than the CRA, is related to the severity of diabetic retinopathy. To test our hypothesis, we designed a cross-sectional study comparing the retinal findings in the two eyes of the same patients with nonproliferative diabetic retinopathy (non-PDR) but with higher peak systolic velocity (PSV) in the CRV than in the CRA unilaterally.

**Subjects and Methods**

Twenty non-insulin-dependent diabetes mellitus patients (40 eyes) with non-PDR and higher PSV in the CRV than in the CRA unilaterally were studied (group D2). They had been referred to the Osaka Medical Center for Cancer and Cardiovascular Diseases between May 2002 and January 2004. The ages of the patients in group D2, ranged from 50 to 81 years with a mean of 66.0 ± 7.1 years (±SD). Each eye was classified into one of two subgroups depending on the velocity in the CRV; the eyes with PSV higher in the CRV than in the CRA were placed in group D2-H (7 right eyes and 13 left eyes), and the fellow eyes were placed in group D2-L. The difference in PSV between the CRV and CRA of group D2-H eyes ranged from 0.3 to 6.3 cm/s with a mean of 2.3 ± 1.9 cm/s. Eyes that had had intraocular surgery, panretinal photocoagulation, or other ocular diseases were excluded.

All subjects received a standard ophthalmic examination, and 8 of the 20 patients in group D2 underwent fluorescein angiography because of their active diabetic retinopathy. The scoring of the pre-PDR stage was done according to the guidelines of the Early Treatment Diabetic Retinopathy Study (ETDRS)5-6 by observers masked to the CDI findings.

CDI was performed on the orbital vessels of all eyes by the same ophthalmologist (SF). An HDI 5000 ultrasound system (Philips, Bothell, WA, USA) with a 5- to 10-MHz broadband linear transducer was used according to the method described by Lieb et al.7-8 In the spectrum analysis mode, the spatial peak temporal average intensity did not exceed the limit of 17 mW/cm² suggested by the U.S. Food and Drug Administration for ophthalmic applications.

The PSV, end diastolic velocity (EDV), and resistive index (RI) in the ophthalmic artery, the temporal short posterior ciliary artery, and the CRA and CRV were measured. More specifically, the ophthalmic artery running parallel to the optic nerve was measured at about 35 mm depth from the eyelid. The temporal short posterior ciliary artery was measured in the vessel nearest the temporal side of the optic nerve head in a horizontal section. The measurements of the blood flow in the CRA and CRV were made at approximately 3 mm depth from the inner edge of the optic nerve head.

For statistical analyses of the blood flow parameters, 20 selected eyes of normal subjects (group N), and 20 selected eyes of non-PDR patients without higher PSV in the CRV than in the CRA (group D1) were studied as CDI controls.

Informed consent was obtained from all patients after an explanation of the purpose of the study and the procedures to be used. This study was conducted to conform to the tenets of the Declaration of Helsinki.

The baseline characteristics, except sex, and the blood flow parameters were analyzed among groups by one-way analysis of variance (one-way ANOVA) with the Tukey test. Sex and retinal differences were analyzed by the χ-squared test. The significance of the difference between the ETDRS scores and our findings in groups D2-H and D2-L was determined by Mann-Whitney U tests. A P value less than 0.05 was considered to be statistically significant.

**Results**

**General Examination**

The demographics of each group (groups N, D1, D2) are shown in Table 1. The mean age, sex, systemic systolic and diastolic blood pressure, and intraocular pressure of the patients in group D2 did not differ significantly from those in groups N and D1 (Table 1).

**Scores of non-PDR Stage and Individual Retinal Findings**

The ETDRS scores indicated that the retinopathy in the group D2-H eyes was significantly more advanced than that in group D2-L eyes (P = 0.001, Table 2). Among all patients in group D2, the ETDRS scores of 17 (85%) were higher in the eyes with higher PSV in the CRV (group D2-H) than in the fellow eyes (group D2-L). In three patients (15%), the ETDRS scores were the same in both eyes.

In the individual retinal findings, cotton wool patch was found in eight eyes in group D2-H and in three eyes in group D2-L. Circinate hard exudate was found in seven eyes in group D2-H and in two eyes in group D2-L. Cystoid macular edema was found in six eyes only in group D2-H. Peripheral hemorrhage was also found in three eyes only in group D2-H. The difference in the number of the eyes with these retinal findings between groups D2-H and D2-L was statistically significant only for cystoid macular edema (P = 0.02, Table 2).