The Risk of Missing Angle Neovascularization by Omitting Screening Gonioscopy in Acute Central Retinal Vein Occlusion

David J. Browning, MD, PhD,[1] *Adelaide Q. Scott, BA,*[1] *Christopher B. Peterson, BA,*[1,2] *Jennifer Warnock,*[1] *Zhiyi Zhang, PhD*[3]

Objective: The purpose of the study was to determine whether angle neovascularization can occur without pupillary margin neovascularization in central retinal vein occlusion (CRVO).

Design: The study design was a prospective study of the main question and a retrospective study of ancillary issues.

Participants: The authors examined 105 eyes of 100 patients with CRVO having clinical evidence of ischemia between July 1, 1986, and March 18, 1996.

Intervention: The authors looked for iris and angle neovascularization with both undilated slit-lamp biomicroscopy and Zeiss four-mirror gonioscopy.

Main Outcome Measures: The presence of anterior segment neovascularization was measured.

Results: Of 34 eyes developing anterior segment neovascularization, 4 (12%) developed angle neovascularization without pupillary margin neovascularization over a mean follow-up of 2.2 ± 2.4 standard deviation years.

Conclusions: Angle neovascularization can occur without pupillary margin involvement in CRVO, implying the necessity of screening gonioscopy and supporting the Central Vein Occlusion Study conclusion (based on a photographic technique not used clinically). *Ophthalmology 1998;105:776–784*

Ischemic central retinal vein occlusion (CRVO) leads to neovascular glaucoma in 40% to 60% of patients if left untreated.[1–3] Angle neovascularization, while not synonymous with eventual neovascular glaucoma, is the best clinical predictor of eventual neovascular glaucoma. Laser panretinal photocoagulation is effective in causing regression of angle neovascularization in 23% to 60% of patients and is the main method effective in preventing the transition from angle neovascularization to neovascular glaucoma.[2–6] Therefore, the clinician does not want to miss angle neovascularization. Some ophthalmologists equate pupillary margin neovascularization with angle neovascularization, assuming that if no pupillary margin neovascularization is present, then neither will angle neovascularization be present. Data from the Central Vein Occlusion Study (CVOS) document that such an assumption is erroneous, but these data were obtained with a photographic technique for rubeosis detection not used clinically.[6] We sought to further resolve this issue using standard clinical techniques for rubeosis detection and report our results from a study concurrent with and independent of CVOS.

Methods

There are two parts to this study: a survey of prevailing practice patterns of ophthalmologists in management of CRVO and a prospective clinical study to ascertain the sequence of anterior segment neovascularization in patients with ischemic CRVO.

The first part was a 3-question survey sent to 376 ophthalmologists registered with the Board of Medical Examiners of the state of North Carolina. The exact questions are shown in Figure 1. All replies were made anonymously to encourage honesty. The purpose of the survey was to assess to what extent omission of screening gonioscopy occurs in clinical practice. The survey was sent out 1 year after the results and recommended follow-up schedule of the CVOS were published.[6]

The clinical study was performed in a private retinal referral practice. It is prospective regarding the question addressed (the sequence of anterior segment neovascularization in CRVO) but retrospective in the ancillary analyses reported, in which data were extracted from the clinical charts of the patients. It is

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[1] Charlotte Eye, Ear, Nose, and Throat Associates, Charlotte, North Carolina.

[2] North Carolina State University, Raleigh, North Carolina.

[3] University of North Carolina at Charlotte, Charlotte, North Carolina.

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Reprint requests to David J. Browning, MD, PhD, 1600 East Third Street, Charlotte, NC 28204.

1. During the first six months after a central retinal vein occlusion, how often do you see the patient?
   a.)_____monthly
   b.)_____4 times
   c.)_____3 times
   d.)_____2 times
   e.)_____other; please comment_____

2. When you see the patient during the first six months after a central retinal vein occlusion, what is your exam sequence?
   a.)_____undilated slit lamp exam, undilated gonioscopy, dilated fundus exam each visit
   b.)_____dilated slit lamp exam, dilated gonioscopy, dilated fundus exam each visit
   c.)_____undilated slit lamp exam, dilated fundus exam each visit
   d.)_____dilated slit lamp exam, dilated fundus exam each visit
   e.)_____other; please comment_____

3. How many patients with central retinal vein occlusion have you seen in the past year (please estimate)
   _____

Figure 1. Questionnaire sent to all ophthalmologists in North Carolina to ascertain prevailing practice patterns regarding diagnosis and rubeosis detection in central retinal vein occlusion.

prospective in the sense that the question to be answered ("How often will angle rubeosis be present in the absence of pupillary margin rubeosis?") was formulated before the first patient was examined. Central retinal vein occlusion was diagnosed when there was history of sudden loss of vision and there was a compatible fundus examination, including disk swelling, retinal hemorrhages in all four quadrants, venous engorgement, and sometimes cotton-wool spots. The study was terminated shortly after the CVOS was published, because it touched on one of the key clinical points of that study and did so in a complementary fashion using a clinical rather than a photographic method of rubeosis detection. One hundred sixty-nine eyes of 161 patients with CRVO were examined between July 1, 1986, and March 18, 1996. Of these 169 eyes, 24 had funduscopic signs of remote CRVO with minimal residual intraretinal hemorrhage, macular pigment epithelial scarring, sheathed veins, and disk collateral vessels. Two of these eyes had anterior segment neovascularization develop but were excluded from the study of the risk of missing rubeosis because of the chronic nature of the occlusion. These eyes are included in Table 2 in which predictors of iris neovascularization are considered. Forty eyes had acute CRVO but no clinical evidence of retinal ischemia, were judged to be at low risk for rubeosis, and were excluded from the study. The remaining 105 eyes of 100 patients all had some characteristics suggesting ischemic, acute CRVO with some risk of subsequent rubeosis (98 eyes) or had rubeosis at the first visit (7 eyes) and constitute the database for the study. The clinical diagnosis of ischemic CRVO is multidimensional[7] and involves an integration of the following data: initial vision,[8] severity of retinal hemorrhage,[6] severity of macular edema,[9] presence and size of a relative afferent pupillary defect,[10] degree of retinal capillary nonperfusion on fluorescein angiography,[11] electroretinographic changes,[12–15] visual field changes,[8] patient age[16]; presence of diabetes, hypertension, and atherosclerotic cardiovascular disease[3]; and presence of pre-existing glaucoma.[3,17] Not all of these tests or pieces of information were obtained in every patient, and there was no standard formula used to reach a diagnosis of ischemic versus nonischemic CRVO, as has been published.[17] The diagnosis was clinical, based on the information obtained on each patient. In contrast to CVOS, patients were not excluded if either eye had diabetic retinopathy or old branched retinal arterial or branched vein occlusions. All eyes with CRVO considered to have some ischemic characteristic were examined first with the slit lamp in an undilated state with white light and high magnification and then with Zeiss four-mirror gonioscopy. Follow-up visits were scheduled monthly for 3 months and then at 6 and 12 months, but logistical problems kept many patients from adhering to this schedule, a difficulty met by previous investigators as well.[3,18] In tabulating the follow-up, patients seen between 2 and 6 weeks were included in the 1-month category, those seen between 6 and 10 weeks were included in the 2-month category, those seen between 10 and 19 weeks were included in the 3-month category, those seen between 19 and 39 weeks were included in the 6-month category, those seen between 39 and 78 weeks in the 1-year category, those seen between 18 and 30 months in the 2-year category, and those seen between 30 and 42 months in the 3-year category. When follow-up appointments were missed, patients were telephoned and rescheduled as soon as they could return to be seen. Rubeosis was defined as fine red tortuous lines coursing in an irregular manner over the iris surface or angle and is the standard clinical definition of rubeosis.[19] All clinical examinations were performed by the same ophthalmologist. Fluorescein angiography always included the posterior pole and inconstantly a sweep of the midperiphery. All measurements of capillary nonperfusion were made using Macular Photocoagulation Study disk area templates applied to frames of the angiogram taken with a 30° Zeiss or Topcon fundus camera and will represent a lower boundary on the true extent of capillary nonperfusion because the midperiphery was photographed incompletely in many patients. When electroretinography was performed, the photopic electroretinogram (ERG) was obtained first. Scotopic ERGs were obtained after dark adaptation for 30 minutes. The ERG was obtained simultaneously from the involved and the fellow eye after one drop of tropicamide 1% and one drop of Neo-Synephrine 2.5% (Winthrop, New York, NY) were instilled in each eye. In one patient, no fellow eye was present. A ganzfeld bowl with uni-

Table 1. Patient and Eye Characteristics*

Patient or Eye Characteristic	Value	Denominator
Unilateral CRVO	92 (92%)	100
Bilateral CRVO	8 (8%)	100
Follow-up (yrs)		
Mean	2.2	105
SD	2.4	
Duration of symptoms (days)		
Median	30	89
Interquartile range	7–180	89
Mean	88	89
SD	185	89
Visual loss ≤ 6 mos	79	105
Visual loss indeterminate	16	105
Visual loss >6 mos	10	105
Age (yrs)		
Median	70	100
Interquartile range	61–77	100
Mean	68	100
SD	14	100
Sex		
Female	52 (52%)	100
Male	48 (48%)	100
Race		
Black	19 (20%)	93
White	74 (80%)	93
Smoking	13 (17%)	77
Hypertension medication	49 (49%)	100
Preexisting glaucoma	22 (21%)	105
Diabetes mellitus	21 (21%)	100
RAPD	57 (55%)	104
Initial vision		
Median	20/200	105
Interquartile range	20/50–CF	105
Mean (logMAR)	−0.9957	105
SD	0.8748	105
ERG		
B/A < 1.0	5 (13%)	38
Intereye > 7.3	7 (18%)	38
Scotopic white flash B Imp ≥ 47.17	22 (56%)	39
Normalized scotopic B < 0.70	11 (29%)	38
Normalized photopic B < 0.70	8 (21%)	38
BRVO before CRVO	0	105
BRVO fellow eye	3	104
BRAO, CRAO same eye	0	105
BRAO, CRAO fellow eye	0	104
Diabetic retinopathy same eye	1	105
Diabetic retinopathy fellow eye	2	104

RAPD = relative afferent pupillary defect; BRVO = branch retinal vein occlusion; BRAO = branch retinal arterial occlusion; CRAO = central retinal arterial occlusion; CRVO = central retinal vein occlusion; CF = counting fingers; SD = standard deviation.

* Characteristics of patients and eyes prospectively studied to determine the sequence of anterior segment neovascularization in CRVO.

form background illumination, jet contact lens electrodes, a Grass stimulator, and a Biologic Systems minicomputer-based control system were used to collect and store the data. A forehead electrode served for reference and a retroauricular electrode served for the ground electrode.

In analyzing the fundus photographs and fluorescein angiograms, a score of 1 point was assigned to an eye for any of the following attributes: hemorrhage greater than standard photograph 2B from the CVOS, more than one cotton-wool spot, more than four cotton-wool spots (i.e., an additional three or more cotton-wool spots over the threshold level of one cotton-wool spot earns the eye another point in the ischemic score), presence of late venous wall staining in the fluorescein angiogram, macular edema greater than a standard stereo photographic pair, angiographic edema greater than or equal to 50% of the area of standard field 2 hyperfluorescent in late frames of the angiogram, and greater than or equal to ten disk areas of capillary nonperfusion. A total photographic score equal to the sum of the points from the photographic categories also was recorded. All photographic interpretations were done by one reader (DJB).

Clinical data were extracted from the patients' charts and collected in a computer database using DBase IV (Borland, Scotts Valley, CA). The finished database was imported to the statistical software JMP (SAS, Cary, NC) for the descriptive statistical analysis and modeling. Statistical testing in Tables 2 and 3 was done using t tests for unpaired data for means or proportions via the software Confidence Interval Analysis (British Medical Journal, London, England) without Bonferroni correction. Patient characteristics, photographic variables, total photographic score, and electroretinographic variables were analyzed for predictive value in development of anterior segment neovascularization using logistic regression. First, these variables were tested for their predictive power individually. This information is important, because in any particular clinical situation, a physician may have access to some of these pieces of information, but not others, so that the predictive ability of each should be investigated. Second, the variables are tested together in a multivariable regression model. The model was run in forward-stepwise fashion using JMP software, with the most predictive single variable as the initial predictor variable and the other individually predictive variables added one at a time. The additional variables were retained only if they kept predictive power within the model at the 0.05 level.

Results

Survey

Of the 376 physicians polled, 2 physicians had died and 3 had retired, leaving 371 practicing physicians. Of these, 153 physicians (41%) replied. Of the 153, 47 (31%) reported examining patients with ischemic CRVO monthly for the first 6 months after diagnosis, 3 (2%) examined patients 5 times in 6 months, 55 (36%) examined patients 4 times, 38 (25%) examined patients 3 times, and 4 (3%) examined patients 2 times. Two ophthalmologists (1%) referred all patients with CRVO and four ophthalmologists (3%) gave unquantifiable responses. Of the 153 respondents, 50 (33%) examined the undilated patient both with slit lamp and gonioscopy at each visit, 14 (9%) examined the dilated patient with the slit lamp and gonioscopy at each visit, 54 (35%) examined the undilated eye with slit lamp and the dilated eye with ophthalmoscopy omitting gonioscopy, and 24 (16%) examined the dilated eye with the slit lamp and with ophthalmoscopy omitting gonioscopy. Seven respondents (5%) had a variety of other examination sequences, two referred all patients with CRVO, and two responses were nebulous. The smallest number of patients with CRVO seen by a respondent in the past year was 0, the largest was 200, the median was 5, and the mean was 9 ± 18 standard deviation (n

Table 2. Comparison of Patients and Eyes with Neovascularization to Those without Neovascularization*

Patient Characterization	Patients Who Developed Anterior Segment Neovascularization	Patients Not Developing Anterior Segment Neovascularization	P
Initial visual acuity			
Median	20/400	20/100	
Interquartile range	20/80–CF	20/40–20/400	
Mean	−1.25057	−0.8268	
SD	0.89499	0.7482	<0.01
Final visual acuity			
Median	CF	20/200	
Interquartile range	DF–2/200	20/40–CF	
Mean	−1.87478	−0.89	
SD	0.93549	0.7461	<0.01
Age			
Median	71	68	
Interquartile range	36–77	56–76	
Mean	70	65	
SD	11	14	<0.05
Hypertension medications			
Yes	23	58	
No	14	73	
Unknown		1	<0.05
Symptom duration			
Median	14	18	
Interquartile range	7–60	5–75	
Mean	84	321	<0.01
SD	167	425	
N	33	100	
RAPD			
Yes	29	45	
No	8	87	<0.01
Diabetes			
Yes	10	26	
No	27	101	NS
ERG			
Mixed ERG B/A ratio	1.1 ± 0.6	1.3 ± 0.6	NS
Intereye difference > 7.3 msec	3.4 ± 5.3	4.9 ± 15.6	NS
B Implicit > 47.17 msec	10/18	11/28	NS
Normalized scotopic B < 0.70	10/18	6/27	<0.05
Normalized photopic B < 0.70	6/18	3/26	NS
Follow-up time	2.4 ± 2.5	1.9 ± 2.4	NS
Posterior neovascularization			
NVD	1	5	NS
NVE	2	4	NS
Disk collaterals			
Yes	16	51	
No	21	81	NS
Previous glaucoma			
Yes	9	20	
No	28	112	NS
Sex			
Male	16	63	
Female	21	64	NS
Race			
Black	7	24	
White	28	91	
Unknown	2	12	NS
Smoking			
Yes	4	17	
No	24	79	
Unknown	9	31	NS

SD = standard deviation; N = number of eyes; NVD = neovascularization of the disc; NVE = neovascularization elsewhere; NS = not significant at the 0.05 level; RAPD = relative afferent pupillary defect.

* Summary of differences in certain patient and eye characteristics between eyes which developed anterior segment neovascularization and those which did not.

Table 3. Photographic Characteristics of Eyes*

Photographic Characteristic	Patients Who Developed Anterior Segment Neovascularization	Patients Not Developing Anterior Segment Neovascularization	P
Hemorrhage ≥ 2B	4	8	NS
CW spots ≥ 4	4	7	NS
CW spots ≥ 1	4	15	NS
Venous wall staining	10	18	NS
ME ≥ standard	13	23	<0.05
≥50% of field 2 Hyper†	13	20	<0.05
≥10 DA capillary NP	3	1	NS
Total score (± SD)	2.0 ± 1.7	1.0 ± 1.5	<0.01
Disc collaterals	2	20	<0.05
Macular lipid	0	5	<0.05
C/D involved eye (± SD)	0.2 ± 0.2	0.2 ± 0.2	NS
C/D fellow eye (± SD)	0.3 ± 0.3	0.2 ± 0.2	<0.05
C/D difference (± SD)	−0.1 ± 0.1	−0.05 ± 0.12	<0.05

NP = nonperfusion; C/D = cup-to-disc ratio judged from stereo photographs of the optic disc with averaging of the vertical and horizontal aspects to yield an overall ratio for the optic nerve, Hemorrhage ≥ 2D = standard photograph 2B from the Central Vein Occlusion Study; ME = macular edema; Hyper = hyperfluorescence in the late frames of the fluorescein angiogram; DA = disc areas; NP = nonperfusion; NS = not significant; SD = standard deviation.

* Summary of photographic characteristics of patients with CRVO who did or did not develop anterior segment neovascularization.

† The proportion of eyes having >50% of standard field 2 hyperfluorescent in the late frames of the fluorescein angiogram (an index of degree and extent of increased retinal vascular permeability).

= 151 responses to this question). The respondents were classified into those physicians seeing fewer than five patients with CRVO per year (group 1) and those seeing five or more patients with CRVO per year (group 2). Twenty-two (29.3%) of 75 group 1 physicians examined patients with undilated slit-lamp examinations and gonioscopy compared to 28 (35.9%) of 78 group 2 physicians. There was no difference in the proportions of these groups performing undilated slit-lamp examinations and gonioscopy (95% confidence interval for the difference of the proportions was −0.214, 0.0825). Seventeen (22.7%) of 75 group 1 physicians examined patients with CRVO monthly for the first 6 months compared to 27 (34.6%) of 78 group 2 physicians, a difference not reaching statistical significance (95% confidence interval for difference of proportions in the two groups was −0.261, 0.0224). Respondents also were classified into those physicians examining patients with CRVO monthly for the first 6 months (group 3) versus those physicians with other follow-up practices (group 4). Twenty-seven (61.4%) of 44 group 3 physicians examined patients with undilated slit-lamp examinations and gonioscopy compared to 23 (21.1%) of 109 group 4 physicians, a statistically significant difference in proportions (99% confidence interval for the difference in proportions was 0.188, 0.617).

Clinical Study

The completeness of follow-up is shown in Figure 2. The completeness declined progressively as follow-up intervals increased. Eighty-one percent of patients were examined at the 1-month visit, falling to 28% of eyes examined at the 3-year follow-up visit.

A number of relevant characteristics of the patients and eyes studied are summarized in Table 1. The demographic characteristics of the patients are similar to those of previous series. Seventy-five percent of the eyes had symptoms for less than 6 months, the time of greatest likelihood of rubeosis developing in these patients after CRVO. All patients had some clinical characteristic suggesting ischemia, but no individual index captured all the patients as "ischemic." In Table 1, the following characteristics apply to patients and have a denominator of 100: laterality of CRVO, age, gender, race, smoking, hypertension medication, and diabetes mellitus. The following characteristics refer to eyes and have a denominator of 105: distribution of symptom durations, pre-existing glaucoma, and initial vision. Of the 105 eyes, 39 had ERGs performed. The denominator of the B-to-A ratio is 38 because 1 patient had an extinguished scotopic white flash A amplitude. The denominator in the row for intereye difference in scotopic white flash B-wave implicit time greater than 7.3 msec is 38 because 1 patient had no fellow eye for computing this value. Mean visions are expressed in logarithm of the minimum angle of resolution (logMAR) form because visions are converted properly to logMAR form before an average is taken. Race was not determined in 7 patients, and a smoking history was not taken in 23 patients, explaining the denominators of 93 and 77, respectively, for these characteristics. One patient had nonproliferative diabetic retinopathy in the eye developing the CRVO before the event, two patients had nonproliferative diabetic retinopathy in the fellow eye of the CRVO eye, no patients had branch retinal vein occlusions in the CRVO eye before the event, three patients had branch retinal vein occlusions in the fellow eye of the CRVO eye, and no patient had a central or branch retinal arterial occlusion in the CRVO eye or the fellow eye. The denominator for relative afferent pupillary defect, branch retinal vein occlusion fellow eye, branch retinal arterial occlusion, central retinal arterial occlusion fellow eye, and diabetic retinopathy fellow eye is 104 because one patient had no fellow eye.

The differences between the patients and eyes of patients who developed anterior segment neovascularization and those who did not for a number of clinical variables are listed in Table 2. The group of 37 eyes that developed anterior segment neovascularization included 34 eyes suspected to be ischemic and studied prospectively with undilated slit-lamp examination and gonioscopy, 1 eye in the group of 40 eyes clinically classified initially as nonischemic acute CRVO and not studied prospectively both with undilated slit-lamp examination and goni-

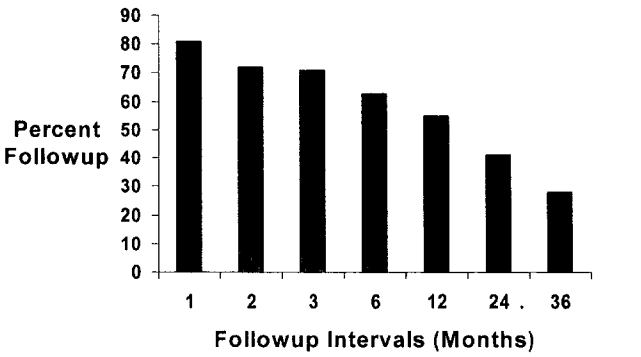

Figure 2. Completeness of follow-up at intervals after diagnosis of central retinal vein occlusion.

oscopy, and 2 eyes with chronic CRVO and rubeosis at the time of initial presentation. Thus, 1 of 40 eyes was either classified erroneously as nonischemic when it was seen initially or else was in fact nonischemic but converted over time to ischemic CRVO. The ERG of this patient was nonischemic with a scotopic B/A amplitude ratio of 2.0 and an intereye difference in scotopic B-wave implicit time of 6.0 msec. The fluorescein angiogram of this patient showed good capillary perfusion. There was no afferent pupillary defect present. With these data, we believe this case represents a conversion from nonischemic CRVO to ischemic CRVO. Patients developing anterior segment neovascularization were older, more likely to use hypertension medication, had worse initial and final vision, were more likely to have a relative afferent pupillary defect, and had a shorter duration of symptoms than the patients not developing anterior segment neovascularization. In contrast, there were no statistically significant differences between the two groups in the following patient characteristics: gender, race, smoking prevalence, several ERG parameters reported previously to be predictive of subsequent rubeosis, prevalence of posterior segment neovascularization, prevalence of disk collaterals, and prevalence of antecedent primary open-angle glaucoma.

The number of eyes not developing anterior segment neovascularization was 132, derived from 127 patients. The number of eyes developing anterior segment neovascularization was 37, derived from 37 patients. These numbers of eyes and patients provide the denominators for columns two and three of Table 2, respectively. Three patients having bilateral CRVO contributed eyes to both groups. In Table 2, B/A amplitude refers to the ratio of the scotopic white flash B-wave amplitude divided by A-wave amplitude,[12] the intereye difference refers to the scotopic white flash B-wave implicit time of the eye with the CRVO minus the analogous implicit time of the fellow eye,[14] and B implicit greater than 47.17 msec refers to the scotopic white flash B-wave implicit time. The entries in this row of Table 2 signify how many patients had this time exceed 47.17 msec.[14] Normalized scotopic B refers to the scotopic B-wave amplitude of the CRVO eye divided by the corresponding value in the normal fellow eye. The entries in this row of Table 2 refer to the number of patients in whom this quantity was less than 0.70.[15] Normalized photopic B refers to the same analysis for the photopic ERG. The number of patients not later developing anterior segment neovascularization who had ERGs was 29. For some of the table entries, the denominator differs from 29 because of extinguished components of the ERG or no fellow eye recording. The number of patients later developing anterior segment neovascularization who had ERGs was 18.

Photographic characteristics of eyes are listed in Table 3 according to whether rubeosis developed or not. The proportions of patients with macular edema greater than the standard stereo pair and of photographs with later hyperfluorescence occupying more than 50% of standard field 2 of the fluorescein angiogram were greater in patients later developing rubeosis, as was the mean photographic score. Eyes developing rubeosis had lower proportions of disk collaterals and macular lipid and had a larger difference between the cup-to-disk ratio of the involved and fellow eye. Other photographic characteristics did not differ between the two groups. Of the patients who later developed anterior segment neovascularization, 27 had color fundus photographs and 24 had fluorescein angiograms. These are the sample sizes used for the first column of Table 3 in computing probability values. Of the patients who later did not develop anterior segment neovascularization, 93 had color fundus photographs and 76 had fluorescein angiograms. These are the sample sizes for column 2 of Table 3 in computing probability values. No Bonferroni correction was used for multiple tests.

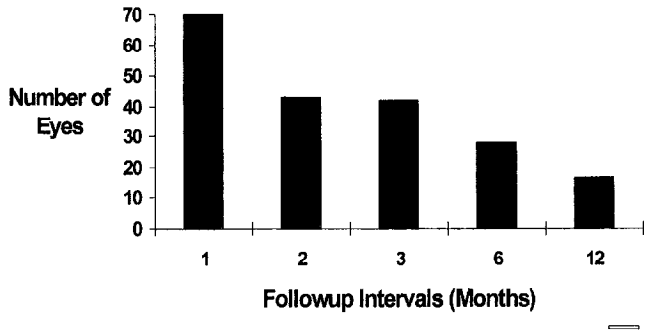

Figure 3. Completeness of gonioscopy examinations at intervals after diagnosis of central retinal vein occlusion.

When all of the patient characteristics and clinical variables obtained from routine ophthalmic testing were analyzed for predictive value for later anterior segment neovascularization, the only predictive variables were the presence of a relative afferent pupillary defect ($P < 0.0001$) and the presence of macular edema ($P = 0.0358$). The initial visual acuity approached significance as a predictor of iris neovascularization ($P = 0.0848$). When all of the photographic variables were examined by logistic regression, only the presence of capillary nonperfusion greater than ten disk areas was predictive of later anterior segment neovascularization ($P = 0.0297$), although the total photographic score approached statistical significance ($P = 0.0516$). When all of the ERG measured variables and the computed variables scotopic white flash ERG B/A amplitude ratio, scotopic white flash ERG intereye B-wave implicit time, normalized scotopic white flash B-wave amplitude, normalized photopic B-wave amplitude, and photopic B/A amplitude ratio were analyzed for predictive value, five variables were predictive for anterior segment neovascularization: scotopic white flash B/A amplitude ratio ($P = 0.0094$), 30-Hz flicker amplitude ($P = 0.0115$), scotopic white flash A-wave implicit time ($P = 0.0123$), photopic B-wave amplitude ($P = 0.0151$), and scotopic blue flash B amplitude ($P = 0.0374$). The afferent pupillary defect (APD) and the ERG variables share some of the same predictive information in the sense that adding the ERG predictive variables to a model containing the APD only added predictive power in the case of the 30-Hz flicker amplitude. When the best model incorporating both APD and 30-Hz flicker amplitude was used to predict later development of anterior segment neovascularization, there were 26 correct predictions and 7 incorrect predictions (21%) of the 33 cases in which both pieces of data were available to apply the model. Interactions of degree 2 were explored for the predictive variables attaining statistical significance and none of statistical significance was found.

The median number of prospective combined slit-lamp and gonioscopic examinations was three per eye. The completeness of these examinations at the different intervals after diagnosis is shown in Figure 3. At 1 month, 81% of eyes had gonioscopic examination, decreasing to 28% at the 3-year visit. Omissions were distributed between failure of patient follow-up and omission of the examination by the ophthalmologist, and the fraction in each category at each interval varied. Of the 105 eyes, 34 (32%) developed anterior segment neovascularization. Of these 34 eyes, 15 had both pupillary margin and angle neovascularization, 15 had pupillary margin neovascularization without angle neovascularization, and 4 had angle neovascularization without pupillary margin neovascularization. The time course for the development of anterior segment neovascularization is shown

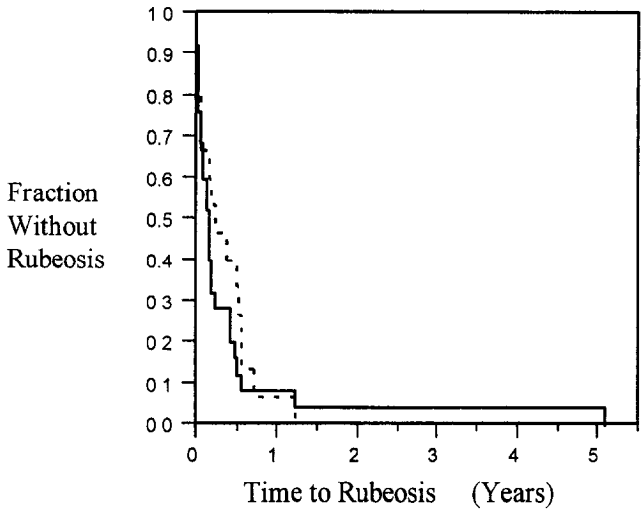

Figure 4. Time course for development of anterior segment neovascularization. The plots are Kaplan–Meier survival curves in which the ordinate represents the fraction of patients who have not yet developed rubeosis at the time being considered. The dashed curve applies to angle neovascularization and the solid curve to pupillary margin neovascularization.

in Figure 4. There were no differences in time course for eyes developing pupillary margin rubeosis only, angle rubeosis only, and eyes developing both pupillary margin and angle rubeosis (log–rank test, $P = 0.6051$).

Panretinal photocoagulation was performed in 31 of the 34 eyes with rubeosis, panretinal cryotherapy in 1 eye, argon laser trabeculoplasty after regression of rubeosis in 3 eyes, glaucoma-filtering surgery in 4 eyes, laser chorioretinal anastomosis in 2 eyes, and trans-scleral YAG cyclophotocoagulation in 2 eyes (some eyes had more than 1 procedure). Of the two eyes not receiving some form of retinal ablation for anterior segment neovascularization, both eyes already had complete angle closure, one with no light perception vision at the initial visit and the other with light perception only. Of the 32 eyes receiving panretinal ablation by photocoagulation or cryotherapy, rubeosis regressed in 29 and still was present at the last visit in 3. Neovascular glaucoma developed in 16 of the 34 eyes. Of these 16 eyes, 10 retained vision and had intraocular pressures less than 22 with medical and various surgical therapies (listed previously), 3 eyes were blind but comfortable with the patients having received topical therapy at last follow-up, 1 eye was that of a patient who died of a stroke 2 months after diagnosis of CRVO, and 2 eyes were those of patients who did not return for treatment despite attempts to contact them. Outcome behavior was similar whether eyes had angle neovascularization alone or pupillary margin neovascularization alone as listed in Table 4. Eyes with both pupillary margin and angle neovascularization had worse outcomes with fewer eyes having regression of rubeosis and ultimate control of intraocular pressure. Of the 34 eyes, the median final visual acuity was counting fingers with the interquartile range of 2/200 to counting fingers.

Discussion

The patients studied were taken from a nonacademic private retina practice, a setting distinct from that reported in other studies of CRVO. It is important, therefore, to compare the patient population to the previously reported series, because site of origin of studies can influence outcomes if the populations studied differ. The age ranges, gender distributions, glaucoma prevalence, diabetes, and hypertension are similar in this series to those in previous reports.[3,16,18] The differences in descriptors for those patients who went on to develop anterior segment neovascularization compared to those who did not also are consistent with previous reports.[3,16] We therefore believe that the proportions of pupillary margin and angle rubeosis observed correctly characterize the sequence of anterior segment neovascularization of CRVO.

All previous reports have found that some eyes classified initially as nonischemic ultimately become ischemic or were misclassified, and we experienced this same problem in one case. In our case, the indications for ischemia from pupil testing, the ERG, and fluorescein angiogram were not present initially, and we believe this case represents a true conversion from nonischemic CRVO to ischemic CRVO. Because no foolproof clinical finding exists for prediction of later anterior segment neovascularization, we believe that it is wise to observe all patients with CRVO frequently until the clinical picture becomes defined.

This study shows that angle neovascularization can occur in CRVO without pupillary margin neovascularization. In an independent publication of work concurrent with that reported here, the CVOS group reported the same finding in both patients with perfused and nonperfused CRVO.[6,18] In the perfused group, of 522 eyes completing the early natural history study, 30 eyes developed anterior segment neovascularization, of which 3 (10%) developed angle neovascularization without iris neovascularization.[18] In the nonperfused group of CRVO, 181 eyes were observed, of which 50 developed anterior segment neovascularization. Of these 50 eyes, 3 (6%) developed angle neovascularization without iris neovascularization.[6] In the CVOS, a masked reader of slit lamp and goniophotographs determined presence of angle and iris neovascularization. Those who have studied anterior seg-

Table 4. Ocular Outcomes of Eyes Developing Anterior Segment Neovascularization*

	Pupil Only	Angle Only	Both†
Last vision			
Median	0.04	0.03	0.04
Interquartile range	(0.01, 0.05)	(0.02, 0.04	(0.002, 0.04)
Last intraocular pressure			
Median	16	14	17
Interquartile range	(14, 19)	(12, 16)	(13, 24)
Last visit presence of rubeosis			
Absent	15	4	12
Present	0	0	3

* Ocular outcomes of eyes developing anterior segment neovascularization after CRVO. The columns refer to locations of rubeosis. The total number of eyes developing rubeosis was 34. Visual acuities are expressed as Snellen decimals.

† Neovascularization was present at the pupillary margin and in the angle.

ment neovascularization realize the difficulty of documenting it in color photographs, and there is reservation in accepting these results with this technique without confirmation. Wand[20] has stated, "The earliest manifestations of neovascularization of the iris (NVI) at the pupillary margin, although visible on high magnification with the slit lamp, are not visible in printed photographs." Our own experience with slit lamp and goniophotography of rubeosis agrees with that of Wand. The rationale behind the CVOS protocol is to provide objectivity to a clinical assessment. The drawback, however, is low sensitivity to the phenomenon of interest. Our study provides confirmation of the CVOS result using the commonly accepted technique of high-magnification slit-lamp biomicroscopy and gonioscopy for the detection of rubeosis. Similar information probably is contained in the data stored from the clinical examinations of the CVOS, and it would be of interest to compare their photographic and clinical detection rates. Our reported rate of 12% for development of angle new vessels in the absence of pupillary margin neovascularization is higher than the combined rate of 7.5% (3 of 30 eyes from group P, those eyes in the CVOS with <10 disk areas of capillary nonperfusion, plus 3 of 50 eyes from group N, those eyes in the CVOS with 10 or more disk areas of retinal capillary nonperfusion) reported in the CVOS, probably reflecting a higher sensitivity of clinical examination compared with photographic rubeosis detection. Not all studies have found that angle neovascularization precedes pupillary margin neovascularization in an important minority of cases. Hayreh et al[21] examined 107 eyes with ischemic CRVO but no anterior segment neovascularization initially and observed them for the development of iris and angle neovascularization, reporting that iris neovascularization preceded angle neovascularization in all cases. We cannot account for the discrepancy in that study.

The clinical implication of our study's result is clear: patients with CRVO require both undilated slit-lamp examination and gonioscopy at frequent intervals through the first 6 months of the occlusion. If gonioscopy is omitted, perhaps 12% of patients with potentially preventable neovascular glaucoma will be missed. The survey portion of the study documents that this possibility is no phantom problem. The preferred practice pattern of monthly undilated slit-lamp and gonioscopic examinations for the first 6 months after CRVO[6] is honored in the breach: only 31% of respondents check patients monthly for 6 months after an ischemic CRVO and only 33% of respondents use gonioscopy of the undilated eye at follow-up visits after CRVO. The survey was sent to ophthalmologists 1 year after publication of the CVOS preferred practice recommendations, enough time for these ophthalmologists to become aware of them. Whether the discrepancy between the preferred practice pattern and the actual practice pattern represents a problem of education (disseminating the CVOS recommendations) or a value judgment by practicing ophthalmologists on the CVOS recommendations is unknown. Our own protocol for follow-up of patients included less-frequent follow-up in the first 6 months than the CVOS recommends, but our study began in 1986 when we could not have known the CVOS recommendations published in 1995. Analysis of the survey results showed that experience in seeing patients with CRVO has little to do with management practices. Physicians seeing fewer than five patients per year with CRVO are just as likely to examine patients monthly for the first 6 months and just as likely to use undilated slit-lamp examination and gonioscopy each visit as would physicians seeing five or more patients with CRVO per year. Preferred practices in follow-up cluster together. Physicians who examine patients monthly for the first 6 months after CRVO were more likely to use undilated slit-lamp examination and gonioscopy compared to physicians who observe patients less frequently during this critical interval.

In summary, we have shown the necessity to screen all patients with ischemic CRVO with gonioscopy in the first 6 months of the process to avoid missing angle neovascularization. We also have shown that actual clinical practice falls short of preferred practice now. Although the follow-up schedule in this study involved four examinations in the first 6 months and was developed 9 years before the CVOS recommendations were published, we believe the CVOS-recommended practice of monthly examinations for the first 6 months in patients with ischemic CRVO to be the ideal, with lengthened follow-up intervals thereafter as the clinical picture dictates. The classification of patients with CRVO into ischemic and nonischemic groups is fraught with uncertainty, and a misclassification as nonischemic may result in longer intervals between follow-up and a chance of missing anterior segment neovascularization that could be treatable. Therefore, we recommend a broad definition of ischemic CRVO, incorporating weighting for poorer vision, greater patient age, presence of a relative afferent pupillary defect, widespread capillary nonperfusion on fluorescein angiography, a higher severity score on fundus photograph and fluorescein angiogram analysis, and greater abnormality in any of a number of ERG indices (30-Hz flicker amplitude, scotopic B/A amplitude ratio, and others). Our confidence in any single test's or any combination of tests' ability to predict later rubeosis when the tests are obtained at the disease onset is low, because the disease is dynamic and because of poor reproducibility between various studies in claimed predictive powers for different tests. In our view, there is no substitute for frequent follow-up when clinical doubt exists as to the classification of the type of CRVO.

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