Graefe's Arch Clin Exp Ophthalmol
(2002) 240:180–196

CLINICAL INVESTIGATION

DOI 10.1007/s00417-001-0421-3

Sohan Singh Hayreh
M. Bridget Zimmerman
Patricia Podhajsky

Hematologic abnormalities associated with various types of retinal vein occlusion

Received: 11 June 2001
Revised: 14 September 2001
Accepted: 3 December 2001
Published online: 9 February 2002

S.S. Hayreh (✉) · P. Podhajsky
Departments of Ophthalmology
and Visual Sciences, College of Medicine,
University of Iowa,
Iowa City, IA 52242, USA
e-mail: sohan-hayreh@uiowa.edu
Tel.: +1-319-3562947
Fax: +1-319-3537996

M.B. Zimmerman
Department of Biostatistics,
College of Public Health,
University of Iowa,
Iowa City, IA 52242, USA

Abstract *Background:* The objective of this study was two-fold: (1) to investigate hematologic abnormalities associated with various types of retinal vein occlusion (RVO) and comparison of their prevalence among those various types of RVO; (2) to review the conflicting literature on the subject, to place the information in perspective. *Methods:* In patients with various types of RVO seen in our clinic since 1973, we conducted planned prospective studies on the prevalence of: (1) routine hematolo-gic tests (535 patients) and (2) certain special hematologic parameters (platelet aggregation, antithrombin III, and α_2 globulin in 110, 81 and 91 patients, respectively). Patients were categorized into six types of RVO, based on defined criteria: non-ischemic and ischemic central RVO (CRVO), non-ischemic and ischemic hemi-CRVO (HCRVO), and major and macular branch RVO (BRVO). The patients had a detailed ophthalmic, systemic and hematologic evaluation. The data were abstracted and analyzed retrospectively from the detailed information originally collected prospectively in the patients' records. For data analysis, patients were divided into young, middle-aged and elderly. Observed prevalence rates of hematologic abnormalities were estimated. Logistic regression, adjusting for age and gender, was used to compare the observed prevalence of hematologic abnormalities among the various types of RVO. *Results:* No generalizations about the prevalence of hematologic disorders in all six types of RVO are possible. Ischemic CRVO showed a significantly higher prevalence of abnormal hematocrit (P=0.044), hemoglobin (P=0.018), and blood urea nitrogen (P=0.025) than non-ischemic CRVO, while a significantly higher prevalence of abnormal antinuclear antibody (ANA; P=0.049) was seen in non-ischemic CRVO than in ischemic CRVO. There was a significant (P=0.011) difference in the prevalence of abnormal uric acid among the three main RVO groups (CRVO, HCRVO, BRVO), highest in BRVO and lowest in HCRVO. There was a higher prevalence of abnormal glucose (P=0.069) and ANA (P=0.071) in CRVO+HCRVO than in BRVO. Results of special hematologic studies are given. *Conclusions:* Our study showed that a variety of hematologic abnormalities may be seen in association with different types of RVO, and any generalization about these disorders applied to all RVO patients may be misleading. The evidence of our study and in the literature indicates that there is no good reason why all patients with RVO should be subjected to extensive, expensive, special hematologic and hypercoagulability investigations, unless, of course, there is some clear indication; the routine, inexpensive hematologic evaluation is usually sufficient for RVO patients. Treatment with anticoagulants or platelet anti-aggregating agents may adversely influence the visual outcome, without any evidence of protective or beneficial effect.

Introduction

In 1878 [66] it was established that retinal vein occlusion (RVO) is caused by thrombosis of the vein; however, the role played by various hematologic abnormalities in its etiology and pathogenesis still remains unclear and controversial. In the literature (see below), it has often been claimed that retinal venous thrombosis is a manifestation of a hypercoagulable state in the patient. Primary hypercoagulable states are attributed to defects in the normal anticoagulant mechanisms, e.g., deficiency of protein C and/or S and antithrombin III. Secondary hypercoagulable states are attributed to underlying systemic diseases associated with increased risk of thrombosis, e.g., hyperviscosity, pregnancy, oral contraceptives and malignancy. A tremendous amount of literature has accumulated over the years on hematologic abnormalities associated with various types of RVO, but most reports are based either on anecdotal cases or on retrospective retrieval of information from case records of variable numbers of patients seen in routine clinical practice, with only a few planned studies. One finds a number of unsupported assumptions, which have caused considerable confusion. For example, it has often been assumed that the presence of an associated hematologic abnormality in a patients with RVO represents a cause-effect relationship. Moreover, in most of the previous literature it was assumed that RVO was a single disease, and the various types of RVO were all grouped together. Our clinical and experimental studies have shown, in fact, that RVO consists of six distinct clinical entities, each different in its clinical picture, prognosis and management, and in some cases even in its pathogenesis [23, 24, 25, 26, 27, 28, 29, 30, 31, 33, 34]. A review of the literature, therefore, reveals conflicting and inconsistent information.

The objective of this study was two-fold: (1) to investigate the prevalence of hematologic abnormalities associated with various types of retinal vein occlusion (RVO) and comparison of their prevalence among various types of RVO; (2) to review the highly conflicting literature on the subject, to place the information in perspective.

Methods

At the Ocular Vascular Clinic of the University of Iowa Hospitals and Clinics, at different times since 1973, we have conducted the following two hematology-related studies (Table 1) in RVO patients who, when first seen in our clinic or shortly thereafter, voluntarily agreed to take part in the studies. For each study, *consecutive* patients seen at our clinic were recruited during the period when that particular study was being done.

1. Routine hematologic abnormalities (on fasting blood samples) were evaluated in all consecutive patients (seen between 1976 and 1990) who voluntarily agreed to have the hematologic tests done either at our clinic or alternatively by their local physician according to our specification, the results being forwarded to us. This non-standardized procedure was necessary because of the difficult population distribution and climate of Iowa; most of our patients have to travel at least 3 h one way by car to come to our clinic for consultation, and Iowa roads are snowy and dangerous in winter. These factors naturally deter long-distance patients, particularly the elderly, from returning for non-essential consultations or tests. Therefore, there was a smaller proportion of the elderly (≥65 years old) in this sample for the hematologic study than in our total population of RVO patients (1090 patients) that were seen in the Ocular Vascular Clinic between 1973 and 1990 [34]. However, there was no bias of any kind in selection of patients who underwent these studies. The methods used in the statistical analyses have corrected for this difference in age distribution from our total RVO population, so that the final results are not influenced by that factor.
2. In addition to those studies, we have also conducted several other studies from time to time during this period, which deal with some special hematologic parameters (e.g., platelet aggregation, antithrombin III, and α_2 globulin).

Classification of RVO

Six types of RVO were differentiated from each other using the following diagnostic criteria.

Table 1 Various studies performed and the number of patients in the various types of retinal vein occlusion (RVO) in each study

Type of retinal vein occlusion	Type of hematologic study performed			
	Routine studies	Special studies		
		Platelet aggregation	Antithrombin III	α_2 Globulin
Central RVO	341	74	42	47
Non-ischemic	279	67	34	44
Ischemic	62	7	8	3
Hemi-central RVO	61	9	9	11
Non-ischemic	49	8	5	6
Ischemic	12	1	4	5
Central + hemi-central RVO	402	83	51	58
Non-ischemic	328	75	39	50
Ischemic	74	8	12	8
Branch RVO	133	27	30	33
Major	95	19	22	22
Macular	38	8	8	11
All types of RVO	535	110	81	91

Table 2 Values for various hematologic parameters considered abnormal in this study

Hematologic parameter	Abnormal level	
	Male	Female
Hematocrit (%)	<40 or >52	<35 or >47
Hemoglobin (g/dl)	<13.2 or >17.7	<11.9 or >15.5
Erythrocyte sedimentation rate (Westergren, mm/h)	>age in years/2	>(age in years +10)/2
White blood cells (×1,000/mm^3)	<3.7 or >10.5	
Platelets (×1,000/mm^3)	<150 or >400	
Blood urea nitrogen (mg/dl)	>20	
Creatinine (mg/dl)	>1.4	
Glucose (mg/dl)	>110	
Cholesterol (mg/dl)	>240	
Triglycerides (mg/dl)	>210	
Total protein (g/dl)	<6 or >8	
Albumin (g/dl)	<3.5 or >5.5	
Uric acid (mg/dl)	<2.4 or >7	
Calcium (mg/dl)	<8.5 or >10.5	
Phosphorus (mg/dl)	<2.5 or >4.5	
Antinuclear antibody titer	>40	

Central retinal vein occlusion (CRVO)

Our experimental [23, 29] and clinical [24, 25, 26, 27, 30, 31, 33, 34] studies have shown that this condition consists of two distinct entities: (1) *non-ischemic CRVO* (venous stasis retinopathy), and (2) *ischemic CRVO* (hemorrhagic retinopathy). CRVO was categorized as non-ischemic or ischemic, based on the combined data acquired from visual acuity, visual fields (determined with a Goldmann perimeter), relative afferent pupillary defect, electroretinography, ophthalmoscopy and fluorescein fundus angiography, as discussed elsewhere [24, 25, 26, 31].

Hemi-central retinal vein occlusion (HCRVO)

This is a variant of CRVO [28], and it also consists of two distinct entities: (1) *non-ischemic*, and (2) *ischemic* HCRVO. The criteria to define these two conditions are reported elsewhere [28].

Branch retinal vein occlusion (BRVO)

This is further subdivided into two distinct entities: (1) *major BRVO* when one of the major branch retinal veins is occluded, usually near, or rarely at, the optic disc, and (2) *macular BRVO* when one of the macular venules is occluded.

Ophthalmic evaluation

At the initial visit, all patients were seen by one of us (SSH) in the Ocular Vascular Clinic and had a detailed ocular and medical history recorded as well as a detailed bilateral ocular examination. We also obtained a detailed medical history of all previous or current systemic diseases. The ocular examination included careful testing of the visual acuity, visual field plotting with a Goldmann perimeter (using I-2e, I-4e and V-4e isopters), a detailed anterior segment examination, intraocular pressure recording with a Goldmann applanation tonometer, relative afferent pupillary defect, detailed fundus evaluation by indirect and direct ophthalmoscopy and, if required, by contact lens, and fluorescein fundus angiography (only in the involved eye). Electroretinography was performed only in CRVO cases during the later years of the study [31]. In addition to these evaluations, a detailed systemic evaluation, as well as electrocardiogram and chest roentgenogram, when indicated, was performed either by an internist at the University of Iowa Hospitals & Clinics, or by their local internist/physician. Criteria used for diagnosis of major systemic diseases and their prevalence are described elsewhere[34]. In patients who voluntarily agreed to participate in hematologic studies, routine hematologic testing was also carried out in our clinic or at their local physician's clinic (for the reasons given above), but the other studies were done in our clinic.

Various evaluations

As mentioned above, we conducted the following two types of investigations in this study (Table 1).

Routine hematologic evaluations

In 535 *consecutive* patients, we performed various routine hematologic evaluations (on a fasting blood sample), including estimation of hematocrit, hemoglobin, white blood cells, platelets, erythrocyte sedimentation rate, blood urea nitrogen (BUN), creatinine, fasting glucose, cholesterol and triglyceride levels, total protein, albumin, uric acid, calcium, phosphorus, antinuclear antibody (ANA), fluorescent treponemal antibody (FTA) and syphilis serology (VDRL, Venereal Disease Research Laboratory antigen). Table 2 gives the values which were considered abnormal for the various hematologic parameters in this study. In a few cases, reliable information on each and every test was not available for a variety of reasons, which explains the discrepancies between the number of patients in Table 3 and those in Tables 4 and 5.

Special hematologic evaluations

At one time, as a part of a joint research project with the hematology department of this University Hospital, we studied in relatively smaller, completely random (without any selection bias) groups of consecutive patients at their initial visit to our clinic: (1) circulating and spontaneous platelet aggregation (in 110 patients), (2) antithrombin III (in 81 patients), and (3) α_2 globulin (in 91 patients). There was no built-in bias for the performance of a particular study on a particular group of patients.

Table 3 Demographic characteristics of retinal vein occlusion (RVO) patients in the study

Ocular diagnosis	*n*	Gender		Age at onset (years)					
		Male	Female	Descriptive statistics			Distribution by age		
				Mean (SD)	Median	Range	<45	45–64	≥65
All types of RVO	535	294 (55%)	241 (45%)	60.2 (15.8)	62.2	14–99	91 (17%)	212 (40%)	232 (43%)
Central RVO	341	194 (57%)	147 (43%)	58.7 (17.3)	61.3	16–100	73 (21%)	128 (38%)	140 (41%)
Non-ischemic	279	153 (55%)	126 (45%)	56.8 (17.2)	59.6	16–100	66 (24%)	112 (40%)	101 (36%)
Ischemic	62	41 (66%)	21 (34%)	67.6 (15.0)	69.9	31–90	7 (11%)	16 (26%)	39 (63%)
Non-ischemic versus ischemic		*P*=0.120		*P*<0.0001			*P*<0.001		
Hemi-central RVO	61	31 (51%)	30 (49%)	62.0 (15.3)	65.7	14–87	11 (18%)	19 (31%)	31 (51%)
Non-ischemic	49	25 (51%)	4 (49%)	62.5 (14.3)	65.7	32–87	9 (18%)	15 (31%)	25 (51%)
Ischemic	12	6 (50%)	6 (50%)	59.9 (19.6)	64.6	14–86	2 (17%)	4 (33%)	6 (50%)
Non-ischemic versus ischemic		*P*=1.0		*P*=0.606			*P*=1.0		
Central + hemi-central RVO	402	225 (56%)	177 (44%)	59.2 (17.1)	61.7	14–100	84 (21%)	147 (37%)	171 (43%)
Non-ischemic	328	178 (54%)	150 (46%)	57.6 (16.9)	60.8	16–100	75 (23%)	127 (39%)	126 (38%)
Ischemic	74	47 (64%)	27(36%)	66.3 (16.0)	68.8	14–90	9 (12%)	20 (27%)	45 (61%)
Non-ischemic versus ischemic		*P*=0.156		*P*<0.0001			*P*=0.002		
Branch RVO	133	69 (52%)	64 (48%)	63.1 (10.8)	63.7	20–85	7 (5%)	65 (49%)	61 (46%)
Major	95	46 (48%)	49 (52%)	65.6 (10.9)	62.7	20–85	6 (6%)	48 (51%)	41 (43%)
Macular	38	23 (61%)	15 (39%)	64.3 (10.9)	66.5	29–85	1 (3%)	17 (45%)	20 (53%)
Major versus macular		*P*=0.251		*P*=0.407			*P*=0.504		
Comparison among RVO types									
Among 3 types		*P*=0.485		*P*=0.017			*P*<0.001		
Central versus branch		–		*P*=0.022			*P*<0.0001		
Hemi-central versus branch		–		*P*=1.0			*P*=0.018		
Central versus hemi-central		–		*P*=0.410			*P*=1.0		
Central + hemi-central versus branch		*P*=0.423(%)		*P*=0.003			*P*<0.0001		

Follow-up information

Hematologic evaluations were performed only once, when the patients were seen initially in our clinic or shortly thereafter, and were not repeated on follow-up**.** However, all patients were followed (by SSH) according to a protocol practiced in this Clinic for RVO patients: at about 3-month intervals for three visits, then 6-month intervals for four visits, and after that at yearly intervals. The follow-up ocular evaluations were the same as those described for the initial visit examination, except for the fluorescein fundus angiography and electroretinography, which were performed only when considered essential**.**

Data management

Demographic as well as hematologic laboratory data were abstracted and analyzed retrospectively from the detailed information originally collected prospectively in the patients' records, and the abstracted data were audited carefully to ensure factual accuracy.

Statistical methods

Patients were classified into one of six types of RVO based on their first episode. Subsequent episodes of the same or a different type of RVO [33] were not considered in these analyses. For data analysis, patients were stratified into three age groups based on age at onset of the first episode for which they were first seen in our clinic: young (less than 45 years of age), middle-aged (45–64 years old), and elderly (65 years or older). Prevalence of various hematologic abnormalities was determined by considering all patients with a hematologic abnormality at or before the onset of the first episode. The observed prevalence of hematologic abnormalities was compared among CRVO, HCRVO and BRVO using a polytomous logistic regression analysis, adjusting for gender and age. In addition, the actual hematologic values were also compared among CRVO, HCRVO and BRVO using the Kruskal-Wallis test. Logistic regression adjusting for age and gender was also used to compare the observed prevalence of hematologic abnormalities in non-ischemic and ischemic CRVO and HCRVO and in major and macular BRVO. The observed prevalence rate of high serum cholesterol (≥240 mg/dl) was compared with those expected in a gender- and age-matched control population based on 1988–1991 estimates of the US National Center for Health Statistics [51] with statistical significance assessed using exact binomial probabilities. For the other hematologic abnormalities, no such comparison with the United States population is possible because of the unavailability of published prevalence rates for these abnormalities for the US Caucasian population or any relevant control group.

Results

Virtually all patients in this study were Caucasian, which is consistent with the racial pattern in this part of the United States.

Table 4 Age-adjusted prevalence of abnormal hematologic values in non-ischemic and ischemic central retinal vein occlusion (RVO) and hemi-central RVO, and in major and macular branch RVO. Data were adjusted for age using the age distribution of total RVO population seen in our Ocular Vascular Clinic from 1973–1990. Values in parentheses are the number of patients examined. Statistical comparison of prevalence rates among various types of RVO (P-value) was made after adjusting for age and gender in a logistic regression model. *FTA* fluorescent treponemal antibody, *VDRL* Venereal Disease Research Laboratory antigen, *ANA* antinuclear antibodies

Hematologic parameter	Central RVO			Hemi-central RVO			Branch RVO			Central + hemi-central RVO		
	Non-ischemic	Ischemic	Ischemic versus non-ischemic *P*-value	Non-ischemic	Ischemic	Ischemic versus non-ischemic *P*-value	Major	Macular	Major versus macular *P*-value	Non-ischemic	Ischemic	Ischemic versus non-ischemic *P*-value
Hematocrit	10.7% (259)	21.5% (57)	0.044	6.1% (45)	23.2% (8)	0.112	9.7% (87)	11.4% (32)	0.905	10.0% (304)	22.0% (65)	0.014
Hemoglobin	12.0% (260)	24.1% (59)	0.018	17.1% (46)	11.6% (10)	0.578	14.1% (89)	11.4% (32)	0.786	12.8% (306)	22.2% (69)	0.039
White blood cells	8.1% (260)	6.7% (57)	0.797	7.3% (46)	8.1% (10)	0.913	7.8% (88)	0.0% (32)	0.187[a]	8.0% (306)	7.2% (67)	0.850
Platelets	6.5% (216)	9.3% (57)	0.502	7.3% (41)	11.6% (9)	0.747	9.3% (80)	3.2% (26)	0.448	6.6% (257)	9.5% (66)	0.443
Erythrocyte edimentation srate	17.1% (184)	7.9% (40)	0.190	11.6% (41)	16.1% (8)	0.832	14.0% (74)	9.1% (22)	0.496	16.2% (225)	8.6% (48)	0.290 0.290
Blood urea nitrogen	23.3% (190)	44.8% (51)	0.025	31.3% (42)	55.4% (9)	0.090	20.3% (82)	28.1% (32)	0.535	24.7% (232)	46.6% (60)	0.008
Creatinine	13.3% (94)	30.0% (28)	0.102	20.5% (13)	0.0% (3)	1.0[a]	23.1% (27)	27.4% (7)	0.666	14.1% (107)	28.2% (31)	0.188
Glucose	27.2% (195)	39.3% (56)	0.141	38.1% (41)	29.0% (9)	0.387	20.2% (79)	21.4% (31)	0.672	29.2% (236)	37.5% (65)	0.314
Cholesterol	25.8% (244)	33.9% (51)	0.111	20.0% (44)	22.4% (9)	0.921	23.9% (86)	27.4% (33)	0.672	24.9% (288)	32.1% (60)	0.133
Triglycerides	15.1% (188)	19.0% (33)	0.354	8.2% (35)	0.0% (5)	1.0[a]	24.7% (63)	17.4% (23)	0.258	14.0% (223)	16.8% (38)	0.479
Total protein	6.6% (243)	7.9% (54)	0.823	8.5% (44)	21.5% (10)	0.317	13.8% (81)	5.9% (31)	0.397	6.9% (287)	10.0% (64)	0.430
Albumin	0.9% (243)	0.0% (54)	1.0[a]	0.0% (44)	0.0% (10)	– –	1.5% (83)	0.0% (32)	1.0[a]	0.7% (287)	0.0% (64)	1.0[a]
Uric acid	22.1% (235)	28.8% (54)	0.262	10.7% (43)	10.8% (9)	0.921	30.8% (82)	37.2% (33)	0.797	20.5% (278)	26.3% (63)	0.275
Calcium	2.9% (239)	6.0% (55)	0.137	3.6% (43)	11.6% (10)	0.527	7.9% (83)	6.9% (33)	0.805	3.1% (282)	6.7% (65)	0.087
Phosphorus	3.9% (233)	8.0% (52)	0.318	2.3% (43)	4.8% (10)	0.283	3.9% (80)	10.3% (32)	0.107	3.6% (276)	7.8% (62)	0.127
FTA	3.0% (129)	12.6% (27)	0.159	15.2% (27)	0.0% (4)	1.0[a]	0.0% (52)	7.8% (15)	0.224[a]	4.6% (156)	10.8% (31)	0.447
VDRL	4.4% (143)	7.7% (30)	0.534	12.4% (28)	0.0% (5)	1.0[a]	0.0% (60)	5.5% (19)	0.241[a]	5.5% (171)	6.2% (35)	0.930
ANA	42.7% (105)	21.6% (22)	0.049	45.7% (19)	.0% (3)	0.523[a]	24.6% (29)	18.2% (9)	0.989	43.1% (124)	18.2% (25)	0.018

[a] Fisher's exact test

Routine hematologic evaluations

These were performed in 535 patients with various types of RVO (Table 1).

Demographic characteristics

Table 3 summarizes the demographic characteristics of patients in the six types of RVO, and the combined data for CRVO+HCRVO (because both represent variants of CRVO pathogenetically [28]) included in this study.

Prevalence rates of various hematologic abnormalities

Age-adjusted prevalence rates of abnormal hematologic values (Table 2) for non-ischemic and ischemic CRVO, HCVRO, and combined CRVO+HCRVO and major and

Table 5 Age-adjusted prevalence of abnormal hematologic values in the three major types of retinal vein occlusion (RVO). Data were adjusted for age using the age distribution of total RVO population seen in our Ocular Vascular Clinic from 1973–1990. Values in parentheses are the number of patients examined. Statistical comparison of prevalence rates among various types of RVO (P-value) was made after adjusting for age and gender in a logistic regression model. *FTA* fluorescent treponemal antibody, *VDRL* Venereal Disease Research Laboratory antigen, *ANA* antinuclear antibodies

Hematologic parameter	Type of RVO				Statistical comparison, *P*-value	
	Central RVO	Hemi-central RVO	Branch RVO	Central + hemi-central RVO	Among 3 types	Central + hemi-central versus branch
Hematocrit	12.7% (316)	9.5% (53)	9.8% (119)	12.3% (369)	0.714	0.638
Hemoglobin	14.5% (319)	16.1% (56)	13.0% (121)	14.8% (375)	0.782	0.529
White blood cells	7.8% (317)	7.5% (56)	5.8% (120)	7.8% (373)	0.798	0.523
Platelets	7.0% (273)	8.2% (50)	8.0% (106)	7.2% (323)	0.862	0.634
Erythrocyte sedimentation rate	15.3% (224)	11.9% (49)	12.8% (96)	14.6% (273)	0.793	0.497
Blood urea nitrogen	27.9% (241)	35.8% (51)	22.8% (114)	29.3% (292)	0.190	0.142
Creatinine	17.0% (122)	14.4% (16)	24.8% (34)	16.8% (138)	0.616	0.357
Glucose	30.2% (251)	36.1% (50)	21.1% (110)	31.2% (301)	0.141	0.069
Cholesterol	27.3% (295)	20.2% (53)	25.4% (119)	26.2% (348)	0.544	0.690
Triglycerides	15.9% (221)	7.2% (40)	22.7% (86)	14.6% (261)	0.183	0.185
Total protein	6.9% (297)	10.7% (54)	11.5% (112)	7.4% (351)	0.179	0.121
Albumin	0.7% (297)	0.0% (54)	1.1% (115)	0.6% (351)	1.0[a]	1.0[a]
Uric acid	23.4% (289)	10.8% (52)	32.5% (115)	21.5% (341)	0.011	0.013
Calcium	3.7% (294)	5.2% (53)	7.1% (116)	3.9% (347)	0.165	0.073
Phosphorus	4.6% (285)	2.9% (53)	5.6% (112)	4.4% (338)	0.621	0.351
FTA	4.8% (156)	10.7% (31)	1.8% (67)	5.6% (187)	0.193	0.177
VDRL	4.9% (173)	9.6% (33)	1.6% (79)	5.7% (206)	0.257	0.151
ANA	38.4% (127)	37.0% (22)	24.4% (38)	38.2% (149)	0.193	0.071

[a] Fisher's exact test

macular BRVO are presented and compared in Table 4. For CRVO, there was a significantly higher prevalence of abnormal hematocrit (P=0.044), hemoglobin (P=0.018), and BUN (P=0.025) in the ischemic type than in the non-ischemic type; there was a significantly higher prevalence of abnormal ANA (P=0.049) in non-ischemic CRVO than in the ischemic type. This was also seen in the combined CRVO+HCRVO group. No statistically significant difference was found between non-ischemic and ischemic HCRVO, or between major and macular BRVO.

The age-adjusted prevalence of hematologic values in the three main types of RVO (CRVO, HCRVO, and BRVO) and combined CRVO+HCRVO are shown in Table 5. There was a significant (P=0.011) difference in prevalence of abnormal uric acid among the three main RVO groups, with the highest prevalence in the BRVO and lowest in HCRVO; it was also significantly (P=0.013) greater in BRVO than in combined CRVO+HCRVO. The data also suggested a higher prevalence of abnormal glucose (P=0.069) and ANA (P=0.071), and a

Table 6 Special hematologic evaluations in retinal vein occlusion (RVO) patients: number and frequency (%) of patients with abnormal findings (*n* refers to number of patients evaluated)

Hematologic evaluations	Central RVO		Hemi-central RVO		Central + hemi-central RVO	Branch RVO		All branch RVOs	Total
	Non-ischemic	Ischemic	Non-ischemic	Ischemic		Major	Macular		
Platelet aggregation	(*n*=67)	(*n*=7)	(*n*=8)	(*n*=1)	(*n*=83)	(*n*=19)	(*n*=8)	(*n*=27)	(*n*=110)
Circulating	5 (7%)	2 (29%)	1 (12%)	0%	10%	3 (16%)	1 (12%)	15%	12 (11%)
Spontaneous	5/66 (8%)	0%	0%	0%	6%	1/18 (6%)	0%	4%	6/108 (6%)
Antithrombin III	(*n*=34) 4 (12%)	(*n*=8) 0%	(*n*=5) 2 (40%)	(*n*=4) 1 (25%)	(*n*=51) 16%	(*n*=22) 3 (14%)	(*n*=8) 2 (25%)	(*n*=30) 17%	(*n*=81) 12 (15%)
α_2 Globulin	(*n*=44) 8 (18%)	(*n*=3) 0%	(*n*=6) 2 (33%)	(*n*=5) 2 (40%)	(*n*=58) 21%	(*n*=22) 7 (32%)	(*n*=11) 4 (36%)	(*n*=33) 33%	(*n*=91) 23 (25%)

lower prevalence of abnormal calcium (*P*=0.073) in CRVO+HCRVO compared with BRVO.

The gender- and age-adjusted comparison of elevated serum cholesterol with that of the 1988–1991 US population rates [51] showed the following results: for CRVO, the observed rate in males was 20.1% compared with an expected rate of 24.0% for an age-matched population (*P*=0.244). In females, it was 34.1% compared with an age-matched expected rate of 33.1% (*P*=0.945). In HCRVO, the males had an observed rate of 10.3%, which is smaller than the expected rate of 24.7% (*P*=0.085). The observed rate in female patients was 32.0% compared with an expected rate of 35.3% (*P*=0.836). The BRVO patients had an observed rate of 24.2% for males and 28.1% for females compared with the age-adjusted expected rate of 27.5% (*P*=0.576) for males and 38.0% (*P*=0.134) for females. Our current comparison of gender-age specific prevalence rates of elevated cholesterol in our patient population is made with the entire US population. Since our patient population was essentially Caucasian, we would have liked to compare it with the US white gender-age-matched population only. However, no such data are available. The overall prevalence of elevated cholesterol is higher in whites than in blacks [51]. As is evident from the above data, comparison of our patients with the overall US population (all races) shows the prevalence rates of elevated cholesterol to be somewhat lower in our population; this would suggest that comparison with the US white population only is not likely to show abnormal elevated cholesterol in our population; if anything, it would be even lower.

For the other hematologic abnormalities, no comparison with the US population was possible because of the unavailability of published US population prevalence rates for those abnormalities. Also, there is no appropriate control group from this part of the world to provide information on those hematologic abnormalities.

Special hematologic evaluations

Special hematologic evaluations included circulating and spontaneous platelet aggregation (on 110 patients), antithrombin III (on 81 patients), and α_2 globulin (on 91 patients) (Table 1). The results of these evaluations are shown in Table 6. There was no significant difference in the prevalence of abnormal findings between the CRVO+HCRVO patients and the BRVO patients for circulating (*P*=0.481; 10% for CRVO+HCRVO and 15% for BRVO) or spontaneous (*P*=1.0; 6% for CRVO+HCRVO and 4% for BRVO) platelet aggregation, antithrombin III (*P*=1.0; 16% for CRVO+HCRVO and 17% for BRVO), or α_2 globulin (*P*=0.214; 21% for CRVO+HCRVO and 33% for BRVO).

For this second study, no comparison with the US population was done because of the unavailability of published US Caucasian population prevalence rates for those abnormalities, and also there is no appropriate control group to provide information on those hematologic abnormalities.

During the period when these hematologic studies were performed, we also investigated the prevalence of various systemic diseases associated with the various types of RVO in patients seen in our clinic; the results of that study are reported elsewhere [34].

Discussion

Our study showed that the prevalence of the various hematologic abnormalities differs considerably in the six types of RVO (Tables 4 and 5). Comparison of prevalence rate showed a significantly higher prevalence of abnormal hematocrit (*P*=0.044), hemoglobin (*P*=0.018), and BUN (*P*=0.025) in ischemic CRVO than in non-ischemic CRVO; abnormal ANA prevalence was significantly (*P*=0.049) higher in non-ischemic CRVO than in the ischemic type. There was a significant (*P*=0.011) difference in prevalence of abnormal uric acid among the

three main RVO groups (i.e. CRVO, HCRVO, BRVO), with the highest prevalence in the BRVO and lowest prevalence in HCRVO; prevalence of abnormal uric acid in BRVO was also significantly (P=0.013) greater than in combined CRVO+HCRVO. The data also suggested a higher prevalence of abnormal glucose (P=0.069) and ANA (P=0.071), and a lower prevalence of abnormal calcium (P=0.073) in CRVO+HCRVO than in BRVO. No significant differences were seen in the other variables evaluated in this study among the various types of RVO. Unfortunately, we cannot address the significance of these abnormalities, or whether patients with RVO have different prevalences of hematologic abnormalities from a population without RVO; the necessary information for comparison is not available, neither in the published US population prevalence rates for these abnormalities nor in an appropriate control group from this part of the world. This is a limitation in our study.

The following case illustrates our usual experience with hematologic evaluation in RVO. A 50-year-old, perfectly healthy man developed non-ischemic CRVO in his right eye which resolved completely in about 18 months. A recurrence of non-ischemic CRVO in the right eye developed 21–22 years later. Nine months after that, non-ischemic CRVO developed in his left eye, which converted within 3 months to ischemic CRVO. When he had bilateral CRVO, an extensive hematologic evaluation, including complete blood count, differential white cell count, hemoglobin, hematocrit, platelet count, erythrocyte sedimentation rate, prothrombin time, partial thromboplastin time, antithrombin III, serum immunoelectrophoresis, serum cryoglobulins, monoclonal protein, serum viscosity, ANA, cardiolipin antibody (IGG, IGM) screen, proteins C and S, factor V Leiden, homocysteine level, blood chemistries, fasting glucose and lipid profile, revealed no abnormality at all. His systemic evaluation also revealed absolutely no abnormality. The lack of abnormal results from special hematologic studies and the hypercoagulability profile seen in this patient are not an exception but are usually the norm for our patients with RVO. One or more of these special hematologic and hypercoagulable abnormalities may occasionally be seen in the RVO cases, which may or may not have any relevance to development of RVO, because such abnormalities do occur in a certain proportion of the general population without RVO, as shown by studies in the literature (see below). On a cost-benefit ratio, our study reveals that it is not worth investigating every patient by performing extensive and expensive special hematologic and hypercoagulability investigations. The routine, inexpensive hematologic evaluation is usually sufficient in the RVO patients.

To sum up, our study showed that no generalization can be made about the prevalence of various hematologic abnormalities in various types of RVO; this is also evident from a review of the literature (see below).

Summary of review of literature on hematologic abnormalities in RVO

During the past three decades significant advances have been made in defining hematologic and genetic risk factors for venous thrombosis in general. This has interested ophthalmologists in the role of hematologic abnormalities in ocular vascular occlusive disorders; consequently, a voluminous literature has accumulated on the subject. Unfortunately, much of the literature is contradictory, which has produced a good deal of confusion, especially concerning possible cause-effect relationships between hematologic abnormalities and RVO. In view of that, the literature on hematologic abnormalities in RVO badly needs a “reality check” to place the information in its true perspective. This is important both from the point of view of clinical management of RVO and as an aid to a better understanding of the role of various hematological abnormalities in the pathophysiology of RVO. It is beyond the scope of this paper to review each and every publication at length; the following is a brief summary of the major studies, reporting either the presence or the absence of various hematologic abnormalities in RVO.

Thrombus formation at the site of damaged endothelium in RVO is due to aggregation of platelets and fibrin formation. Conversion of fibrinogen to fibrin involves a cascade of reactions and a large number of clotting factors. To prevent *in vivo* coagulation, there is an anticoagulant protein system, the most important factors of which are protein C, protein S and antithrombin III. Normal vascular endothelium liberates thrombomodulin which inactivates thrombin. The complex of thrombin with thrombomodulin activates protein C, which inhibits coagulation by degrading coagulation factors Va and VIIIa [58]. However, in some persons activated protein C does not inhibit coagulation; this resistance to activated protein C is due to a point mutation in the factor V gene, which is inherited dominantly [58]. Injury to the endothelium alters the balance between the coagulation and anticoagulation systems and results in thrombosis. It has been postulated that imbalance of the various systems involved in this cascade, including those discussed below, can cause thrombosis.

Anticoagulant proteins

Positive studies. Williamson et al. [70] studied 87 patients with CRVO and an age-matched control group, and reported that protein S was lower (P=0.03) in ischemic than non-ischemic CRVO, and demonstrated higher antithrombin III (P=0.02), von Willebrand factor (P=0.05), and plasminogen activator inhibitor (P=0.0001) in the CRVO patients than in the controls. In 100 CRVO cases, Marcucci et al. [48] found plasminogen activator inhibitor-1 significantly (P<0.001) elevated compared

with the controls. Iijima et al. [38], on evaluation of ten CRVO, six HCRVO, 33 major BRVO and eight macular BRVO cases, found levels of thrombin-antithrombin III complex significantly higher in CRVO and HCRVO than in BRVO and controls (P=0.02), with no difference between the BRVO and the controls. Tekeli et al. [59] found decreased levels of protein C in six of 14 (42.9%) CRVO and three of 31 (9.7%) BRVO patients, and decreased protein S in one of 14 (7.1%) CRVO and one of 31 (3.2%) BRVO, and of antithrombin III in one of 31 (3.2%) BRVO, but in none of the 20 healthy controls; they concluded that there was a statistically significant difference in protein C deficiency between the CRVO and BRVO cases (P<0.05). In 37 young (<50 years) CRVO patients, Larsson et al. [45] found anticoagulant proteins deficiencies in four (10.8%), and concluded that these deficiencies seem to be important factors in the etiology of CRVO in the young.

Negative studies. In contrast, Glueck et al. [20], in 17 patients with RVO, found proteins C and S levels no different from those of controls. Similarly, Greiner et al. [22] found no case of protein C and protein S deficiencies in 35 CRVO and 21 BRVO patients. Hodgkins et al. [36] found no cases of antithrombin mutation among 50 CRVO patients. Engesser et al. [15] investigated protein S deficiency in 136 members of 12 families with hereditary protein S deficiency, and found venous thrombosis in 55% – none had it in the eye. Marcucci et al. [48] found no deficiency of physiological clotting inhibitors (proteins C and S, and antithrombin) in 100 patients with CRVO compared with the controls. Increased risk of venous thrombosis in carriers of hereditary protein C deficiency has been reported [1], but there is no definite case report of this with RVO.

In our study, we tested 81 patients (42 CRVO, 9 HCRVO, 30 BRVO) for antithrombin III, and found 15% of them had lower than normal levels; there was no significant difference in the prevalence of abnormal findings between the CRVO+HCRVO patients and the BRVO patients for antithrombin III.

Comments From this review, it seems that there is no strong evidence that deficiency of anticoagulant proteins plays a role in the majority of RVO patients.

Activated protein C resistance (APCR) and factor V Leiden mutation

APCR has recently been described as a cause of venous thrombosis [10] and a number of conflicting reports have lately appeared, several of them anecdotal, dealing with its presence in RVO.

Positive studies. Dhote et al. [11] reported one 49-year-old woman with CRVO who had APCR. From 31 young patients (<50 years) with CRVO, Larsson et al. [43] reported 26% (eight patients) of all the patients, and 36% of those <45 years, had APCR; the normal incidence of this was 2–7%. The same group [45] reported APCR in seven (18.9%) of 37 young (<50 years) CRVO patients, and concluded that APCR seems to be an important factor in the etiology of CRVO in the young. Williamson et al. [70], in 87 patients with CRVO compared with an age-matched control group, found a lower (P=0.05) overall level of APCR in the CRVO patients than in the controls but concluded that a higher percentage of the patients with CRVO (12%) had APCR than did controls (5%). Greiner et al. [22] found factor V R506Q mutation in 29% (ten of 35) of CRVO patients and in 19% (four of 21) with BRVO, while in the normal population it was 9%, and they concluded that prevalence was significantly high in CRVO but not in BRVO. From those findings they concluded that factor V R506Q mutation is similar in CRVO and deep vein thrombosis and represents a risk factor, and recommended screening for this mutation in CRVO patients. Glueck et al. [20] reported heterozygous factor V factor G1691A mutation in 18% of 17 patients with RVO compared with 7% in 233 controls (P=0.02), with no difference in prothrombin gene. In a study of 100 CRVO patients, Marcucci et al. [48] reported a significantly higher prevalence of APCR (P<0.005) and factor V Leiden polymorphism (P=0.05) than in controls.

Negative studies. In sharp contrast to these reports, a much larger number of studies found no significant difference in the prevalence of APCR and factor V Leiden mutation between RVO patients and controls. Larsson et al. [44] found APCR in 11% of 83 patients with CRVO, older than 50 years, and stated that its normal incidence in the same geographical area was 10–11%. Based on a study of 46 patients with CRVO and BRVO for factor V Leiden mutation, Linna et al. [46] concluded that it is not a significant risk factor for RVO. Samama et al. [54], in a review of 135 patients with factor V Q506 mutant gene, found only one person developing CRVO. Hodgkins et al. [36] found only one of 50 CRVO patients with factor V mutation and concluded that resistance to activated protein C does not play a major role in CRVO. Gottlieb et al. [21] found resistance to APCR and the presence of factor V Leiden in only one of 21 patients with CRVO, who was less than 50 years old, a prevalence similar to that seen in the general population. In 45 CRVO, 48 BRVO and 9 HCRVO cases, Salomon et al. [53] found the prevalence of factor V Leiden G1691A and factor II G20210A to be similar to that in 105 controls. Kalayci et al. [40] found no significant difference in frequencies of Factor V Leiden mutation and prothrombin 20210 A mutation between RVO patients (25 with CRVO or HCRVO, 27 with BRVO) and 168 controls. They concluded that these were not risk factors in

either type of RVO. Faude et al. [16] examined 107 patients with CRVO, 112 patients with deep vein thrombosis and 70 healthy individuals, and found APCR in 5.6% of patients with CRVO, in 5.7% of the control group and in 23.2% of the deep vein thrombosis group. Vine and Samama [65] stated that in the majority of cases with venous thrombosis and the presence of factor V mutation, it is the associated risk factors (e.g., pregnancy, oral contraceptives, trauma or surgery) that cause thrombosis and not the factor V abnormality per se. They further point out that there are cases of acquired resistance to activated protein C in certain conditions including pregnancy, surgical interventions, oral contraceptive use, lupus anticoagulants and elevated factor VIII. In the light of all the available evidence so far, they concluded that testing for resistance to activated protein C, as a screening test for factor V, is not indicated in CRVO; even in the unusual situation of recurrent retinal venous occlusion, it is not clear whether the presence of abnormal factor V constitutes a causal relationship or merely a coincidental finding. Ciardella et al. [7], based on a study of 84 RVO patients and 70 controls, concluded that routine testing for the presence of the factor V Leiden mutant is not advisable in RVO. Vine and Samama [65], commenting on the study by Greiner et al. [22], stated that findings in the literature do not support the high prevalence in CRVO reported by those authors, and asserted that screening for factor V Q506 mutation is not indicated except in patients with recurrent retinal venous occlusion. Most recently, Scott et al. [55] found among 45 patients <55 years old with BRVO (21), CRVO (22) or HCRVO (2) that no patient had the factor V Q506 mutation. Boyd et al. [5] found no significant difference in factor VIII levels between CRVO and controls. Therefore, many authors have concluded that routine testing for the presence of the factor V Leiden mutant has little justification and is not advisable for patients with CRVO or BRVO [7, 16, 39, 47, 55, 65].

We recently conducted a small pilot study to investigate APCR and heterozygosity for the factor V Leiden allele in ten patients with CRVO (seven non-ischemic and three ischemic CRVO), aged 20–50 years. Only one of them had a positive result and that was a young woman with a history of miscarriages.

Comments. From the above brief review of the literature and our pilot study on the subject, it is clear that there is overwhelming evidence that APCR and factor V Leiden mutation do not play an appreciable role in the development of RVO, and that estimation of them routinely is not indicated, except maybe in patients with a history of recurrent venous thrombosis. In the case example cited above from our study with multiple and recurrent CRVOs, factor V Leiden mutation was not found. Moreover, in our study of 1090 patients with RVO investigated for associated systemic diseases [34], the incidence of systemic venous thrombotic disease in various types of RVO was extremely low (present in 1.0% CRVO, 2.3% HCRVO, and 3.4% BRVO patients). In some studies, a high prevalence of APCR and factor V Leiden mutation has been found because of multiple inherent confounding factors and artifacts in their estimation and in the studies. These factors include the following:

1. Differences in ethnic groups examined; factor V Leiden mutation is found in about 5% of Caucasians but appears to be almost absent in non-Caucasian groups, including Chinese, Japanese, black Africans and Native Americans [47].
2. Confounding factors such as laboratory methodology and sample size; it has also been shown that variations in sample procurement and handling render the APCR assay less reliable [47]. Ciardella et al. [7], based on repeat assay of APCR in RVO patients and controls, concluded that the first generation of the commercial assay for APCR was not a useful screening test; the practical implication of the inaccuracy of early versions of testing is that the results it yielded about the presence of APCR and factor V Leiden mutation in patients were misleading.
3. Bias in cases investigated can also give misleading information. For example, Vine [63] rightly pointed out that the two studies that demonstrated the highest frequency of factor V Q506 in patients with CRVO [20, 22] (see above) occurred in patients who had been referred to either a hospital or a laboratory setting for investigation of possible thrombophilic conditions; in both studies there was a large percentage of patients with a history of systemic thrombotic events (24% [20] and 12% [22]) so that there was a built-in bias in the cases investigated.

Thus, one has to place the results of various studies in their true perspective, in the light of the limitations and artifacts in the studies and methods of testing.

Antiphospholipid antibodies and anticardiolipin antibodies

The presence of autoimmune antibodies reactive against various components of cellular phospholipids has been recognized as another risk factor for thrombosis, and these occur as anticardiolipin antibodies and/or lupus anticoagulants [9].

Positive studies. These have been reported in anecdotal case reports of CRVO and BRVO [2, 41, 56, 65] (Kleiner et al. [41] have summarized seven more cases from five other anecdotal reports in the literature). These reports have proposed that antiphospholipid antibodies/anticardiolipin antibodies are factors in the pathogenesis of RVO. Cobo-Soriano et al. [8] reported the presence of

antiphospholipid antibodies in a small series of RVO patients (in two of eight CRVO, three of 11 major BRVO, and two of six macular BRVO) and compared the incidence with that of a control group (in two of 40).

Negative studies. By contrast, in a study of the prevalence of antiphospholipid antibodies in 75 RVO patients (44 CRVO, 29 BRVO, and two arterial occlusion), Glacet-Bernard et al. [18] found no difference between the RVO group and a control group. They concluded that antiphospholipid antibodies did not seem to be a feature of RVO, although in rare cases (5%) they may contribute to an occlusive phenomenon. Larsson et al. [45] found that none of 37 young (<50 years) CRVO patients had anticardiolipin antibodies or lupus anticoagulants. Glueck et al. [20] found no difference in the prevalence of anticardiolipin antibodies, IgG and IgM between a group of 17 RVO patients and the control group. Greiner et al. [22] found that none of their 35 CRVO patients had lupus anticoagulants. Among 45 patients, ≤55 years old, with BRVO (21), CRVO (22) and HCRVO (2), Scott et al. [55] found that no patient had anti-endothelial cell reactivity, and a low titer of anticardiolipin antibody represented a non-specific response to vascular injury. Marcucci et al. [48] did not find a higher prevalence of positive antiphospholipid antibody (either lupus anticoagulants or anticardiolipin antibodies) in 100 CRVO patients compared with that in the controls.

Comments. From this review, it is evident that most of the RVO patients studied had no evidence of these antibodies. It seems that they do not usually play a role in RVO.

Platelet aggregation disorders

These have been mentioned in RVO in a few reports. For example, Mazza et al. [49] reported a significant increase of platelet aggregation in patients with RVO. Walsh et al. [67] noted that, during the first 6 months of development of RVO, platelet coagulant activity increased 2- to 4-fold, but not after that, and platelet aggregation was normal. We investigated circulating and spontaneous platelet aggregation in 110 patients with various types of RVO at their initial visit; these were abnormal in 11% and 6%, respectively. We do not know the incidence of these disorders in the age-matched general population. There was no significant difference in the prevalence of abnormal findings between the CRVO+HCRVO patients and the BRVO patients for circulating and spontaneous platelet aggregation.

Other clotting abnormalities

Speicher et al. [57] reported factor XII deficiency and no other systemic or hematologic abnormality in two young (39- and 35-year-old) CRVO patients – one with ischemic and the other non-ischemic condition.

Hyperhomocysteinemia

This has been described as a risk factor in venous thrombosis because, in patients with typical homocysteinuria, half the vascular complications are of venous origin [50]. High plasma homocysteine levels are a risk factor for thromboembolism, deep vein thrombosis and stroke in the general population [6, 35].

Positive studies. Biousse et al. [4] reported a 24-year-old man with bilateral CRVO associated with an increased plasma homocysteine level. Wenzler et al. [68] evaluated 14 CRVO (nine non-ischemic and five ischemic) patients under 50 years old, and found hyperhomocysteinemia in 14.3% (two of 14 – both patients had non-ischemic CRVO); in their normal controls the prevalence was one in 70 (1.4%). They concluded that hyperhomocysteinemia is significantly (P<0.01) more prevalent in patients with RVO than in controls and predisposes to the development of premature RVO. Vine [64], in a case-control study of 74 patients with documented CRVO and 74 control subjects, found that hyperhomocysteinemia was significantly (P=0.003) more prevalent in CRVO cases (21.6%) than the controls – it was present in five of nine (55%) patients with bilateral CRVO, nine of 30 (30%) with ischemic CRVO, and 45 of 83 (31%) eyes with severe visual loss. Based on these findings, he concluded that hyperhomocysteinemia is a risk factor for CRVO and may indicate a poor prognosis. In 100 CRVO patients, Marcucci et al. [48] found that homocysteine levels were significantly (P<0.001) higher than in controls and the levels were affected by C677T methylenetetrahydrofolate reductase polymorphism.

Negative studies. By contrast, Boyd et al. [5] found no difference in plasma homocysteine level and C677T methylenetetrahydrofolate reductase polymorphism in 63 CRVO patients compared with 63 age-matched controls. We conducted a pilot study recently to investigate the level of homocysteine in 23 young (≤50 years) patients (14 with non-ischemic CRVO, three ischemic CRVO, and six major BRVO). None of them showed any abnormal levels of homocysteine, not even the one with multiple and recurrent CRVOs (see above). Dudman [13], reviewing the role of homocysteine in venous thrombosis, stated that although previous reports have claimed a direct relation between the degrees of homocysteinemia and the risk of vascular occlusion, there is still no answer to the question of whether homocysteine itself induces thrombosis or the development of arteriosclerosis.

Comments. From this it seems that the role of hyperhomocysteinemia in causing RVO is debatable and deserves additional study. The techniques of measuring homocysteine may also have differed from study to study as techniques of measuring homocysteine have continued to evolve. There is evidence that homocysteine is released from damaged tissues, e.g. it is increased in the days after a myocardial infarction and after stroke. In these cases plasma homocysteine concentrations return to normal quite early in some patients. Thus, according to Dudman [13], timing is important in measuring plasma homocysteine.

Plasma viscosity

Plasma viscosity can be increased either by an increase in formed elements in the blood, e.g. red blood cell or white blood cells, or by an abnormality of serum protein, as in macroglobulinemia, cryoglobulinemia, multiple myeloma and other paraproteinemias. Increased viscosity can also be associated with other systemic diseases, e.g. malignancies, Behçet's disease and chronic pulmonary disease (due to polycythemia).

Positive studies. There are several reports of increased plasma viscosity in RVO and it has been postulated that it plays a role in the pathogenesis of CRVO and BRVO [3, 19, 42]. There are anecdotal case reports of CRVO in patients with paraproteinemias, including multiple myeloma [71] and Waldenstrom's macroglobulinemia [17].

The Eye Disease Case-Control Study Group found higher serum levels of $\propto_2$ globulin in BRVO (P=0.002) [60] and HCRVO (P=0.03) [62], and of $\propto_1$ globulin in CRVO (odds ratio 2.1) [61] than in their control group. In our study, abnormal levels of $\propto_2$ globulin values were found in 25% of 91 consecutive patients investigated, and there was no significant difference in prevalence of abnormal findings between the CRVO+HCRVO patients and the BRVO patients.

High values of packed cell volume are associated with high viscosity. Hemoglobin is an index of the packed cell volume of red blood cells. Glacet-Bernard et al. [19] reported a significantly increased hematocrit level (P<0.05) in CRVO, and found abnormal blood rheologic tests more frequent in 50% of the subgroup of patients who changed from non-ischemic to ischemic CRVO. Arend et al. [3] found hematocrit and plasma viscosity significantly (P<0.01) increased in both ischemic and non-ischemic CRVO compared with controls (although the differences between the patients with CRVO and control group were relatively small), but no difference was seen between ischemic and non-ischemic types. They also found no significant differences in erythrocyte aggregation or erythrocyte rigidity values between the clinical subsets of CRVO and controls. Remky et al. [52] found hematocrit and plasma viscosity significantly higher in the acute BRVO group than the controls. In our study, there was a significantly higher prevalence of abnormal hematocrit (P=0.044) and hemoglobin (P=0.018) in the ischemic CRVO than in the non-ischemic type (Table 4); however, no statistically significant difference was found between non-ischemic and ischemic HCRVO, or between major and macular BRVO.

Negative studies. Dodson et al. [12] found no significant difference in the mean plasma viscosities in CRVO and BRVO, compared with their controls.

Oncologic diseases

Ellis et al. [14] found carcinomas in some of their RVO cases but no definite relationship could be established. Similarly, Kohner and Cappin [42] found no evidence to suggest that malignancy contributes to the development of CRVO. In our study [34] of 1090 patients with various types of RVO, the prevalence of oncologic diseases prior to diagnosis of RVO was 8.5% (52 of 612) in CRVO, 15.4% (20 of 130) in HCRVO and 9.2% (32 of 348) in BRVO patients. The comparison among the three major types of RVO showed no significant differences in oncologic diseases among them. No comparison could be made between the prevalence of oncologic diseases in RVO in our study [34] and that in the general US population, because in the general US population the data on oncologic diseases are available for the incidence only and not the prevalence.

Hyperlipidemia

This has also been described in RVO.

Positive studies. Kohner and Cappin [42] reported significantly higher fasting serum cholesterol (P<0.05) and triglycerides (P<0.01 in males and P<0.005 in females) in CRVO than in a control population. Dodson et al. [12] reported the incidence of hyperlipidemia and hypercholesterolemia was significantly (P<0.001) higher in CRVO and BRVO, and hypertriglyceridemia was more common in CRVO (P<0.001) than in their control group. They concluded that, in type IV and V hyperlipidemias, both CRVO and BRVO are associated with similar risk factors to those for large vessel disease. In 16 RVO patients, Glueck et al. [20] found high total cholesterol in ten (63%), high triglyceride levels in two (13%), low high density lipoproteins in one (6%) and high low density lipoproteins in eight patients (50%). Marcucci et al. [48] found elevated lipoprotein (a) significantly (P<0.005) more often in 100 CRVO patients than in the controls.

Negative studies. We conducted a study in 1090 patients to evaluate hyperlipidemia in different types of RVO and the results are reported elsewhere [34]. The gender- and age-adjusted comparison of the prevalence of elevated serum cholesterol in various types of RVO in our study versus that in the 1988–1991 US population [51] showed no significant differences. Comparison among the three major types of RVO, showed a significantly greater prevalence of hyperlipidemia in the CRVO patients than in the BRVO patients (P=0.033). This was also true for the combined CRVO and HCRVO types (P=0.050).

Miscellaneous

Iannaccone et al. [37] reported significantly increased circulating endothelin-1 plasma levels in patients with RVO compared with healthy controls and patients with essential hypertension in the same age range. Circulating endothelin-1 levels were higher in patients with the ischemic type of RVO (three BRVO and four CRVO) than non-ischemic RVO (six BRVO and five CRVO). Systemic hypertension alone did not account for the observed increase in endothelin-1 levels. They speculated that endothelin-1 homeostasis may be relevant to RVO pathogenesis and retinal ischemic manifestations.

Systemic diseases associated with RVO

We investigated exhaustively the prevalence of arterial hypertension, cardiovascular and cerebrovascular diseases, diabetes mellitus, oncologic diseases, systemic venous thrombosis and various other systemic diseases, as well as smoking and medications, in 1090 RVO patients; the findings are described in detail elsewhere [34].

Practical implications of various reported associated hematologic abnormalities

From this brief review of the literature, one may conclude that, contrary to many claims, we have no definite evidence of a cause-effect relationship between the various hematologic abnormalities and development of various types of RVO for the vast majority of the RVO patients; a chance occurrence of some of these hematologic abnormalities in the RVO cases or the possibility of the findings being due to unrelated concomitant systemic disease cannot be ruled out. So from the clinical point of view, what is the practical implication of all this? Ingerslev [39] very well summarized the state of our knowledge on the subject when he stated “Most well-characterised (hematologic) risk factors for general venous thrombosis occur sporadically only in RVO, and it seems these have no major importance in the pathophysiology of RVO”. In view of this, he rightly recommended that “there seems to be no particular reason that this should include a complete haemostasiological investigation like that offered to patients with spontaneous major venous thromboembolism”. Our study supports this view.

Role of anticoagulants/platelet aggregation reducing agents in RVO

For many of the major systemic venous thromboembolic disorders (e.g., deep vein thrombosis, pulmonary embolism), the required treatment is with anticoagulants or agents which reduce platelet aggregation. Consequently, hematologists invariably recommend these therapies in RVO and that has resulted in a common impression among ophthalmologists that these therapeutic agents should help patients with RVO. Based on our experimental and clinical studies on RVO [23, 24, 25, 26, 27, 28, 29, 30, 31, 33, 34], we feel that equating RVO to deep vein thrombosis and other major systemic thrombotic diseases is a serious misconception among hematologists; in fact RVO differs greatly from systemic thromboembolic diseases in its pathogenesis, risk factors and other aspects [27]; also, unlike deep vein thrombosis, RVO does not produce any embolic complications. This would suggest that a therapy that is beneficial in deep vein thrombosis and other major systemic thrombotic diseases is not necessarily indicated in RVO.

In our experience of managing more than 1,300 eyes with various types of RVO for more than three decades, we have regularly observed that these treatment modalities markedly increase retinal hemorrhages and almost invariably influence the outcome of various types of RVO adversely rather than favorably. Furthermore, we have also seen patients who developed RVO when they were already taking anticoagulants (e.g., heparin or warfarin sodium) or platelet anti-aggregating agents (e.g., aspirin) for other cardiovascular or cerebrovascular disorders. Therefore, we have found no evidence that these treatments help to prevent the development of RVO or benefit patients when they have developed RVO. Indeed, our experience suggests that in RVO these therapeutic agents can be harmful because an increase in retinal hemorrhages (caused by these medicines) can be destructive to the very delicate, thin retinal neural tissue; this is not a problem with other types of tissues, as in, for example, deep vein thrombosis. Moreover, there is no scientifically valid evidence in the literature that these agents benefit RVO patients, either in the prevention of RVO or in improved visual outcome. We are aware that this conclusion contradicts the common practice in the management of RVO advocated by hematologists and followed by most ophthalmologists, and that we have not presented in this paper definitive data in support of our

experience. We are now, however, in the process of collating information from thousands of fundus photographs as well as clinical evaluations of more than 1,300 patients in our study, and hope to present it as soon as possible. Unfortunately, this laborious and time consuming work will take several years. In the meantime, since we have almost uniformly observed this typical pattern, we feel it would be unethical on our part not to warn ophthalmologists about these important potential problems immediately.

Role of various systemic and hematologic abnormalities in pathogenesis of various types of RVO

There is an almost universal tendency to blame only one or two factors for the development of the various types of RVO, or to generalize from an anecdotal reported association. Association, of course, does not necessarily imply a cause-effect relationship. Available evidence strongly suggests that the pathogenesis of the various types of RVO, like many other ocular vascular occlusive disorders [32], is a multifactorial process. It would seem that some risk factors predispose an individual or an eye to develop RVO (predisposing factors), whereas others act as the final insult to produce clinically evident disease (precipitating factors) [34]. The various risk factors for the various types of RVO may be systemic [34], hematologic or local [27], and the local factors may be in the eye or in the relevant retinal vein itself; they may vary widely from person to person or even from eye to eye, and it is not essential for every person with RVO to have the same combination of risk factors, nor, conversely, for persons with some of the same risk factors to develop RVO. Once an eye and an individual have the critical number or intensity of risk factors required for the development of a particular type of RVO, that type of RVO develops. This explains why patients rarely develop bilateral RVO, and even in the same eye it is rare to have more than one type of BRVO or HCRVO [33]. The retinal venous occlusive process would not be so very localized and individualized if, as is often claimed, just one or two particular hematologic or systemic factors were causative of venous thrombosis; in that case, surely the involvement of the retinal veins would be widespread in an individual, involving both eyes or, in the case of BRVO or HCRVO, other retinal veins in the same eye would also be involved. Once this basic concept is understood, one can attach appropriate significance to the various risk factors. It is possible that some systemic diseases and hematologic abnormalities may sometimes play some role in *some* people and in *some* RVOs, but not necessarily on all or most occasions, in all types of RVOs. Moreover, the role played by various abnormalities may vary from eye to eye and from one type of RVO to another type. Thus, the root of the controversy and confusion on the role of these associated hematologic abnormalities in the development of the various types of RVO may be this oversimplification and generalization of a complex multifactorial phenomenon.

Do our different findings in different types of RVO suggest differences in their pathogeneses?

It is tempting to speculate upon this topic. However, scientific research is like collecting innumerable pieces of a complex jigsaw puzzle, with the hope that one day someone will have all the pieces and will be able to fit them together to form a clear picture. It is unwise to theorize on the basis of only a few incongruous pieces of the jigsaw puzzle. There is evidence that the mechanism of the disease process in RVO is a multifactorial phenomenon. We are reporting a few pieces of that complex jigsaw puzzle, and it would not be appropriate on our part to speculate as to their full significance at this stage.

Limitations in our study

Ours is the first such long-term and exhaustive study on the subject and it is but natural for it to have some limitations. We feel the major limitation of our study is the lack of a normative control group for most of the parameters. We did not collect normative control data ourselves for various logistic reasons; instead, we used normative data from a gender- and age-matched control population based on 1988–1991 estimates from the US National Center for Health Statistics [51]. Those normative data are based on a large epidemiologic study conducted by the US National Center for Health and can be applied to our study group without any reservation. Unfortunately, in the US National Center for Health Statistics, information is not available for many of the hematologic abnormalities evaluated by us. Indeed, there is no appropriate control group to provide information on those hematologic abnormalities (as emphasized above). This limitation is also shared by most previously published studies on the subject. In fact, in several of the published studies, the validity of the “control group” is open to criticism.

Conclusions

The findings of our study and review of the literature reveal that a variety of hematologic abnormalities may be seen in association with different types of RVO. The presence of a particular associated hematologic disorder does not necessarily mean a cause-effect relationship ex-

ists for that type of RVO; the possibility of a chance occurrence of some of these disorders in RVO cases cannot be ruled out. It is misleading to make generalizations about these hematologic disorders for all RVO patients. Available evidence strongly suggests that the pathogenesis of the various types of RVO is a multifactorial process and that there is no one cause of RVO. The presence of a particular hematologic abnormality may or may not be one of the risk factors in a multifactorial scenario that predisposes an eye to develop a particular type of RVO. All the available evidence indicates that the hematologic risk factors responsible for major systemic venous thrombosis occur only sporadically in RVO [1, 15, 16, 39]; in view of this, unlike patients with spontaneous major systemic venous thrombosis, there is no particular reason why all patients with RVO should be subjected to the expensive, extensive special hematologic and hypercoagulability investigations – unless, of course, there is some clear indication. The routine, inexpensive hematologic evaluation is the one required by RVO patients. Our experience with about 1,300 patients with RVO over three decades appears to show that giving anticoagulants (e.g., heparin or warfarin sodium) or platelet anti-aggregating agents (e.g., aspirin) increases the retinal hemorrhages and thereby adversely influences the visual outcome, without any evidence of protective or beneficial effect.

Acknowledgements Dr. S.S. Hayreh is a Research to Prevent Blindness Senior Scientific Investigator. This study was supported by grants EY-1151 and RR-59 from the National Institutes of Health, and in part by unrestricted grants from Research to Prevent Blindness, Inc., New York. We would like to thank our colleagues in our Retina Clinic for their help with some of the pilot studies, Dr. Mark McCarthy with his help in collating the data on systemic diseases, and Ms. Georgiane Parkes-Perret for her secretarial help.

References

1. Allaart CF, Poort SR, Rosendaal FR, Reitsma PH, Bertina RM, Briët E (1993) Increased risk of venous thrombosis in carriers of hereditary protein C deficiency defect. Lancet 341:134–138
2. Andrews A, Hickling P (1997) Thrombosis associated with antiphospholipid antibody in juvenile chronic arthritis. Lupus 6:556–557
3. Arend O, Remky A, Jung F, Kiesewetter H, Reim M, Wolf S (1996) Role of rheologic factors in patients with acute central retinal vein occlusion. Ophthalmology 103:80–86
4. Biousse V, Newman NJ, Sternberg P (1997) Retinal vein occlusion and transient monocular visual loss associated with hyperhomocysteinemia. Am J Ophthalmol 124:257–260
5. Boyd S, Owens D, Gin T, Bunce T, Sherafat H, Perry D, Hykin PG (2001) Plasma homocysteine, methylene tetrahydrofolate reductase C677 T and factor II G20210 A polymorphisms, factor VIII, and VWF in central retinal vein occlusion. Br J Ophthalmol 85:1313–1315
6. Cattaneo M (1999) Hyperhomocysteinemia, atherosclerosis and thrombosis. Thromb Haemost 81:165–176
7. Ciardella AP, Yannuzzi LA, Freund KB, DiMichele D, Nejat M, De Rosa JT, Daly JR, Sisco L (1998) Factor V Leiden, activated protein C resistance, and retinal vein occlusion. Retina 18:308–315
8. Cobo-Soriano R, Sánchez-Ramón S, Aparicio MJ, Teijeiro A, Vidal P, Suárez-Leoz M, Rodriguez-Mahou M, Rodriguez-Huerta A, Fernández-Cruz E, Cortés C (1999) Antiphospholipid antibodies and retinal thrombosis in patients with risk factors: a prospective case-control study. Am J Ophthalmol 128:725–732
9. Coniglio M, Platania A, Di Nucci GD, Arcieri P, Modzrewska R, Mariani G (1996) Antiphospholipid-protein antibodies are not an uncommon feature in retinal venous occlusion. Thromb Res 83:183–188
10. Dahlbäck B (1994) Physiological anticoagulation: resistance to activated protein C and venous thromboembolism. J Clin Invest 94:923–927
11. Dhôte R, Bachmeyer C, Horellou MH, Toulon P, Christoforov B (1995) Central retinal vein thrombosis associated with resistance to activated protein C. Am J Ophthalmol 120:388–389
12. Dodson PM, Galton DJ, Winder AF (1981) Retinal vascular abnormalities in the hyperlipidemias. Trans Ophthalmol Soc UK 101:17–21
13. Dudman NP (1999) An alternative view of homocysteine. Lancet 354:2072–2074
14. Ellis CJ, Hamer DB, Hunt RW, Lever AF, Lever RS, Pearl WS, Walker SM (1964) Medical investigation of retinal vascular occlusion. Br Med J 2:1093–1098
15. Engesser L, Broekmans AW, Briët E, Brommer EJP, Bertina RM (1987) Hereditary protein S deficiency: clinical manifestations. Ann Intern Med 106:677–682
16. Faude S, Faude F, Siegemund A, Wiedemann P (1999) APC-Resistenz bei Patienten mit Zentralvenenverschluss. Vergleich mit Patienten mit tiefer Becken- un Veinvenenthrombose und gesunder Kontrollgruppe. Ophthalmologe 96:594–599
17. Feman SS, Stein RS (1981) Waldenstrom's macroglobulinemia, a hyperviscosity manifestation of venous stasis retinopathy. Int Ophthalmol 4:107–112
18. Glacet-Bernard A, Bayani N, Chretien P, Cochard C, Lelong F, Coscas G (1994) Antiphospholipid antibodies in retinal vascular occlusions. Arch Ophthalmol 112:790–795
19. Glacet-Bernard A, Chabanel A, Lelong F, Samama MM, Coscas G (1994) Elevated erythrocyte aggregation in patients with central retinal vein occlusion and without conventional risk factors. Ophthalmology 101:1483–1487
20. Glueck CJ, Bell H, Vadlamani L, Gupta A, Fontaine RN, Wang P, Stroop D, Gruppo R (1999) Heritable thrombophilia and hypofibrinolysis: possible causes of retinal vein occlusion. Arch Ophthalmol 117:43–49
21. Gottlieb JL, Blice JP, Mestichelli B, Konkle BA, Benson WE (1998) Activated protein C resistance, factor V Leiden, and central retinal vein occlusion in young adults. Arch Ophthalmol 116:577–579
22. Greiner K, Hafner G, Dick B, Peetz D, Prellwitz W, Pfeiffer N (1999) Retinal vascular occlusion and deficiencies in protein C pathway. Am J Ophthalmol 128:69–74

23. Hayreh SS (1965) Occlusion of the central retinal vessels. Br J Ophthalmol 49:626–645
24. Hayreh SS (1976) So-called 'central retinal vein occlusion'. I. Pathogenesis, terminology, clinical features. Ophthalmologica 172:1–13
25. Hayreh SS (1980) Central retinal vein occlusion. In: Mausolf FA (ed). The eye and systemic disease, 2nd edn. C.V. Mosby, St. Louis, pp 223–275
26. Hayreh SS (1983) Classification of central retinal vein occlusion. Ophthalmology 90:458–474
27. Hayreh SS (1998) Central retinal vein occlusion. Ophthalmol Clin North Am 11:559–590
28. Hayreh SS, Hayreh MS (1980) Hemicentral retinal vein occlusion. Pathogenesis, clinical features, and natural history. Arch Ophthalmol 98:1600–1609
29. Hayreh SS, van Heuven WAJ, Hayreh MS (1978) Experimental retinal vascular occlusion. I. Pathogenesis of central retinal vein occlusion. Arch Ophthalmol 96:311–323
30. Hayreh SS, Rojas P, Podhajsky P, Montague P, Woolson RF (1983) Ocular neovascularization with retinal vascular occlusion. III. Incidence of ocular neovascularization with retinal vein occlusion. Ophthalmology 90:488–506
31. Hayreh SS, Klugman MR, Beri M, Kimura AE, Podhajsky P (1990) Differentiation of ischemic from non-ischemic central retinal vein occlusion during the early acute phase. Graefes Arch Clin Exp Ophthalmol 228:201–217
32. Hayreh SS, Joos KM, Podhajsky PA, Long CR (1994) Systemic diseases associated with non-arteritic anterior ischemic optic neuropathy. Am J Ophthalmol 118:766–780
33. Hayreh SS, Zimmerman MB, Podhajsky P (1994) Incidence of various types of retinal vein occlusion and their recurrence and demographic characteristics. Am J Ophthalmol 117:429–441
34. Hayreh SS, Zimmerman B, McCarthy MJ, Podhajsky P (2001) Systemic diseases associated with various types of retinal vein occlusion. Am J Ophthalmol 131:61–77
35. den Heijer M, Koster T, Blom HJ, Bos GM, Briët E, Reitsma PH, Vandenbroucke JP, Rosendaal FR (1996) Hyperhomocysteinemia as a risk factor for deep-vein thrombosis. N Engl J Med 334:759–762
36. Hodgkins PR, Perry DJ, Sawcer SJ, Keast-Butler J (1995) Factor V and antithrombin gene mutations in patients with idiopathic central retinal vein occlusion. Eye 9:760–762
37. Iannaccone A, Letizia C, Pazzaglia S, Vingolo EM, Clemente G, Pannarale MR (1998) Plasma endothelin-1 concentrations in patients with retinal vein occlusion. Br J Ophthalmol 82:498–503
38. Iijima H, Gohdo T, Imai M, Tsukahara S (1998) Thrombin-antithrombin III complex in acute retinal vein occlusion. Am J Ophthalmol 126:677–682
39. Ingerslev J (1999) Thrombophilia: a feature of importance in retinal vein thrombosis? Acta Ophthalmol Scand 77:619–621
40. Kalayci D, Gurgey A, Guven D, Parlak H, Hasirpi H (1999) Factor V Leiden and prothrombin 20210 A mutations in patients with central and branch retinal vein occlusion. Acta Ophthalmol Scand 77:622–624
41. Kleiner RC, Najarian LV, Schatten S, Jabs DA, Patz A, Kaplan HJ (1989) Vaso-occlusive retinopathy associated with anti-phospholipid antibodies (lupus anticoagulant retinopathy). Ophthalmology 96:896–904
42. Kohner EM, Cappin JM (1974) Do medical conditions have an influence on central retinal vein occlusion? Proc Roy Soc Med 67:20–22
43. Larsson J, Olafsdottir E, Bauer B (1996) Activated protein C resistance in young adults with central retinal vein occlusion. Br J Ophthalmol 80:200–202
44. Larsson J, Sellman A, Bauer B (1997) Activated protein C resistance in patients with central retinal vein occlusion. Br J Ophthalmol 81:832–834
45. Larsson J, Hillarp A, Olafsdottir E, Bauer B. (1999) Activated protein C resistance and anticoagulant proteins in young adults with central retinal vein occlusion. Acta Ophthalmol Scand 77:634–637
46. Linna T, Ylikorkala A, Kontula K, Puska P, Tervo T (1997) Prevalence of factor V Leiden in young adults with retinal vein occlusion. Thromb Haemost 77:214–216
47. Ma AD, Abrams CS (1998) Activated protein C resistance, Factor V Leiden, and retinal vessel occlusion. Retina 18:297–300
48. Marcucci R, Bertini L, Giusti B, Brunelli T, Fedi S, Cellai AP, Poli D, Pepe G, Abbate R, Prisco D. (2001) Thrombophilic risk factors in patients with central retinal vein occlusion. Thromb Haemost 86:772–776
49. Mazza C, Palmieri L, Mazzilli G (1968) L'aggregazione piastrinica nelle trombosi venose della retina. Ann Ottal 94:133–139
50. Mudd SH, Skovby F, Levy HL, Pettigrew KD, Wilcken B, Pyeritz RE, Andria G, Boers GH, Bromberg IL, Cerone R, et al. (1985) The natural history of homocystinuria due to cystathionine β-synthase deficiency. Am J Hum Genet 37:1–31
51. National Center for Health Statistics (1994) Health, United States, 1994. Public Health Service, Hyattsville, MD, p 164
52. Remky A, Arend O, Jung F, Kiesewetter H, Reim M, Wolf S (1996) Haemorheology in patients with branch retinal vein occlusion with and without risk factors. Graefes Arch Clin Exp Ophthalmol 234:S8-S12
53. Salomon O, Moisseiev J, Rosenberg N, Vidne O, Yassur I, Treister G, Steinberg DM, Seligsohn U (1998) Analysis of genetic polymorphisms related to thrombosis and other risk factors in patients with retinal vein occlusion. Blood Coagul Fibrinolysis 9:617–622
54. Samama MM, Simon D, Horellou MH, Trossaert M, Elalamy I, Conard J (1996) Diagnosis and clinical characteristics of inherited activated protein C resistance. Hemostasis 26[Suppl 4]:315–330
55. Scott JA, Arnold JJ, Currie JM, Broadfoot C, Davidson M, Kelly KF, Graham A, Kirkpatrick JNP, Greaves M (2001) No excess of factor V:Q506 genotype but high prevalence of anticardiolipin antibodies without antiendothelial cell antibodies in retinal vein occlusion in young patients. Ophthalmologica 215:217–221
56. Snyers B, Lambert M, Hardy J-P (1990) Retinal and choroidal vaso-occlusive disease in systemic lupus erythematosus associated with antiphospholipid antibodies. Retina 10:255–260
57. Speicher L, Philipp W, Kunz FJ (1992) Factor XII deficiency and central retinal vein occlusion. Lancet 340:237
58. Svensson PJ, Dahlbäck B (1994) Resistance to activated protein C as a basis for venous thrombosis. N Engl J Med 330:517–522
59. Tekeli O, Gursel E, Buyurgan H (1999) Protein C, protein S and antithrombin III deficiencies in retinal vein occlusion. Acta Ophthalmol Scand 77:628–630
60. The Eye Disease Case-Control Study Group (1993) Risk factors for branch retinal vein occlusion. Am J Ophthalmol 116:286–296
61. The Eye Disease Case-Control Study Group (1996) Risk factors for central retinal vein occlusion. Arch Ophthalmol 114:545–554
62. The Eye Disease Case-Control Study Group (1998) Risk factors for hemicentral retinal vein occlusion: comparison with risk factors for central and branch retinal vein occlusion. Ophthalmology 105:765–771

63. Vine AK (2000) Retinal vascular occlusion and deficiencies in the protein C pathway. Am J Ophthalmol 129:112–114
64. Vine AK (2000) Hyperhomocysteinemia: a risk factor for central retinal vein occlusion. Am J Ophthalmol 129:640–644
65. Vine AK, Samama MM (1997) Screening for resistance to activated protein C and the mutant gene for factor V:Q506 in patients with central retinal vein occlusion. Am J Ophthalmol 124:673–676
66. von Michel J (1878) Die spontane Thrombose der vena centralis des Opticus. Graefes Arch Clin Exp Ophthalmol 24(2):37–70
67. Walsh PN, Goldberg RE, Tax RL, Magargal LE (1977) Platelet coagulant activities and retinal vein thrombosis. Thromb Haemost 38:399–406
68. Wenzler EM, Rademakers AJ, Boers GH, Cruysberg JR, Webers CA, Deutman AF (1993) Hyperhomocysteinemia in retinal artery and retinal vein occlusion. Am J Ophthalmol 115:162–167
69. Wiechens B, Schroder JO, Potzsch B, Rochels R (1997) Primary antiphospholipid antibody syndrome and retinal occlusive vasculopathy. Am J Ophthalmol 123:848–850
70. Williamson TH, Rumley A, Lowe GDO (1996) Blood viscosity, coagulation, and activated protein C resistance in central retinal vein occlusion: a population controlled study. Br J Ophthalmol 80:203–208
71. Zirm M, Schmut O (1974) Zur immunologischen Diagnostik bei Zentralvenenthrombosen. Klin Monatsbl Augenheilkd 164:478–485