

PERSPECTIVE

Central retinal vein occlusion: what's the story?

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Central retinal vein occlusion (CRVO) has been a profitable area of study for many investigators. Shameful then that we still do not understand its pathogenesis or know, definitively, how to treat the condition. Many questions still arise when CRVO is considered. Some of these are outlined in this perspective, hopefully as a guide to future investigation.

Terminology

If confusion over nomenclature is an indicator of confusion over the subject then CRVO is no different. Leibreich in 1854 first described the clinical appearance of CRVO as 'retinal apoplexy'¹ followed closely by Leber in 1877 who preferred 'haemorrhagic retinitis'.² We now use 'central retinal vein occlusion' assuming the presence of a blockage of the vein in the optic nerve head. Hayreh coined the phrases 'venous stasis retinopathy' for the milder types of CRVO and 'haemorrhagic retinopathy' for the more severe disease.³ Similarly, the terms 'ischaemic' and 'non-ischaemic' CRVO have been employed⁴ and 'indeterminate' used for those cases which did not fit easily into the previous categories.⁵ Gass has described some eyes as 'impending, incipient, partial or incomplete' when patients are asymptomatic or have mild transient visual disturbance.⁴ 'Impending' and also 'incipient' tend to suggest a risk of the development of CRVO in the future but a progressive situation which is not part of the natural history of the condition needs to be proved. Do these patients develop an acute CRVO at a future date or do they gradually develop cystoid macular oedema and capillary dropout as is expected in other cases of CRVO? Walsh further classified a mixed group of retinal vein occlusions into primary retinal vein occlusion when there is no systemic disease and secondary CRVO in which systemic disease is present.⁶ These varied terminologies can lead to some confusion—for example, the term 'venous stasis retinopathy' may be confused with the stasis retinopathy from carotid artery disease for which the same name has been used,⁷ and 'haemorrhagic retinopathy' leads the clinician to believe that extensive retinal haemorrhages must be present for ischaemia, but this is not always so. Therefore, it may be more appropriate to employ non-ischaemic and ischaemic CRVO perhaps with partial ischaemia used to locate those eyes which cannot be placed into the previous two categories.

Pathogenesis

IS THROMBUS PRESENT IN THE CENTRAL RETINAL VEIN?

Von Michel in 1878 reported the pathological findings of two cases of CRVO one with proliferation of the intima of the vein and one with thrombus formation in the lumen.⁸ Many of his contemporaries believed that stagnation in the central retinal artery caused secondary thrombosis and obstruction of the central retinal vein.⁹⁻¹² Arguing against the presence of thrombosis, Verhoeff reviewed 39 cases in the literature and concluded that only two had pathological evidence of thrombosis. He believed that the blockage was

due to a venous channel dissecting through intimal thickening of the wall of the vein,¹³ a finding however which he also found in patients with glaucoma.¹⁴ Some felt at this time that congenital vascular anomalies caused CRVO^{9 15 16} while collateral venous channels were protective.¹⁷ Pathological studies performed on cases of rubeotic glaucoma demonstrate thrombus but has this occurred secondarily to the glaucoma?¹⁸ Not until Green *et al* examined 29 eyes were thrombi found in the venous lumen of a few cases of non-rubeotic eyes.¹⁹ A small group of four patients was examined within 24 hours of occlusion and found to have thrombus in the vein close to the lamina cribrosa. None were typical cases of CRVO, consisting of an infant of 8 months with Reye's syndrome, a patient with massive intracranial haemorrhage and papilloedema, another with acute myelogenous leukaemia, and the remaining patient with myocardial infarction but no clinical evidence of CRVO. Attempts to find impaired haemostasis and therefore a risk of thrombosis in CRVO have shown that, although differences exist between cohorts of patients, specific abnormalities in individuals are rare (Table 1).²⁰ Recently, activated protein C (APC) resistance was found in 12% of patients with CRVO compared with 5% of controls taken from the general population.^{20 21} This factor is implicated in haemostatic disease^{22 23} and is much commoner than antithrombin III, protein C and S deficiency. An even higher proportion (26%) was found in a study of patients of less than 50 years of age but no controls were examined.²⁴ The cut off value for the diagnosis of APC resistance in this study was higher (<2.8) than our study (<2.1) which may explain the increased proportion of young patients diagnosed. No difference with age was noted by us but the numbers of patients were small.

DOES STASIS OF VENOUS BLOOD FLOW OCCUR BECAUSE OF INCREASED BLOOD VISCOSITY?

Has the drainage of the retina faltered not because of thrombus formation but because of stasis of blood flow from increased blood viscosity? Blood viscosity is important in venous circulations because the pseudoplastic properties of blood lead to a disproportionate rise in viscosity at low shear rates (for example, slow venous flow). The effects of this can be seen in the hyperviscosity syndromes which manifest retinal features which are indistinguishable from CRVO.²⁵⁻²⁸ Blood viscosity factors are increased in CRVO compared with controls,^{29 30}—for example, in our studies reduced red cell deformability was the key abnormality²⁰ but a variety of abnormalities have been found.²⁹⁻³⁶ In addition the viscosity appears to be temporarily raised at the time of occlusion.²⁰ Our blood viscosity variables were correlated with blood flow factors on Doppler ultrasound but the correlations were weak and do not explain all of the reductions in blood velocities (Table 2). Therefore, although viscosity is associated with the condition and may play some role in the pathogenesis other factors must also be present. Of course the measures of systemic viscosity do not directly measure the viscosity

Table 1 Haemostatic variables which have shown differences between patients with CRVO and controls

	Increased	Decreased
Trope <i>et al</i> ²⁹	Factor VIII Fibrinopeptide A	Antithrombin 3 Platelets
Dodson <i>et al</i> ¹³²	β Thromboglobulin Platelet factor 4	
Walsh <i>et al</i> ⁶	Platelet coagulant	
Gonder <i>et al</i> ¹³³	Platelet coagulant	
Pandolfi <i>et al</i> ¹³⁴	Platelet adhesiveness Factor V Factor VIII Inhibitors of urokinase Inhibitors of plasmin	Fibrinolytic activity venous walls
Williamson <i>et al</i> ²⁰	Antithrombin III Von Willebrand factor Plasminogen activator inhibitor	Activated protein C resistance

Table 2 Blood viscosity correlations with Doppler velocities in the central retinal vein (*b* values from multivariate linear regression analysis, $p < 0.05$)

Eyes with CRVO	Minimum velocity
Red cell aggregation	-0.29
Fellow eyes	Maximum velocity
Relative blood viscosity	-0.29

present in the vein which may be higher than that recorded in the laboratory.

WHAT ABOUT THE ARTERIES?

Coats in 1904 noted that angiosclerosis was associated with CRVO³⁷ since when common systemic vascular disorders such as hypertension, arteriosclerosis, and diabetes have been linked to the condition (Table 3). Could thickening of the arterial wall from sclerosis be reducing the calibre of the vein or perhaps disturbing the pulsatile blood flow relation that exist between the central retinal artery and vein?³⁸⁻⁴⁰

Hayreh among others argued that central retinal artery occlusion is an essential component in the pathogenesis of CRVO and once believed that the ischaemic form of CRVO was due to a combination of arterial and venous occlusion. Evidence for the hypothesis was provided by experimental studies on monkeys. Occlusion of the central retinal vein and temporary occlusion of the central retinal artery at their emergence from the optic nerve produced a clinical appearance in the retina with some similarities to CRVO.⁴¹ Occlusion of the central retinal vein alone at this site did not.⁴¹ Experimental blockage of the central retinal vein distal to the optic nerve head ignored the influence of collateral venous channels around the nerve. Fujino and colleagues, therefore, injected Neoprene into owl monkeys to occlude the vein at the optic nerve head⁴² producing a haemorrhagic retinopathy with evidence of back pressure on the arterial circulation. In the same set of experiments occlusion of the vein at its emergence from the nerve produced only a temporary and reversible increase in retinal venous congestion.

Reduced arterial perfusion pressure on ophthalmodynamometry and prolonged arteriovenous dye transit times on fluorescein angiography have also been used as indica-

Table 3 Reported prevalences of systemic abnormalities in CRVO

Hypertension	38-61% ^{70 74 135 136}
Diabetes mellitus	13-15% ^{70 136}
Arteriosclerosis	21% ⁵⁴
Abnormal glucose tolerance test	17.5-34% ^{93 135}
Hypercholesterolaemia or hypertriglyceridaemia	32-57% ^{93 135 136}
Increased plasma gammaglobulin levels	28% (increased IgA levels in 17%) ¹³⁵
Cryofibrinogenaemia	12% ¹³⁵
Increased plasma antiphospholipid antibodies	Occasional cases ^{111 137 138}

tors of a primary arterial problem.^{43 44} The findings could easily be due to back pressure on the arterial circulation from the congested veins. Doppler studies have indicated reduced blood velocities in the retinal vein and artery, being more pronounced in the vein and particularly marked within 3 months of onset of the occlusion.^{45 46} These suggest that unlike the acute episodes usually associated with retinal artery occlusion there is a prolonged reduction in retinal blood flow lasting a few months. This is a feature which should allow application of therapeutic methods but which has yet to be fully exploited.

Carotico-cavernous sinus fistula which produces increased venous pressure in the orbit may demonstrate the retinal features of CRVO.⁴⁷⁻⁴⁹ Secondary central retinal arterial occlusion or 'steal' from the arterial circulation cannot be excluded but most likely the condition provides evidence for an outflow obstruction. Carotid artery stenosis however can produce a venous stasis retinopathy with venous dilatation and retinal haemorrhages but micro-aneurysms, retinal emboli, and low intraocular pressure are also seen.⁷ Hayreh *et al* have suggested that systemic arterial hypotension during sleep is implicated in the pathogenesis of CRVO.⁵⁰

McLeod investigated patients with combined occlusion of the cilio-retinal artery and central retinal vein showing that retinal haemorrhages a key feature of CRVO were less prominent in the area of the arterial infarct than in the surrounding retina.^{51 52} He cited this as evidence that arterial occlusion was less likely as a primary mechanism. Indeed video fluorescein angiography of such patients shows pulsations of dye in the arteries suggesting back pressure without occlusion.⁵³ These may also be seen in the retinal circulation of cases of CRVO with dye gradually progressing through the arterioles (unpublished data).

DOES CRVO SHARE SIMILAR RISK FACTORS TO ARTERIAL DISEASE?

The condition is associated with common systemic vascular disorders such as hypertension, arteriosclerosis, and diabetes. However, dissimilarities with arterial disease exist. Ellis *et al* found that 51% of patients with vein occlusion smoked compared with 40% of controls but that all patients with central retinal artery occlusion smoked.⁵⁴ Carotid artery disease is associated with retinal artery occlusion but not with CRVO.⁵⁵ Reduced mean optic disc area, a risk factor for anterior ischaemic optic neuropathy, is not found in eyes with CRVO.⁵⁶⁻⁵⁸ An increase in mortality is expected in patients suffering arterial occlusion but this has not been reliably found in CRVO.⁵⁹⁻⁶² Furthermore, it is uncertain whether an increase in cardiovascular or cerebral vascular mishaps affects these patients.⁶³ In a recent comparison of arteriopathic risk factors including smoking, systemic hypertension, history of myocardial infarction, or cerebrovascular accident and hypercholesterolaemia we were unable to show an increased prevalence compared with a sample of the general population (unpublished data). In contrast, two larger studies using hospital based controls have shown increased risk of CRVO with arteriopathy, plasma glucose level, and systemic blood pressure.^{64 65} Reduced risk was associated with regular exercise, alcohol intake, and high density lipoprotein levels.

WHAT ROLE HAS INTRAOCULAR PRESSURE?

A popular theory exists that raised intraocular pressure causes external compression of the central retinal vein as it passes through the lamina cribrosa. This results in turbulent blood flow distal to the constriction and subsequent thrombus formation. An association with CRVO and raised intraocular pressure has been described

but turbulent flow is not present on Doppler studies.⁴⁵⁻⁶⁶ This is not surprising because low blood velocity, reduced vessel calibre, and increased viscosity protect against turbulence (according to Reynold's equation) and are all present in the central retinal vein.⁶⁷

CRVO is detected in 4% to 4.5% of eyes with primary open angle glaucoma⁶⁸⁻⁶⁹ and primary open angle glaucoma or ocular hypertension in 4% to 43% of patients with CRVO.⁷⁰⁻⁷⁵ Although CRVO causes an initial drop in intraocular pressure which recovers within a few weeks⁷¹⁻⁷⁶ an increase in average intraocular pressures has been found compared with controls.⁷⁷ Large rises in intraocular pressure with changes in posture with CRVO have been measured,⁷⁸⁻⁷⁹ reflecting the presence of open angle glaucoma in the condition.⁸⁰ The role of intraocular pressure in the aetiology of CRVO has been questioned⁸¹ because a similar incidence of underlying medical conditions has been reported in patients with and without raised intraocular pressure⁷⁴ and recurrent CRVO is as common whether intraocular pressure was raised or not. Even so there does appear to be a connection between raised intraocular pressure and CRVO but the mechanism by which these interact remains obscure.

IS THERE INFLAMMATION?

An inflammatory aetiology was first suggested by finding young patients with influenza and CRVO.¹⁵ Cases of tubercle of the vein, paranasal sinusitis, cavernous sinus thrombosis, facial erysipelas, ophthalmic herpes zoster associated with CRVO added weight to this contention.⁸²⁻⁸³ Later increased C reactive protein levels and increased erythrocyte aggregation rates were found.⁷⁰⁻⁸⁴ Local inflammation has been detected pathologically but usually in rubeotic eyes¹⁹ and immunological diseases have been associated with CRVO (Table 4) but a definitive inflammatory process has not been determined. Also young patients show no predilection for inflammation in recent studies.⁸⁵⁻⁹⁰

ARE BRANCH RETINAL VEIN OCCLUSIONS A SPECTRUM OF THE SAME DISEASE AS CRVO?

Retinal vein occlusions are often grouped together in studies. While this may be appropriate with central and hemiretinal vein occlusions where the sites of blockage are likely to be anatomically very close this does not apply to branch retinal vein occlusion (BRVO) which also has aetiological differences. For example, raised intraocular pressure is more common in CRVO than BRVO (6% to 13% with raised intraocular pressure).⁵⁴⁻⁷⁰⁻⁷⁷ Likewise, only 1% of glaucoma patients have evidence of branch vein occlusion.⁶⁸ Hypermetropia, arteriosclerosis, and high blood pressure are commoner in BRVO, whereas raised erythrocyte sedimentation rate is commoner in CRVO.⁷⁰ Separation of the two conditions during studies is prudent.

WHAT TESTS SHOULD BE CARRIED OUT IN THE CLINIC?

The primary roles of investigation of CRVO in the clinical setting have been to identify underlying systemic and ocular conditions which require treatment. Intraocular pressure should be tested and carotid bruits auscultated in case of ocular ischaemic syndrome. For the latter, ophthalmology

Table 4 Case associations of CRVO with inflammatory or immunological disease

Moyamoya disease ¹³⁹
Systemic lupus erythematosus ¹⁴⁰
Tuberculosis ¹⁴¹
Acute multifocal placoid pigment epitheliopathy ¹⁴²
Optic neuritis ⁹⁰
AIDS ⁹⁷⁻¹⁴³⁻¹⁴⁴

Table 5 Positive blood results in the author's studies

Full blood count	7% anaemia (<10 mg/dl) 7% polycythaemia (>0.45)
Erythrocyte sedimentation rate	7% (>50 mm/h)
Hypercholesterolaemia	28% (>6.5 mmol/l)

dynamometry of the central retinal artery perfusion pressure may be helpful and colour Doppler imaging of the orbit and carotid arteries performed when suspicion is high. In a cohort of 90 patients with occlusion investigated for various general medical conditions the laboratory tests shown in Table 5 yielded fruitful results. These are worth investigating routinely because the recurrence rate of CRVO may be reduced if general medical conditions are treated.⁹¹⁻⁹² Whether the results of these investigations only reflect the elderly age of the patients is a contention but recent studies suggest that systemic blood pressure and glaucoma are increased relative to controls.⁶⁴⁻⁶⁵ Blood cholesterol levels, although often increased in patients with vein occlusion,⁹³ are not higher than age matched controls.⁶⁴ High density lipoprotein levels are significantly lower⁶⁴; therefore, the clinician should offer the patient dietary advice if raised cholesterol levels are found especially considering the association of CRVO with arteriosclerosis.

Testing for multiple myeloma with plasma protein electrophoresis should be restricted to patients in whom there is a high index of suspicion—for example, bilateral CRVO. The therapeutic indications of relative changes in viscosity or coagulation are still poorly defined because abnormalities warranting specific intervention are likely to be rare. Viscosity could be investigated if rheological therapy is being considered and haemostasis perhaps tested in young patients. Treatment of patients with abnormalities—for example, APC resistance, has not yet been assessed.

Neovascularisation and neovascular glaucoma

Twenty one per cent of cases of CRVO develop iris neovascularisation usually by 6 or 7 months after onset although it can occur as late as 24 months from presentation.⁹⁴⁻⁹⁶ Neovascular glaucoma develops in 8% of CRVO⁹⁷ overall, 67–82% of ischaemic CRVO,⁵⁻⁹⁵⁻⁹⁷ and as little as 1% of those with non-ischaemic disease.⁸⁵⁻⁹⁵⁻⁹⁷ Although iris neovascularisation may occur as late as 24 months after onset⁹⁴ the majority of cases, 71% patients in one study,⁹⁵ occur within the first 6 months. Patients may experience a late reduction in vision followed by development of ischaemia and neovascularisation, probably indicating a reblockage of the vein. Progressive development of ischaemia can also occur, the mechanism of which is unknown. Left untreated, iris neovascularisation causes blindness (no perception of light) in 76% and results in phthisis bulbi or enucleation for pain in 26%.⁹⁸

New vessels in the posterior segment usually occur in only 5–7% of eyes.⁹⁷ In contrast, retinal new vessels in BRVO occur in 23%.⁹⁷ Whereas new vessels of the iris appear within the first 6 months new vessels of the disc and retina take longer to appear, usually 1 year after the occlusion occurs.⁹⁹ Theoretically, a lack of viable retinal vascular endothelium (demonstrated histologically) prevents neovascularisation whereas the iris vasculature can still respond.¹⁰⁰

HOW CAN WE PREDICT THOSE PATIENTS WITH A RISK OF IRIS NEOVASCULARISATION?

For classification visual acuity, ophthalmoscopy, relative afferent pupillary defect, visual field assessment, and investigations such as electroretinography, fluorescein angiography and colour Doppler imaging have been used. An

Table 6 A suggested management protocol for patients with CRVO

<i>Less than 3 months from onset:</i>	
If neovascularisation treat with panretinal photocoagulation	
If no neovascularisation and:	
ERG	Reduced flash photopic wave amplitude
RAPD	20 degrees or more (cross polarised filters, if other eye normal)
Visual acuity	Less than 6/60 (if no cystoid macular oedema)
Doppler ultrasound	Vmin less than 3 cm/s (repeated examinations)
Manage with frequent observation (every 2 weeks) or prophylactic panretinal photocoagulation and monthly observation	
<i>After 3 months from onset:</i>	
If neovascularisation treat with panretinal photocoagulation	
If no neovascularisation and:	
ERG	Reduced flash photopic wave amplitude
RAPD	20 degrees or more (cross polarised filters, if other eye normal)
Visual acuity	Less than 6/60 (if no cystoid macular oedema)
Fluorescein angiography	Capillary dropout 10 disc diameters or more
Manage with frequent observation (monthly up to 6 months then 2 monthly) or panretinal photocoagulation	

appropriate protocol for this purpose from our own studies is provided in Table 6.

Visual acuity shows some predictive power for the development of neovascular glaucoma^{6,96} but its value is lessened because cystoid macular oedema is a common complication of CRVO reducing visual acuity in many non-ischaemic vein occlusions. A quantitative assessment of relative afferent pupillary defect (RAPD) can be performed using neutral density filters^{101,102} or cross polarising filters.¹⁰³ The test is dependent upon the presence of a healthy fellow eye which may preclude the investigation of a significant proportion of patients. Ophthalmoscopic variables such as retinal haemorrhages or cotton wool spots are unreliable.⁴⁵

FLUORESCEIN ANGIOGRAPHY

Paton in 1964 first described the fluorescein angiographic appearance of CRVO.¹⁰⁴ Retinal capillary non-perfusion is seen in 22%¹⁰⁵ and 36%⁸⁵ and has been shown repeatedly to predict the development of rubeosis.^{98,106–108} Unfortunately, the identification and quantification of this sign is subjective and difficult to standardise. Serial fluorescein angiograms have shown that capillary closure increases with time, up to 3 months, so that early examination may underestimate the final extent of the retinal ischaemia.^{96,98,109} The progressive loss of capillaries with time has also been demonstrated histologically in experiments using monkeys.⁴¹ Some of the high so called 'conversion' rates (9–20%) from non-ischaemic to ischaemic CRVO can be explained by the slow loss of capillaries and gradual increase in non-perfusion.^{3,85,94,95}

Up to one third of fluorescein angiograms in CRVO are inadequately assessed because of the presence of such factors as retinal haemorrhages and medial opacities¹¹⁰ and in 11% assessment of the perifoveal arcade cannot be performed.⁹⁶ In addition, because of the largely subjective nature of fluorescein angiography, agreement between two assessments by the same observer may be as low as 68%.¹¹¹ Using forced choice methodology only 35% of examiners make what is considered to be a correct classification of ischaemia.

An intact perifoveal arcade provides a good indicator for recovery of visual acuity, cystoid macular oedema occurring if there are breaks in the continuity or if severe venous leakage is present.^{96,106} Transit of fluorescein dye from the arterial to the venous retinal circulations can be used to indicate a risk of ischaemia⁹⁵ especially in patients examined less than 3 months after onset.¹⁰⁶

Table 7 The measurements from ERG which were most predictive of iris neovascularisation in various studies

<i>Scotopic measurements:</i>	
Sabates <i>et al</i> ¹⁴⁵	b/a ratio
Kaye <i>et al</i> ¹¹⁶	b wave implicit time
Hayreh <i>et al</i> ¹¹⁴	b wave amplitude
Johnson <i>et al</i> ¹¹⁵	log K
Breton <i>et al</i> ¹¹³	multiple combined measures
<i>Photopic measurements:</i>	
Morrell <i>et al</i> ¹¹⁷	flicker implicit times
Williamson <i>et al</i> ¹¹⁸	b/a ratio

ELECTRORETINOGRAPHY (ERG)

Henkes in 1953 provided the first large series on electroretinography in CRVO.¹¹² Since then a number of investigators have found that ERG is a useful test for detecting ischaemia (Table 7).^{6,28,110,113–117} The predictive potential may be superior to fluorescein angiography but the most efficient testing strategy to employ or part of the ERG waveform to measure is uncertain.

A common abnormality is a reduction in the b wave or b/a ratio but many other measurements are available such as a and b wave implicit times or variables from the physiological compression formula of Naka and Rushton. The ERG may be used to measure photopic or scotopic responses, colour response, or flicker response. Recently, shortened protocols have been identified from receiver operator coefficient curves—for example, a light adapted flash response, and b wave amplitude can be used effectively in the busy clinical environment.¹¹⁸

COLOUR DOPPLER IMAGING

This new technique has recently been used to predict the onset of iris neovascularisation in CRVO from low venous velocities.^{40,45,66} It can be used to examine patients within 3 months of onset of the occlusion when fluorescein angiographic assessment is difficult (because capillary occlusion may not have developed and retinal haemorrhages are present). The non-invasive nature of the test allows repeated examinations. The machinery although expensive is usually available in radiology departments where colour Doppler imaging is used routinely to examine other organs. However, the inconvenience of referring patients to radiology means there is a need for Doppler facilities on ocular ultrasound devices in eye clinics if the method is to be used regularly.

WHAT IS THE VISUAL PROGNOSIS?

Non-ischaemic CRVO has good recovery of visual acuity³ whereas ischaemic cases have a poor prognosis for the recovery of vision,^{85,95,107}—for example, a prospective study found that the final visual acuity was 3/60 or worse in 87% of the ischaemic group whereas the non-ischaemic group had 6/18 vision or better in 80%,⁹⁵ and in a retrospective study 93% of ischaemic CRVO culminated in a final visual acuity of less than 6/60 in contrast with 50% of non-ischaemic eyes.⁸⁵ In our own studies the presenting visual acuity was the best predictor of final visual acuity because most patients did not change (57%). Almost equal proportions deteriorated and improved their visual acuities (23% and 20% respectively). The frequency of bilaterally severely reduced vision was 11% because these patients often had CRVO bilaterally or other ocular pathology affecting their fellow eyes.

Treatment of CRVO

The prolonged partial occlusion of the retinal vein (as opposed to the rapid and short occlusion seen with artery occlusion) and the slowly progressive development of ischaemia or macular oedema should make planned treatment of the condition possible. Despite this, the mainstay

of treatment of CRVO is by panretinal photocoagulation to prevent or treat neovascularisation. Laatikainen *et al*, in a prospective randomised trial, determined that prophylactic xenon panretinal photocoagulation reduced the incidence of neovascularisation and cystoid macular oedema but had no effect on visual acuity.¹¹⁹ These findings have been confirmed¹²⁰ and others have used panretinal photocoagulation to reverse neovascular glaucoma and rubeosis.^{98 99 108 121} More recently, however, the CRVO study group recommended providing frequent follow up of at risk patients and application of laser when neovascularisation occurs¹²² because there was no benefit of prophylactic therapy over therapy when complications arise. The follow up recommended was at least monthly and perhaps more in the early stages of the condition. Also, larger numbers of personnel were employed in follow up (ophthalmologists, photographic reading centres, and optometrists) than would be employed in the usual clinical environment. Twenty per cent of the early treatment group developed iris neovascularisation so that even these patients require follow up but fewer of this group ultimately had uncontrolled neovascular glaucoma despite worse entry level criteria. Hayreh *et al* found no benefit from laser photocoagulation in CRVO, stating that photocoagulation has a detrimental effect on visual field. Unfortunately, the process used for patient selection in their study was flawed which may have affected the results.¹²³

Anticoagulants and fibrinolytic agents have been tried unsuccessfully to treat the condition.¹²⁴⁻¹²⁶ Although streptokinase was successful in improving visual recovery it was thought inappropriate because of a risk of vitreous haemorrhage. With improved vitrectomy techniques now available this agent might warrant reappraisal. Anticoagulation might also be targeted to patients with specific thrombogenic abnormalities such as APC resistance.

An exciting but unpredictable therapy is inducement of chorioretinal anastomosis by high energy argon laser to retinal venules.¹²⁷⁻¹²⁹ If successful this can rapidly resolve macular oedema and improve vision in non-ischaemic CRVO (33.3% of patients). Personal communications from other centres have indicated some risk of neovascularisation, retinal tear formation, and detachment.

Haemodilution to reduce the viscosity of the blood and thereby increase the perfusion of the retina has been effective in randomised controlled trials, improving the visual outcome in non-ischaemic CRVO.¹³⁰ This requires intensive venesection and considerable reduction of the haematocrit by replacement of whole blood by plasma expanders a process which may only be appropriate in younger patients or under general medical supervision. Administration of troxerutin also reportedly improves visual recovery.¹³¹

There is still need for a definitive therapy perhaps targeted at the period within 3 months of onset when haemodynamic abnormalities are greatest and before cystoid macular oedema and capillary closure have developed. Also different approaches may be necessary for different subgroups of the condition—for example, those with APC resistance. In the later stages when ischaemia has been allowed to develop panretinal photocoagulation is likely to remain the mainstay of management.

Conclusions

It has been difficult to prove anything conclusively in the pathogenesis of CRVO but there is evidence for a role for viscosity, raised intraocular pressure, arteriosclerosis, and perhaps thrombosis of the vein. Although the chronic nature of the 'occlusive' process makes the condition amenable to therapeutic intervention, further innovation, or reassessment of existing strategies is required. In the

meantime, the clinician should perform some routine clinical and laboratory investigations because of the associations with systemic medical problems. As yet no test alone can predict all those patients who will develop iris neovascularisation; therefore, multiple tests and in some cases repeated tests are appropriate. Once present neovascularisation should be treated by panretinal photocoagulation. CRVO causes severe impairment of vision in a significant proportion of patients because of the frequency of bilateral ocular disease.

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