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# Photocoagulation for retinal vein occlusion

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ABSTRACT

The role of photocoagulation in retinal vein occlusion (RVO) has been studied since 1974. The most serious complications of central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) are: (i) visual deterioration, most commonly due to macular edema, and (ii) the development of ocular neovascularization (NV), particularly neovascular glaucoma (NVG), with hazardous consequences for vision and even the eye itself.

Before discussing the role of photocoagulation in the management of NV and macular edema in RVO, it is crucial to gain a basic scientific understanding of the following relevant issues: classification of RVO, ocular NV in RVO, and the natural history of macular edema and visual outcome of RVO. These topics are discussed.

In CRVO, ocular NV is a complication of ischemic CRVO but not of nonischemic CRVO. Photocoagulation has been advocated to prevent and/or treat the development of ocular NV and NVG. Since NVG is the most dreaded, intractable and blinding complication of ischemic CRVO, the role of photocoagulation and its management are discussed. Findings of three randomized, prospective clinical trials dealing with photocoagulation in ischemic CRVO are discussed.

The role of photocoagulation in the management of ocular NV and macular edema in BRVO, and three randomized, prospective clinical trials dealing with those are discussed.

Recent advent of intravitreal anti-VEGF and corticosteroid therapies has drastically changed the role of photocoagulation in the management of macular edema and NV in CRVO and BRVO. This is discussed in detail.

## 1. Introduction

Since 1974 in ischemic central retinal vein occlusion (CRVO) panretinal photocoagulation (PRP) has been considered as the treatment of choice for the prevention of ocular neovascularization (NV), particularly neovascular glaucoma (NVG) (Hayreh et al., 1990a). A critical review of all those accounts, however, reveals serious flaws in most of the studies, as discussed elsewhere (Hayreh et al., 1990a). The views in this manuscript are based on my comprehensive studies, as well as a review of all the relevant studies found on Medline literature Search up to 2021.

The most common cause of visual deterioration in various types of retinal venous occlusions (RVO) is development of macular edema. The developments of NV, particularly NVG, have hazardous consequences for vision. Therefore, in the management of RVO, photocoagulation has been used for macular edema and NV. With the discovery of the beneficial role of intravitreal anti-VEGF and corticosteroid therapies, the question arises: "Does photocoagulation still have a role in the management of RVO?"

Before discussing the role of photocoagulation in the management of NV and macular edema in RVO, it is crucial to gain a basic scientific understanding of the following relevant issues: classification of RVO, ocular NV in RVO, and the natural history of macular edema and visual outcome of RVO. These topics are discussed.

## 2. Classification of retinal vein occlusion

Studies in the literature, when describing various aspects of the RVO, often tend to consider RVO as one disease. However, RVO actually consists of 6 distinct clinical entities (Hayreh et al. 1983, 1994), each with a different pathogenesis, clinical manifestations, prognosis, course, complications, demographic characteristics, and management. It is evident that, for any logical discussion and clinical management of RVO, it is imperative to classify RVO into its six distinct clinical entities:

*Abbreviations:* BRVO, Branch retinal vein occlusion; CRVO, Central retinal vein occlusion; ERG, Electroretinography; HCRVO, Hemi-central retinal vein occlusion; NV, Neovascularization; NVG, Neovascular glaucoma; PRP, Panretinal photocoagulation; RAPD, Relative afferent pupillary defect; RVO, Retinal vein occlusion; VA, Visual acuity; VEGF, Vascular endothelial growth factor.

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A. Central retinal vein occlusion (CRVO): This consists of:
   1. Nonischemic CRVO
   2. Ischemic CRVO
B. Hemi-central retinal vein occlusion (HCRVO): This also comprises of:
   3. Nonischemic HCRVO
   4. Ischemic HCRVO
C. Branch retinal vein occlusion (BRVO): This comprises of:
   5. Major BRVO
   6. Macular BRVO

### 2.1. Misconceptions about terminology for the two types of CRVO

The use of an accurate, descriptive and universally accepted name for a disease is essential for proper communication and understanding of its true nature. The terms "partial", "incomplete", "imminent", "threatened", "incipient" or "impending" CRVO and "papillophlebitis" to describe nonischemic CRVO are all confusing and invalid. For nonischemic CRVO the terms "hyperpermeability-response-macular-edema-type" or "hyperpermeable type" are incorrect, because macular edema: (a) is seen in both nonischemic and ischemic CRVO, significantly ($p < 0.001$) more marked in ischemic CRVO (Hayreh and Zimmerman 2015a), (b) it is always secondary to hyperpermeability of retinal capillaries in CRVO, and (c) it is absent in a number of nonischemic CRVOs. The terms "perfused" and "non-perfused" have been used for nonischemic and ischemic CRVO respectively - these terms again are inaccurate, because nonischemic CRVO can also have isolated, small, focal retinal capillary nonperfusion spots (Hayreh et al., 1990b; Hayreh and Zimmerman 2015a), and ischemic CRVO usually does have a variable amount of retinal capillary perfusion. A third category of CRVO, called "mixed", "indeterminant" or "indeterminant perfusion ", has been used by some authors; I feel this third category simply represents testing artifacts, because of the poor differentiating power of the two tests (ophthalmoscopy and fluorescein fundus angiography) used in those studies (see below). When combined information from the 6 clinical tests discussed below is used, this third category disappears. Strictly speaking, even the term "*nonischemic CRVO*" is not 100% accurate, because a study (Hayreh et al., 1990b) has shown that these eyes may have of up to 0.6 log units of relative afferent pupillary defect (RAPD), and a mild reduction in mean b-wave amplitude on electroretinography (ERG) even when they fulfil all the criteria of nonischemic CRVO otherwise; moreover, isolated, small, focal retinal capillary nonperfusion spots are seen in some of these eyes (Hayreh and Zimmerman 2015a). Since in nonischemic CRVO, there is primarily retinal venous stasis, a more appropriate term would be "venous stasis retinopathy". The term "hemorrhagic retinopathy" has been used since 1855 (Liebreich 1855) for "ischemic CRVO". Nevertheless the terms "nonischemic CRVO" and "ischemic CRVO" are now established and relatively accurate descriptions of the two conditions.

Studies in the literature, dealing with photocoagulation and other aspects of CRVO, almost invariably consider CRVO as one disease, in spite of the fact that ischemic and nonischemic CRVOs have very different clinical features, visual outcomes, complications, prognoses and managements. Therefore, first of all it is critical to differentiate CRVO into its two types.

## 3. Differentiation of ischemic from nonischemic CRVO

The criteria to differentiate between the two types of CRVO are highly controversial in the literature. A "*10-disc area of retinal capillary obliteration*" on fluorescein fundus angiography has invariably been considered as the gold standard to differentiate the two types of CRVO. But a prospective study (discussed below) showed that this is not at all a valid criterion. Comprehensive studies (Hayreh et al., 1990b; Hayreh and Zimmerman 2015a) on CRVO showed that the presence of isolated, small, focal retinal capillary obliteration is compatible with nonischemic CRVO. The results of a large multicenter CRVO study (Central Vein Occlusion Study Group 1995) clearly showed that eyes with less than 30 disc diameters of retinal capillary nonperfusion and no other risk factor are at low risk for developing iris/angle NV (i.e. ischemic CRVO), "whereas eyes with 75 disc diameters or more are at highest risk". Thus, "*10 disc area of retinal capillary obliteration*" on fluorescein angiography is a totally unreliable parameter for differentiating ischemic from non-ishemic CRVO. It can result in incorrect diagnosis, prognosis, management and consequently misleading information.

It is well established now that in various retinopathies associated with retinal capillary obliteration, such as ischemic CRVO, BRVO, diabetic retinopathy, and others, the retinal capillary obliteration usually starts first in the peripheral retina, and then slowly progresses toward the posterior pole (Hayreh 1998). Therefore, standard fluorescein fundus angiography covering usually only the central 30°(and, rarely, 60°), of the posterior pole (i.e., optic disc and macular region) may provide no information about the peripheral retina. This results in misleading information about retinal capillary obliteration.

A prospective study (Hayreh et al., 1990b) used the following six routine, clinical tests, in 140 consecutive untreated eyes, to determine the most useful criteria to differentiate the two types of CRVO *during the early acute phase*.

### 3.1. Functional tests

These included (1) visual acuity; (2) visual fields plotted with kinetic perimetry (with a Goldmann perimeter); (3) relative afferent pupillary defect (RAPD); and (4) electroretinography (ERG).

Table 1 summarizes the sensitivity and specificity of these 4 functional tests to differentiate ischemic from nonchemical CRVO, *during the early acute phase* when these patients are usually seen.

### 3.2. Morphological tests

These included (1) ophthalmoscopy and (2) fluorescein fundus angiography.

### 3.3. Overall order of reliability of these tests

The results in this study (Hayreh et al., 1990b) were: RAPD is a highly reliable test in eyes with uniocular CRVO, followed closely by ERG in all cases; and the combined information from these two objective tests can make such a differentiation in almost all cases. Visual fields plotted with a Goldmann perimeter, followed by visual acuity, proved to be the next most reliable parameters. Fluorescein fundus angiography, because of multiple limitations in it, performed much worse overall than any of the functional tests; although extensive capillary obliteration was always present in ischemic CRVO, and isolated patchy capillary obliteration in nonischemic CRVO was present in less than 10% of these eyes (Hayreh and Zimmerman 2015a). The ophthalmoscopic appearance is the least reliable, most misleading parameter, because of its constantly evolving pattern (Hayreh and Zimmerman 2015a). I have discussed misconceptions about this differentiation at length elsewhere (Hayreh

**Table 1**
Sensitivity and specificity of the 4 functional tests in ischemic central retinal vein occlusion (CRVO).

| Ischemic CRVO | | | |
|---|---|---|---|
| Functional tests | | Sensitivity | Specificity |
| Visual acuity | ≤20/400 | 91% | 88% |
| Peripheral visual field (Plotted with a Goldmann perimeter) | I-2e not seen | 97% | 73% |
| | Defective V-4e | 100% | 100% |
| Relative afferent pupillary defect | ≥0.9 log units | 80% | 97% |
| Electroretinography | b-wave amplitude<60% | 80% | 80% |

2005).

This study employed time-honored reliable tests. Since then, more modern tests have emerged; for example, automated perimetry, optical coherence tomography angiography, and ultra-wide field fundus fluorescein angiography. Following discussion deals briefly with limitations in some of them.

### 3.4. Controversy about automated perimetry and manual kinetic perimetry

Currently automated perimetry is most commonly used in clinical practice, because it is cheaper and does not require expensive highly trained technicians for manual kinetic perimetry, but it has the following serious drawbacks.

Visual field information provided by manual kinetic perimetry performed with a Goldmann perimeter, is very different from that provided by current, widely used Humphrey 30-2 or 24-2 SITA automated static threshold perimetry. They provide peripheral visual fields information only up to $30^0$ or $24^0$; by contrast, kinetic perimetry provides that all the way to approximately 80°–90° temporally, 70° inferiorly, 60°–70° nasally, and 50°–60° superiorly. Newer perimeters, such as the Metrovision system, however, allow not only a wider field of vision to be tested (e.g. $105^0$ in the temporal side) but the ability to overlap retinal sensitivity values on the fundus image (e.g. fundus photograph or fluorescein angiogram), so that sensitivity loss can be interpreted in the context of fundus changes, including retinal ischemia. However, on Medline search I found no study dealing with retinal vein occlusion or any other ophthalmic disease using this perimeter so far. Moreover, prospective diagnostic accuracy studies with this method are indeed required.

The importance of that lies in determining the role of peripheral visual loss in CRVO and BRVO in functional disability.

#### 3.4.1. Extent of Visual Functional Disability Produced By Peripheral Visual Field Loss

Most clinical studies are focused on central visual acuity, and have not paid much attention to the peripheral visual fields. It is well established that the constant tracking provided by the peripheral visual fields is essential for sensory input in our day-to-day activities, for example, driving and "navigating" generally. So to assess the visual function disability produced by CRVO and BRVO, it is important to have complete information about the peripheral visual fields as well and any impairment in them.

Thus, for evaluating visual functional disability in CRVO and BRVO, the visual fields plotted with the widely used automated perimetry do not provided that critical information at all, kinetic perimetry does; however, as mentioned above, newer perimeters, such as the Metrovision system, allow a wider field of vision to be tested (e.g. 105° in the temporal side); but, unfortunately, so far that is not available for routine use in clinics. For example, panretinal photocoagulation (PRP) in ischemic CRVO destroys peripheral fields (as shown in Figs. 2–7, and 10); Humphrey 30-2 or 24-2 SITA automated perimetry does not provide that crucial information at all, and that is a very serious drawback in it.

### 3.5. Ultra-wide field fundus fluorescein angiography

This new angiographic method is helpful to evaluate peripheral retinal vascular network, which was previously done by scanning of the retinal periphery by routine angiography, in addition to the central part of the fundus (as shown Fig. 8B below). However, it is truly not possible with a composite made from a standard camera to image the far peripheral retina, as done with ultra-wide field fundus imaging. The latter allows a $200^0$ field of view.

### 3.6. Optical coherence tomography angiography

It is still a new investigational method. We need to learn a lot more about the information provided by it. Moreover, to date, ultra-wide field OCT angiography is not possible (Seknazi et al., 2018; Yeung et al., 2019), and, thus, this technology may not allow differentiation between ischemic and non-ischemic CRVO.

### 3.7. New ERG technology (RETeval)

Thia makes it possible now to do photopic ERG in clinic within minutes (as well as testing of pupillary responses). This, could be potentially incorporated in clinical practice for the evaluation of people with RVO. However, prospective diagnostic accuracy studies with this method are indeed required.

## 4. Macular edema due to RVO

In nonischemic CRVO and BRVO, macular edema is the primary cause of poor visual acuity.

### 4.1. Natural history of macular edema

Understanding the natural history of a disease is paramount to its management. If it is not understood, natural recovery may be attributed to a treatment that is actually ineffective.

#### 4.1.1. Natural history of macular edema associated with CRVO

In a prospective study (Hayreh and Zimmerman 2015) of 581 consecutive eyes with CRVO (492 nonischemic and 89 ischemic CRVO eyes) seen within 3 months of onset, macular edema grade in those with ischemic CRVO at the initial diagnosis was 12% none/mild, 34% moderate, and 53% severe. In nonischemic CRVO, there were 68% none/mild, 24% moderate, and 9% severe.

The resolution time of macular edema did not significantly differ between ischemic and nonischemic CRVO ($P = 0.238$). For eyes with ischemic CRVO at the first diagnosis, 20.8 ± 6.0% had resolved within 12 months from onset, and 38.8 ± 8.6% had resolved within 24 months, with a median time to resolution of 28.8 months (interquartile range [IQR], 17.6–50.4 months). For nonischemic CRVO, 31.5 ± 2.8% resolved within 12 months from onset, and 50.9 ± 3.2% resolved within 24 months, with a median time to resolution of 23.8 months (IQR, 9.5–58.6 months). Limiting the comparison of resolution times among those who had severe macular edema at initial visit, also did not show any significant difference between two types of CRVO ($P = 0.362$).

Chronic macular edema leads to development of microcystic edema, foveal pigmentary degeneration and epiretinal membrane, which adversely influence the visual outcome after resolution of macular edema in nonischemic CRVO. However, in ischemic CRVO there was no significant association of change in visual acuity by these late changes, because of ischemic damage to begin with in the macular region in those eyes.

#### 4.1.2. Natural history of macular edema associated with BRVO

A prospective study (Hayreh and Zimmerman 2015b) of 214 consecutive RVO (144 major BRVO and 72 macular BRVO eyes) seen within 3 months of onset, showed macular edema grade in those with major BRVO was none/mild in 50%, moderate in 33%, and severe in18%, compared with 72% none/mild, 23% moderate, and 6% severe in macular BRVO.

The resolution time of macular edema did not significantly differ between major and macular BRVOs ($P = 0.647$). In major BRVO, resolution of macular edema was 33.1 ± 4.6% within 12 months from onset, 42.6 ± 4.9% within 18 months, and 50.8 ± 5.1% within 24 months. The median time to resolution of macular edema in major BRVO was 20.8 months ([IQR 10.3–54.8 months). For macular BRVO, 30.4 ± 6.4%

resolved within 12 months from onset, 49.4 ± 7.4% within 18 months, and 56.7 ± 7.4% within 24 months; median time to resolution was 18.2 months (IQR, 9.7–58.4 months).

## 5. Natural history of visual outcome

### 5.1. Natural history of visual outcome in CRVO

In a study (Hayreh et al., 2011) comprising 697 consecutive eyes of CRVO (588 nonischemic and 109 ischemic CRVO eyes), first seen within 3 months of onset, in nonischemic CRVO eyes with initial visual acuity of 20/70 or worse, visual acuity improved at 3 months of follow-up in 32%, and during the 2 to 5-year follow-up in 47%, and in ischemic CRVO it was seen in 10% and 23%, respectively. Overall, the rate of improvement in nonischemic CRVO was significantly higher (P = 0.0004) than in ischemic CRVO.

In ischemic CRVO some claims of visual acuity improvement have been reported with treatments. These may be due to (1) incorrect diagnosis of nonischemic as ischemic CRVO, (2) eccentric fixation, or (3) reduction of macular edema in those with minimal ischemia. These claims deal with those not related to the natural history findings.

### 5.2. Natural history of visual outcome in BRVO

In a study (Hayreh and Zimmerman 2014) of 216 consecutive eyes with BRVO (144 eyes with major and 72 eyes with macular BRVO) seen within 3 months of onset, overall, for eyes with initial visual acuity of 20/60 or better, it improved or remained stable in 75% for major BRVO and in 86% for macular BRVO. In those with initial visual acuity of 20/70 or worse, it improved in 69% for major BRVO and in 53% for macular BRVO, with median final visual acuity of 20/60 for both BRVO types.

## 6. Ocular neovascularization in various types of RVO

### 6.1. Ocular neovascularization associated with CRVO and HCVRO

The most serious complication of RVO is the development of various types of ocular NV with hazardous consequences for vision and even the eye itself. In 1869 von Graefe (von Graefe 1869) summarized findings from 22 cases of NVG associated with CRVO. Since then, innumerable publications have appeared, describing the various types of NV complications of RVO. In the older literature, the stress was mostly been laid on NVG in CRVO. The advent of fluorescein angiography enabled us not only to recognize other forms of ocular NV in RVO but also to understand their pathogenesis. In the pre-angiography era, NV was a very loosely used term, encompassing collaterals, shunts, NV, and any abnormal-looking vessel.

Following were the findings of a prospective study (Hayreh and Zimmerman 2012b) dealing with ocular NV in 912 consecutive CRVO eyes (673 nonischemic and 239 ischemic) and 190 HCRVO (147 nonischemic, 43 ischemic).

#### 6.1.1. Ischemic CRVO

In 239 eyes, the cumulative probability of development of various types of NV from onset of ischemic CRVO is shown in Fig. 1.

#### 6.1.2. Nonischemic CRVO

In 673 eyes, one or another type of NV was seen in only 9 eyes due to associated diabetes or ocular ischemic syndrome, *but not due to nonischemic CRVO.*

#### 6.1.3. Ischemic HCRVO

In 43 eyes, the cumulative probability of development of various types of NV was as follows: within 6 months of onset, angle NV in 10% and NVG in 5%; and within 12 months of onset, retinal NV in 29%, iris NV in 12%, and disc NV in 12%.

#### 6.1.4. Nonischemic HCRVO

None of the eyes developed any NV.

Fig. 1 provides instructive information about the development of various types of ocular NV in ischemic CRVO, and its cumulative probability and management. It shows that there is a sharp increase in development of NV during the first 6–7 months, particularly in the anterior segment; after that, there is a dramatic decline in its development. NVG is the most dreaded and devastating complication of ischemic CRVO; its cumulative probability for development from the time of onset of ischemic CRVO was 4% within 1 month, 11% within 2 months, 20% within 3 months, 29% within 6 months, and 34% within 9 months, and about 38% within 4½ years. Of the 72 eyes that developed NVG, 74% had it by 6 months from onset, with 90% eyes within 12 months from onset, and none after about 4½ years.

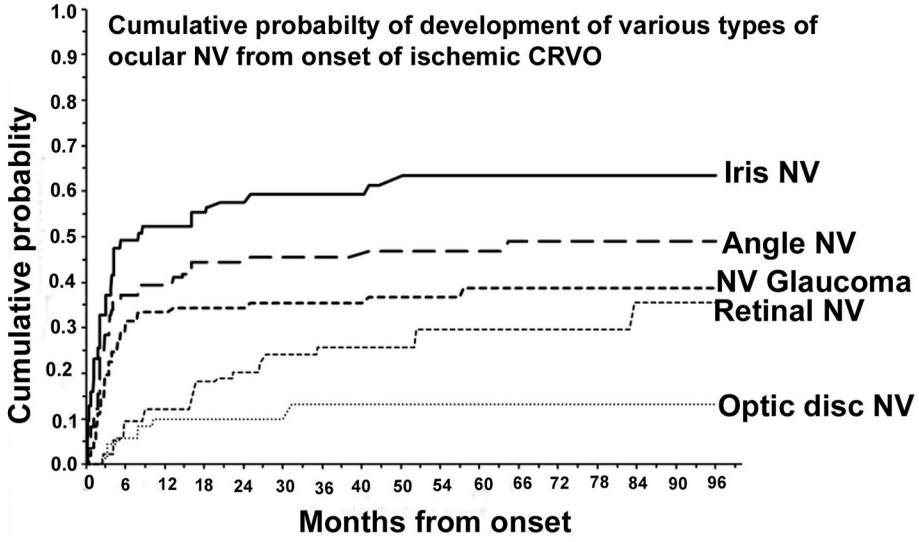


**Fig. 1.** A graphic representation of cumulative probability of development of various types of ocular neovascularization (NV) from onset of ischemic CRVO.

### 6.2. Natural history of ischemic CRVO and associated anterior segment NV

As discussed above, it is essential to know the natural history of a disease before judging the effectiveness of various treatments advocated for it. Our natural history studies on the course of ischemic CRVO have revealed that the retinopathy runs a self-limited course, in that it usually burns itself out and, consequently, gradually resolves spontaneously after a variable length of time. This is very well demonstrated by the pattern of development of NV shown in Fig. 1. This shows that as the retinopathy starts to resolve, the stimulus for NV gradually becomes less and less, consequently the NV spontaneously starts to resolve, especially the anterior segment NV, a fact usually not appreciated in the management of these eyes. These findings contradict the commonly held belief (based on diabetic retinopathy) that retinopathy and ocular NV in ischemic CRVO are progressive in nature. An understanding of this important fact must change our approach to the management of ischemic CRVO and associated anterior segment NV.

### 6.3. Ocular NV associated with BRVO

A prospective study (Hayreh and Zimmerman 2015b) of 214 consecutive BRVO (144 major and 72 macular) eyes seen within 3 months of onset, showed that retinal and disc NV was seen only in major BRVO. In it, retinal NV developed in 9% within 12 months from onset, and in 15% within 36 months. Optic disc NV was seen in 8% within 12 months from onset and in 10% within 30 months. Anterior segment NV was not seen.

## 7. Photocoagulation in CRVO

### 7.1. In nonischemic CRVO

As discussed above, there is no risk of NV attributable to nonischemic CRVO; therefore, there is absolutely **NO** indication or justification for PRP in this disease. Yet, in my clinic, I have seen patients with nonischemic CRVO in whom ophthalmologists had performed PRP; this, in my opinion, is an unjustified and unethical practice.

### 7.2. In ischemic CRVO

Since 1974, there are many reports of the beneficial effects of PRP (using xenon or argon photocoagulators) in ischemic CRVO, to prevent and/or treat the development of ocular NV and the associated blinding complications of NVG, vitreous hemorrhage, or both (Hayreh et al., 1990a). Three randomized, prospective clinical trials (Laatikainen et al., 1977; Hayreh et al., 1990a; Central Vein Occlusion Study Group 1995) evaluated the role of PRP treatment, using argon laser/xenon arc photocoagulators in eyes with ischemic CRVO.

#### 7.2.1. First PRP study in ischemic CRVO

Laatikainen et al., (1977) in 1977 reported their prospective, randomized study of PRP in 23 eyes (12 had PRP and 11 no PRP) ischemic CRVO, using xenon arc photocoagulator. Follow-up examination after entering the trial was at 1 month and 3 monthly thereafter until 1 year, except that 5 eyes were not followed for 1 year. In the PRP group, the treatment did not benefit the visual acuity. In most PRP eyes the visual fields deteriorated, particularly the peripheral visual fields. In the 12 eyes of the PRP group, at the time of treatment, 5 eyes already had iris NV, two optic disc NV and one retinal NV. After PRP, there was iris NV in three, disc NV in one, retinal NV in three and vitreous hemorrhages in one eye.

Since this study was based on only 12 PRP eyes, with 5 eyes having less than 1 year follow-up, its usefulness is severely limited.

#### 7.2.2. Second PRP study in ischemic CRVO

This study was reported in 1990 (Hayreh et al., 1990a). This comprehensive, randomised study was a part of the National Institutes of Health of the USA approved planned, prospective studies dealing with "*ocular vascular occlusive disorders*". This study was originally planned soon after the Diabetic Retinopathy Study Research Group (Diabetic Retinopathy Study Research Group 1976) showed beneficial influence of PRP, and the purpose of this study was to confirm similar beneficial influence of PRP in ischemic CRVO as well.

This study was based on 123 eyes (47 in the PRP group and 76 in the no PRP group (Hayreh et al., 1990a). The diagnosis of ischemic CRVO was based on the criteria discussed above (Hayreh et al., 1990b). Exclusion criteria for the study were patients with nonischemic CRVO, with diabetic retinopathy, with previous PRP, NVG or retinal or optic disc NV. PRP was performed using argon laser, in a scatter fashion, similar to the protocol advocated in the Diabetic Retinopathy Study (Diabetic Retinopathy Study Research Group 1976). The patients were seen for follow-up evaluation at 1, 2, 5, 8, 11, 14, 17, 20, 23, 26, 32, 38, 44, and 50 months after the initial PRP visit. Thereafter, the follow-up was every 6 months or yearly if the retinopathy showed no activity.

On comparison of the lasered eyes with the nonlasered eyes, there was no statistically significant difference between the two groups in the incidence of development of angle NV, NVG, retinal NV, optic disc NV, vitreous hemorrhage, or visual acuity. This study, however, did show a statistically significant ($P = 0.04$) difference in the incidence of iris NV between the two groups, with iris NV less prevalent in the lasered group than in the nonlasered group, but only when the PRP was performed within 3 months after the onset of CRVO. Iris NV *per se*, however, is of little importance as a deleterious complication compared to NVG or vitreous hemorrhage. The most significant finding was a statistically significant ($P \leq 0.03$) difference between the lasered and nonlasered eyes in the loss of peripheral visual fields, as shown in Figs. 2–7 in that study.

The results of this study were the opposite of that in proliferative diabetic retinopathy. They were also the opposite of the view which regarded PRP as the well-established treatment for ischemic CRVO; the conclusions of this study were therefore unwelcomed (discussed at length elsewhere – Hayreh et al., 1990a). No one else, among those who have advocated and practiced PRP in CRVO, had ever systematically recorded the visual fields to determine the extent of the deleterious effect of PRP on the peripheral visual fields, which is a blinding complication of PRP, as is evident from Figs. 2–7.

In our natural history study (Fig. 1) of nonlasered eyes with iris NV, and even angle NV, we found that those NVs persisted for months or even years without ever progressing to NVG, and those later on resolved spontaneously as the retinopathy resolved with time. Thus, our study entirely refuted the general opinion that every eye with ischemic CRVO and iris NV and/or angle NV will ultimately progress to NVG; Fig. 1 testifies to this, showing that only about one third of the eyes with iris NV and about a quarter of the eyes with angle NV never progressed to NVG.

It could be argued that study did not see a beneficial influence from PRP in ischemic CRVO because an adequate amount of PRP was not done. This criticism is answered by the following two facts, among others: firstly, the standard amount of PRP advocated in the literature by all concerned was done, and many eyes developed roaring NVG in spite of having had 3000 or more laser burns - no different from that seen in eyes with the usual amount of PRP. Second, the extensive and significant ($P \leq 0.03$) loss of peripheral visual field in the laser group as compared with the nonlasered group in this study (Figs. 2–7) is clear proof of the more-than-adequate amount of PRP application in these eyes. Giving much more PRP would have almost blinded all the eyes - even those which would have never developed NVG anyway (about 50% of eye with ischemic CRVO, Fig. 1); to blind an eye with extensive PRP in an effort to prevent its possibly developing NVG would be both unethical and irrational.

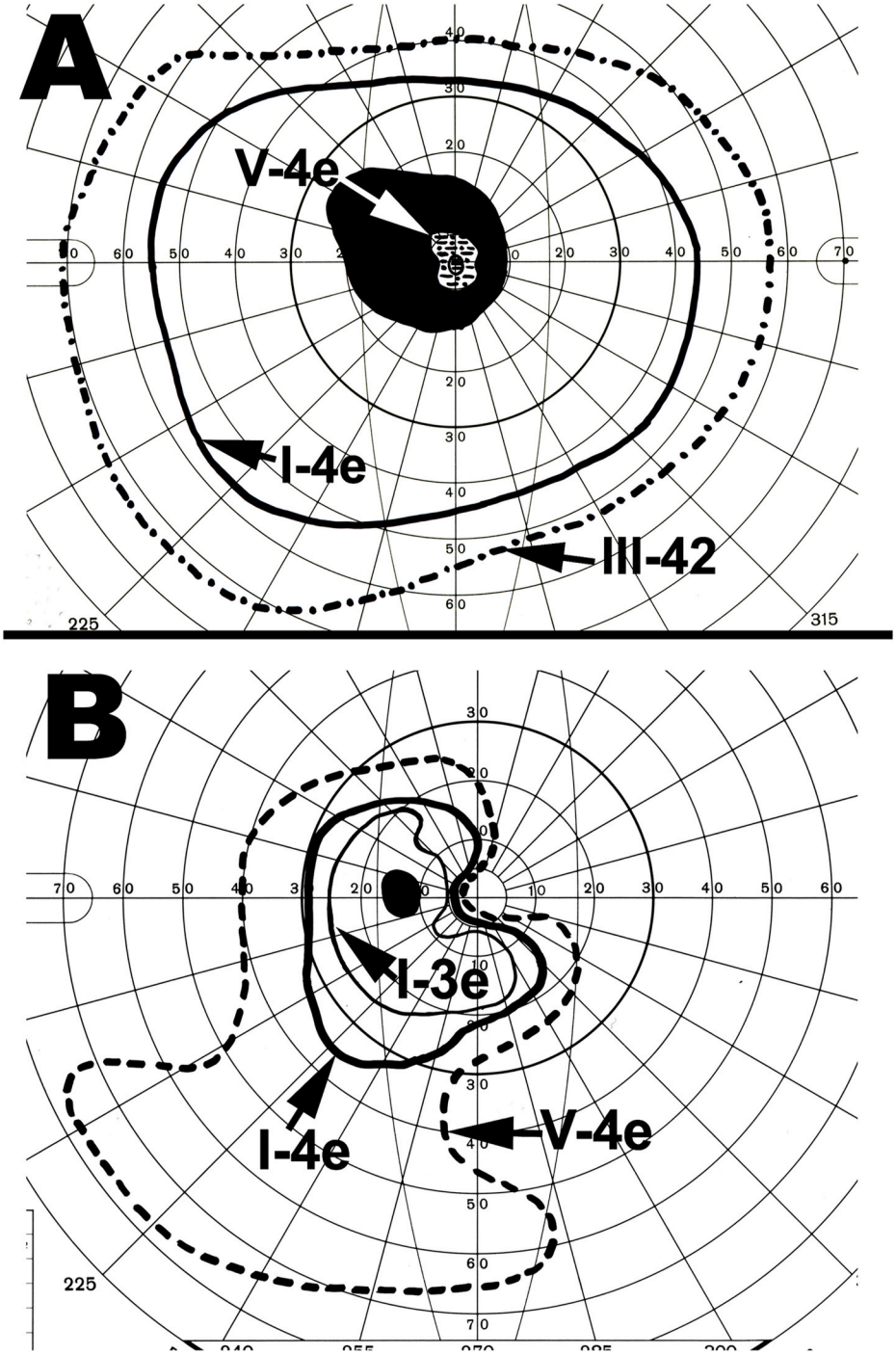


**Fig. 2.** Visual fields of left eye of a 44-year old man with ischemic CRVO. **(A)** Before PRP, and shows a large central scotoma with normal peripheral visual field. The eye developed iris NV one year after onset and that produced vitreous hemorrhage. PRP was performed 5 months after that when the vitreous hemorrhage had cleared. (B) After PRP, and shows marked loss of peripheral fields with only inferior temporal island field left.

In conclusion, this long-term prospective study showed that argon laser PRP had no statistically significant overall beneficial influence in ischemic CRVO; on the contrary, it caused a definite deterioration of the peripheral visual fields in a significant ($P \leq 0.03$) proportion of eyes. It is possible that a study with a much larger sample size may show some beneficial effects of argon laser PRP in certain circumstances, which are not evident in the sample size of this study; however, the incontrovertible fact is that none of the dramatic, universally claimed beneficial effects on ischemic CRVO claimed by some advocates for PRP were shown by this study.

*7.2.2.1. PRP in ischemic CRVO vis-a-vis PRP in proliferative diabetic retinopathy.* It is invariably argued by the advocates of PRP in ischemic CRVO that PRP has been proved to reduce the incidence of ocular NV in proliferative diabetic retinopathy, including NVG. That has led a highly prevalent impression that ischemic CRVO should respond to PRP similar to proliferative diabetic retinopathy. This was the original rationale for promoting and justifying PRP in ischemic CRVO, and at the start of our above PRP study (Hayreh et al., 1990a). The underlying assumption was that proliferative diabetic retinopathy and ischemic CRVO are identical in nature as regards NV development; it was argued that extensive retinal capillary nonperfusion (and associated retinal ischemia) is the

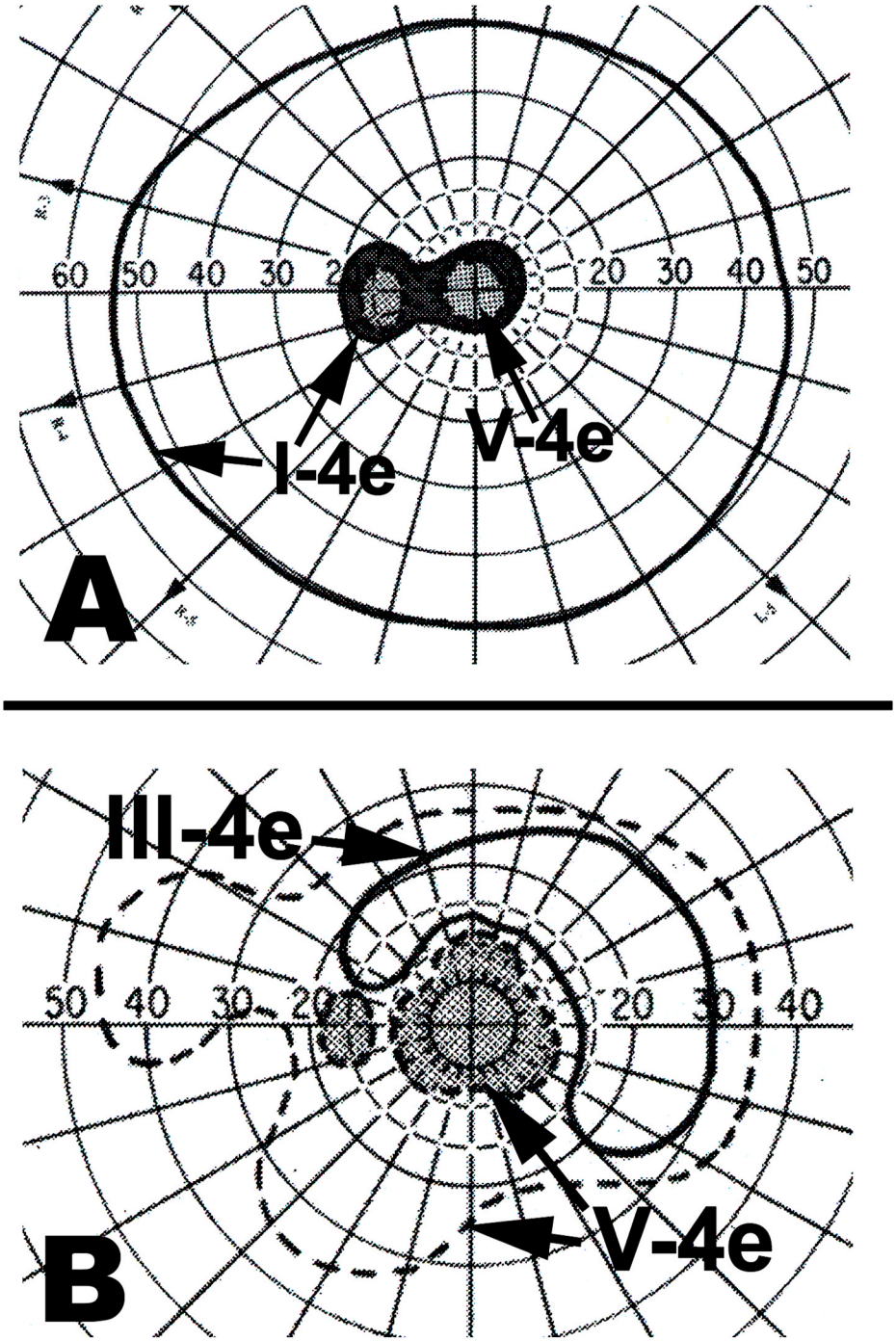


**Fig. 3.** Visual fields of left eye of a 57-year-old man with ischemic CRVO. **(A)** Before PRP, and shows centrocecal scotoma with normal peripheral visual field. The eye had 2250 argon laser burns, starting 112 days after onset of ischemic CRVO. **(B)** After PRP, and shows marked loss of peripheral field and visual field deterioration. This eye developed retinal NV 5 months after the PRP, and that produced vitreous hemorrhage; the NV persisted till the patient died 4 years after PRP.

basic lesion responsible for the ocular NV and NVG in both - hence both types of retinopathies should respond identically to PRP. *This is a fundamental misconception*. A study of the onset, course, natural history, and fundus findings of proliferative diabetic retinopathy and that of ischemic CRVO shows that the two are very different diseases. One could compare ischemic CRVO to a hurricane which develops suddenly and inflicts extensive, devastating damage to the property within a few minutes or hours. By contrast, diabetic retinopathy is like a slow leak in a house, which would undermine the house gradually over a period of years, very slowly and insidiously. Measures which would successfully control the damage to the property caused by a slow leak are totally useless against a devastating hurricane! The extent of retinal ischemia, and hence the quantity of the vasoproliferative factor(s), in ischemic CRVO are many, many times more extensive and sudden in onset than the slow and gradually progressive process in proliferative diabetic retinopathy. PRP may be able to cope with the mild amount of retinal ischemia seen in the usual proliferative diabetic retinopathy, but is totally inadequate and ineffective when there is the severe, extensive, sudden development of retinal ischemia in ischemic CRVO. This basic fact has been ignored by the advocates of PRP who have claimed success in ischemic CRVO. Tasman et al. (Tasman et al., 1980), on comparing the effect of PRP in controlling iris NV in proliferative diabetic

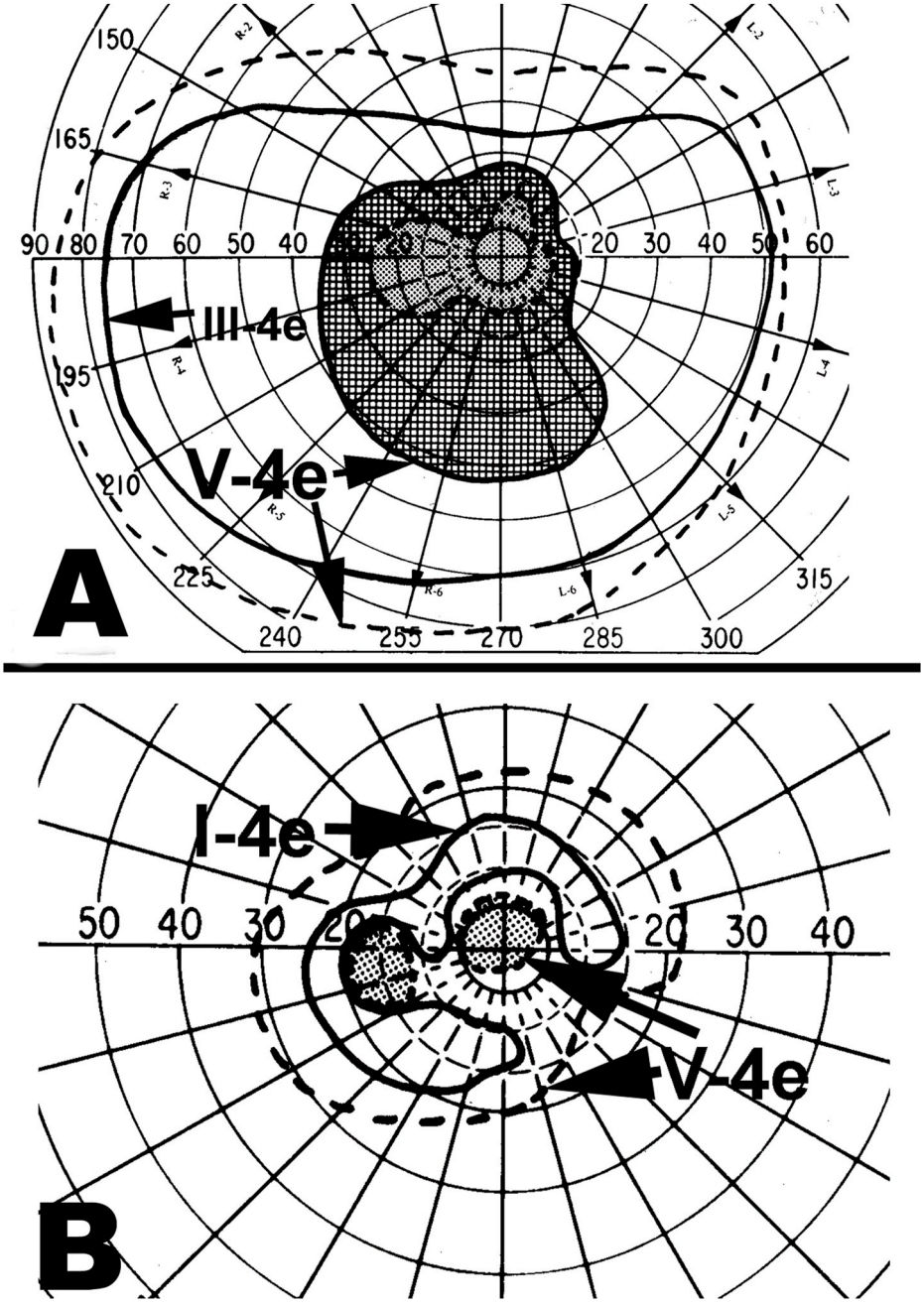


**Fig. 4.** Visual fields of left eye of a 68-year-old woman with ischemic CRVO. **(A)** Before PRP, showing normal peripheral field with a large absolute central scotoma. The eye had 2716 argon laser burns, starting about 7 weeks after onset of ischemic CRVO. **(B)** Five months after PRP, and shows marked loss of peripheral field and visual field deterioration. At first visit (the same as PRP visit) the eye had iris and angle NV and these lasted for 17 months after PRP. The eye developed fairly marked retinal NV about 9 months after PRP, which produced vitreous hemorrhage 27 months later, and the NV was still the same when seen last 6¼ years after PRP.

retinopathy and ischemic CRVO, concluded that "Panretinal photocoagulation was more effective in controlling rubeosis in diabetics than in patients with central retinal vein occlusion." Moreover, the presence of much more extensive retinal hemorrhages and edema in ischemic CRVO as compared with ordinary proliferative diabetic retinopathy requires much greater intensity and power of argon laser to get an adequate reaction; consequently, the higher heat and much greater absorption of energy by hemorrhages results in much more extensive retinal damage in ischemic CRVO than in diabetic retinopathy, which accounts for the marked worsening of the visual fields in the lasered eyes in the former compared with the latter. This is further supported by the fact that in visual field data analysis, statistically significant visual loss in lasered cases occurred in eyes with marked severity of retinopathy and during the early stages of ischemic CRVO where the retinal edema and hemorrhages were most marked. In ordinary diabetic retinopathy, by contrast, there is much less retinal hemorrhage and little or no retinal edema, and consequently not so much worsening of visual fields after PRP. It is possible that in a few ischemic CRVO eyes with only mild retinal ischemia (like that in proliferative diabetic retinopathy), PRP may be beneficial. There were a few eyes in this study (Hayreh et al., 1990a) in which one got a distinct impression that iris and angle NV resolved soon after PRP, and by including only such eyes, this study could have claimed beneficial effects from PRP; but the study also had eyes which responded exactly the same way without any PRP.

### *7.2.3. Third PRP STUDY in ISCHEMIC CRVO*

In 1995, the Central Vein Occlusion Study (CVOS) Group published a study dealing with laser PRP in ischemic CRVO (Central Vein Occlusion Study Group 1995). The purpose of that study was twofold: (1) to find out whether prophylactic PRP prevents development of iris and angle NV, and (2) whether PRP prevents progression of iris or angle NV to NVG.

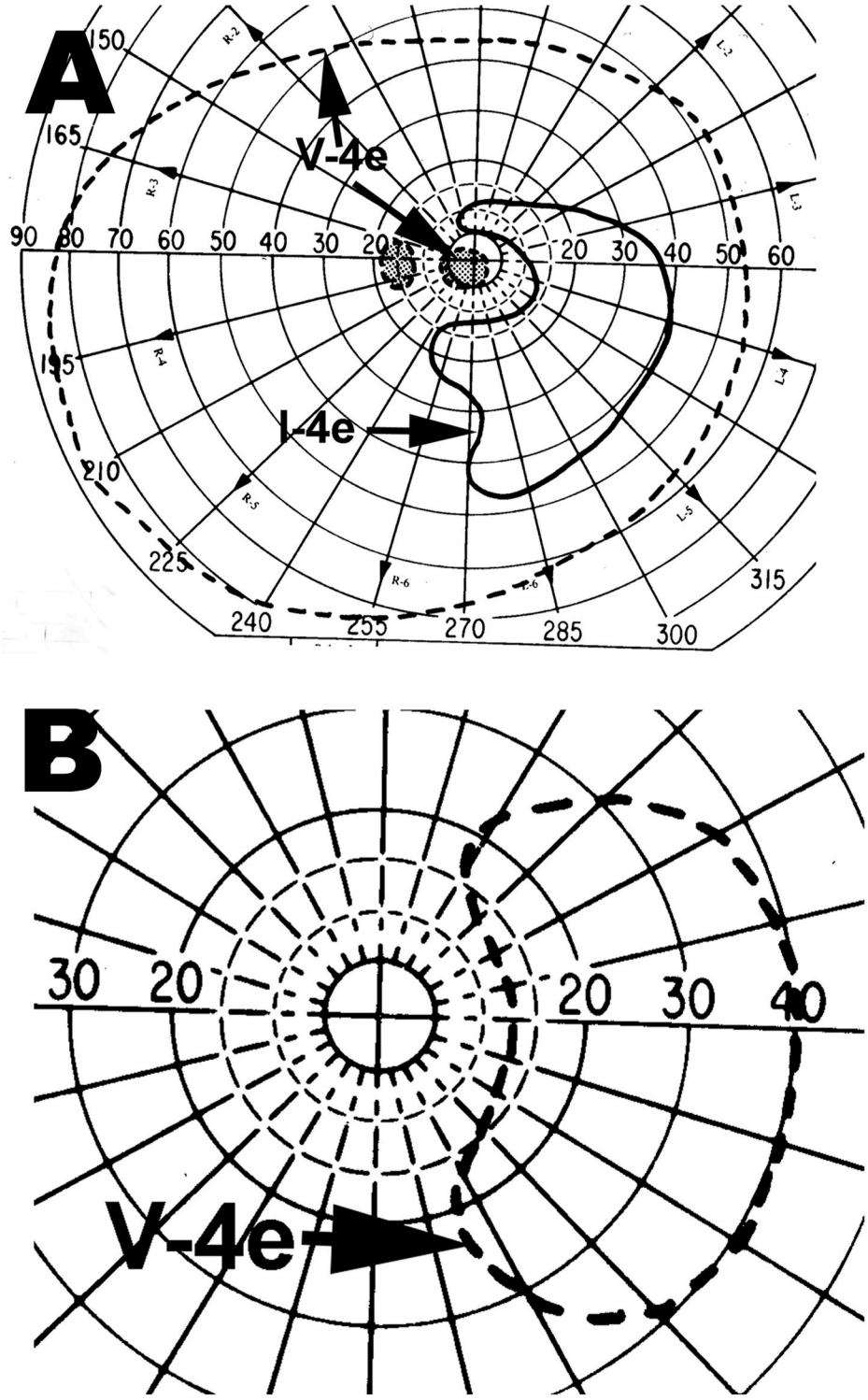


**Fig. 5.** Visual fields of left eye of a 78-year-old woman with ischemic CRVO. **(A)** Before PRP, and shows normal peripheral fields with V4e, small central scotoma and an island field with I4e. The eye had 2789 argon laser burns, starting about 2 months after onset of ischemic CRVO. (B) Six months after PRP, and it shows loss of peripheral field and only a very small island with V4e is left.

In answer to the first question, the study reported that "prophylactic PRP does not totally prevent" development of iris or angle NV, and concluded that prompt regression of iris and angle NV in response to PRP is more likely to occur in eyes that have not been treated previously prophylactically. This study should lay to rest the claims that prophylactic PRP in ischemic CRVO prevents the development of iris and angle NV.

As for as the second aspect of the study, the authors recommended "careful observation with frequent follow-up examinations in the early months including undilated slitlamp examination of the iris and gonioscopy and prompt PRP of eyes in which 2-o'clock iris/angle NV develops."

Such a multicenter, multimillion dollar study conducted under the aegis of the National Institutes of Health carries tremendous prestige and

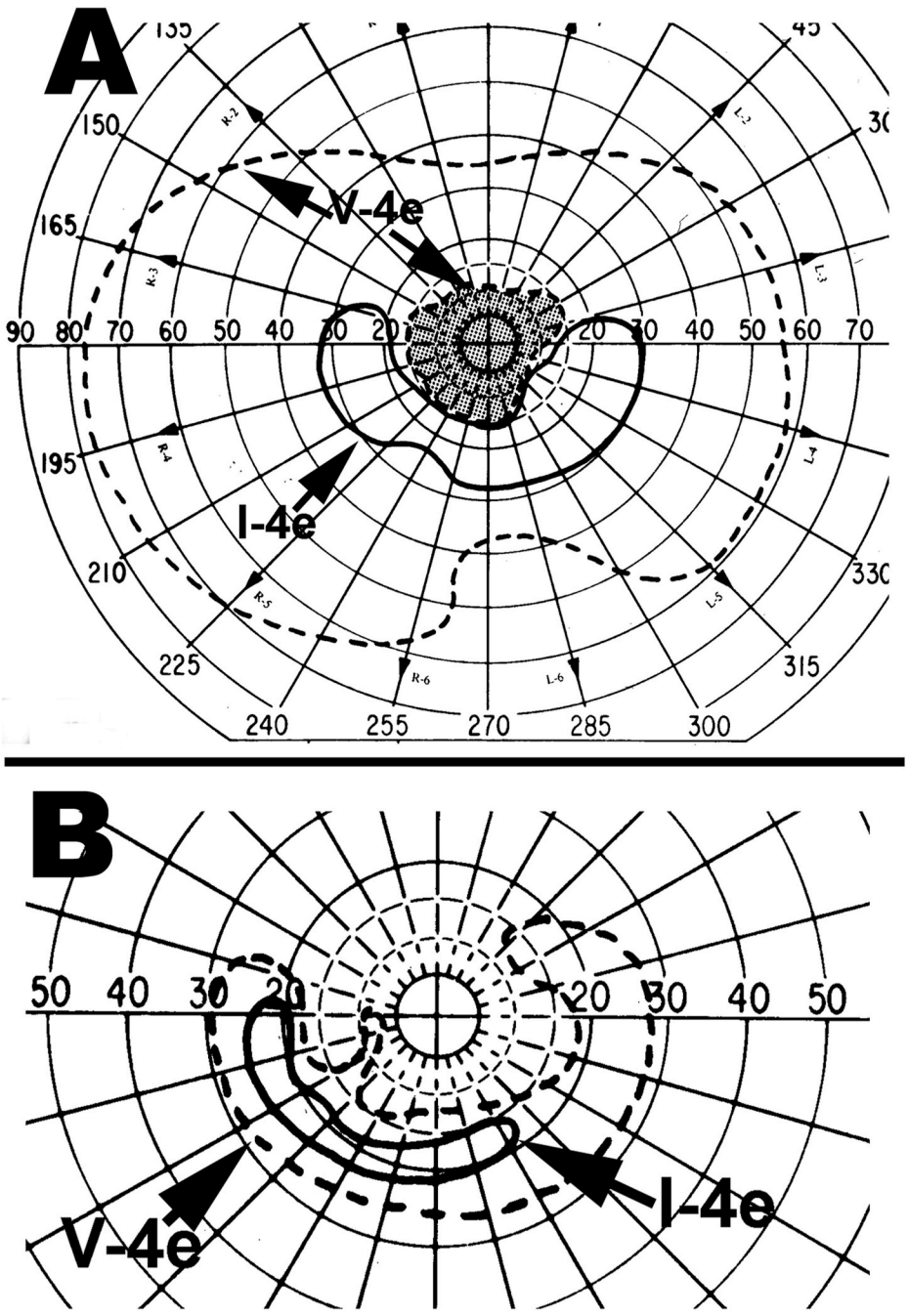


**Fig. 6.** Visual fields of left eye of a 60-year-old man with ischemic CRVO. **(A)** Before PRP, and shows almost normal peripheral fields with V4e, with a central scotoma and an inferior island field with I4e. The eye had 2203 argon laser burns, starting 71 days after onset of ischemic CRVO. **(B)** 27 days after PRP, and shows the visual field is reduced to only a tiny crescentic island with both V4e and I4e. The eye had iris and angle NV at the time of PRP and it resolved 8 months later.

its conclusions become a weighty verdict. It is considered a gold standard for PRP in ischemic CRVO.

With regard to the issue of reported PRP preventing development of NVG in ischemic CRVO, there are some serious concerns regarding the validity of the findings in this study.

I (Hayreh 1996) have discussed at length my concerns about the study; they include the following.

The most important feature of any study is its design; that can determine its conclusions and their validity. Based on my clinical and experimental study on CRVO, I have some important concerns about the baseline design of the study (Baseline and early natural history report 1993). It is now well accepted that NVG is a complication only of ischemic CRVO and is not seen in nonischemic CRVO. For a study claiming beneficial effects of PRP on anterior segment NV in ischemic CRVO, it is imperative to ask at least the following three basic questions.

*7.2.3.1. Did all the patients in the study have ischemic CRVO?.* Since ocular NV is a complication of ischemic CRVO, and not of nonischemic CRVO, the first logical step in conducting such a study is to differentiate ischemic from nonischemic CRVO accurately. For this, one has to evaluate the baseline design and data of this multicenter CVOS (Baseline and early natural history report, 1993). The design used in the study to differentiate the two types of CRVO at the baseline entry level had serious problems for the following reason.

A. They used a "*10 disc area of retinal capillary nonperfusion*" on fluorescein angiography as almost the sole criterion for differentiation

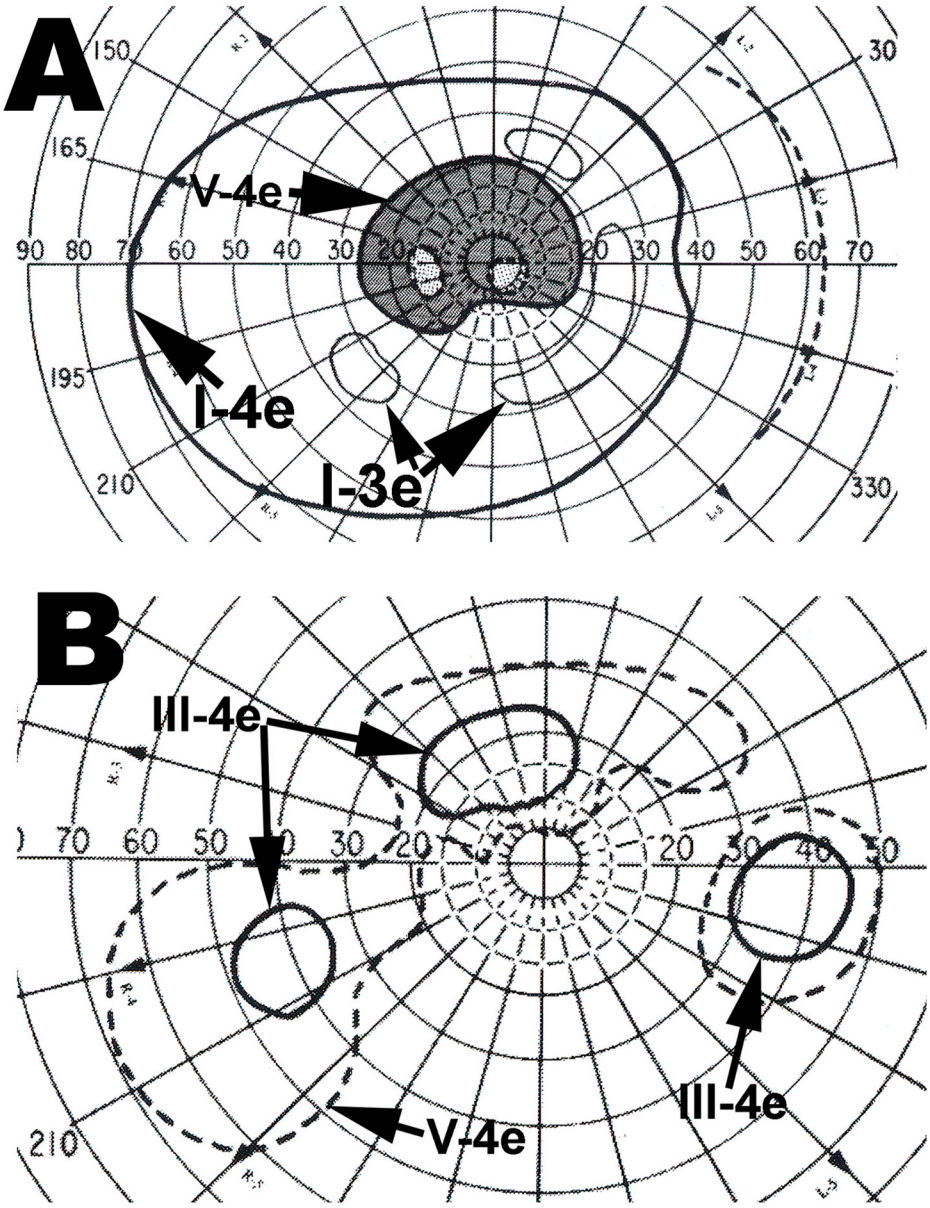


**Fig. 7.** Visual fields of left eye of a 63-year-old man with ischemic CRVO. **(A)** Before PRP, and shows normal peripheral field with a large central scotoma. The eye had 1754 argon laser burns, starting 81 days after onset of ischemic CRVO. **(B)** Six months after PRP, and shows a few island fields only, with marked deterioration and constriction. This eye developed iris NV 2 months after PRP, which lasted for almost 4½ years.

between ischemic and nonischemic CRVO. As discussed above, there are many pitfalls in using this criterion. All the available evidence indicates that anterior segment NV in ischemic CRVO depends on the global retinal ischemia - the more marked the retinal ischemia, the earlier and more frequent is the ocular NV (Hayreh and Zimmerman 2012b). The CVOS (Central Vein Occlusion Study Group 1995), like our study (Hayreh et al., 1990b), also showed that iris or angle NV correlated with the amount of nonperfused retina ($P = 0.0001$). The findings in the CVOS study itself proved that their criterion of a "*10-disc diameter area of retinal capillary nonperfusion*" was ineffective in differentiating the two types of CRVO; this is because they found that eyes with less than 30 disc diameters of nonperfusion and no other risk factors are at low risk for iris or angle NV, "whereas eyes with 75 disc diameters or more (i.e., eyes that show virtually no intact capillaries in the posterior pole) are at highest risk." This has also been demonstrated by my studies (Hayreh and Zimmerman 2012b). Also, "eight standard views" by 30° fundus photography (utilized in a proportion of their cases) do not usually outline the peripheral retinal vascular bed satisfactorily, and therefore do not reveal the changes in the entire peripheral part of the retinal vascular bed (Fig. 8B), which is frequently the first area to develop capillary nonperfusion (Hayreh 1998). Moreover, as discussed above, the "10 disc area of retinal capillary nonperfusion" may simply represent the focal retinal ischemia seen in some nonischemic CRVO.

In contrast to the criterion of "*10 disc area of retinal capillary non perfusion*" as the differentiating measure, our study (Hayreh et al., 1990b) showed that, during the acute phase, the information provided by four visual function tests (i.e., visual acuity, kinetic perimetry, RAPD, and ERG – see Table 1), taken together, is far superior, not only in separating the ischemic from nonischemic CRVO more effectively and reliably than fluorescein angiography alone, but also in giving good information about the extent of global retinal ischemia. Our study (Hayreh et al., 1990b), using all these visual function tests in addition to ophthalmoscopy and wide-angle fluorescein fundus angiography (Fig. 8B), proved that fluorescein angiography is a weak staff to lean on in making such a differentiation *during the early acute phase* of CRVO; angiography at this stage may provide no information or misleading information on retinal capillary nonperfusion in at

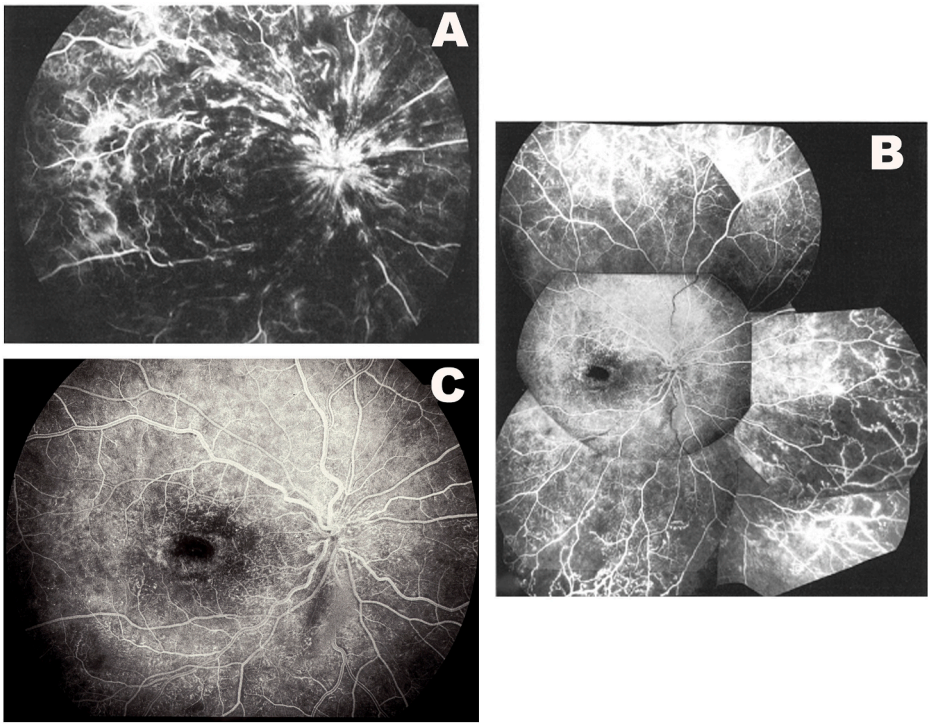


**Fig. 8.** Fluorescein fundus angiograms are of right eye of a 26-year old woman with ischemic CRVO, with a $60^0$ camera. **(A)** Angiogram 2 weeks after onset, gives no worthwhile information about retinal capillary perfusion because of extensive retinal hemorrhages. **(B,C)** Angiograms 20 months after onset: **(B)** A composite angiogram, showing extensive peripheral capillary nonperfusion with a spot of retinal NV on the nasal side. **(C)** A magnified view of the posterior pole (with $60^0$ view) showing no appreciable retinal capillary nonperfusion.

least one third of patients, for a variety of reasons (Hayreh et al., 1990b). As is evident from the above discussion, this was also proved by the CVOS.

B. Other evidence in the CVOS baseline data (Baseline and early natural history report, 1993) suggest that to begin with some of their eyes classified as nonischemic CRVO probably had ischemic CRVO and vice versa. For example,

(i) In the CVOS baseline information, 21% of the eyes classified as having ischemic CRVO had a visual acuity of 20/20 to 20/100; in our study we found that in only 1% of eyes with ischemic CRV0 (Hayreh et al., 2011a).

(ii) In their eyes where PRP was not performed until they developed iris or angle NV, the NV developed in 35% of eyes overall, during the study period (Central Vein Occlusion Study Group 1995). I investigated the same in our natural history study (Hayreh and Zimmerman 2012b) on ocular NV in ischemic CRVO, and found that 52% of ischemic CRVO eyes develop iris NV (see Fig. 1). This, again, suggests that some of the 91 eyes in the CVOS group did not have ischemic CRVO.

(iii) In the CVOS baseline data (Baseline and early natural history report, 1993), at 4-month follow-up at least 16% of the non-ischemic CRVO eyes "developed evidence of ischemia" (i.e., converted to ischemic CRV0). In our study (Hayreh et al., 1994) of 500 eyes with nonischemic CRVO studied prospectively, we found the cumulative chance of conversion to be only 8%–9% at 6 months after onset. This suggests again, that some of their "nonischemic CRVO" eyes probably originally had ischemic CRVO. As discussed previously, this misinterpretation may have been caused by a fluorescein angiographic artifact, because during the very early stages of ischemic CRVO, despite retinal ischemia, angiography may show minimal retinal capillary nonperfusion (Fig. 9A and B); we have found that the extent and severity of retinal capillary nonperfusion in ischemic CRVO tends to increase with time (Hayreh et al., 1990b; Hayreh and Zimmerman 2012b).

Thus, it is evident that the criterion of a "*10 disc area of retinal capillary obliteration*" is a poor and unreliable parameter for

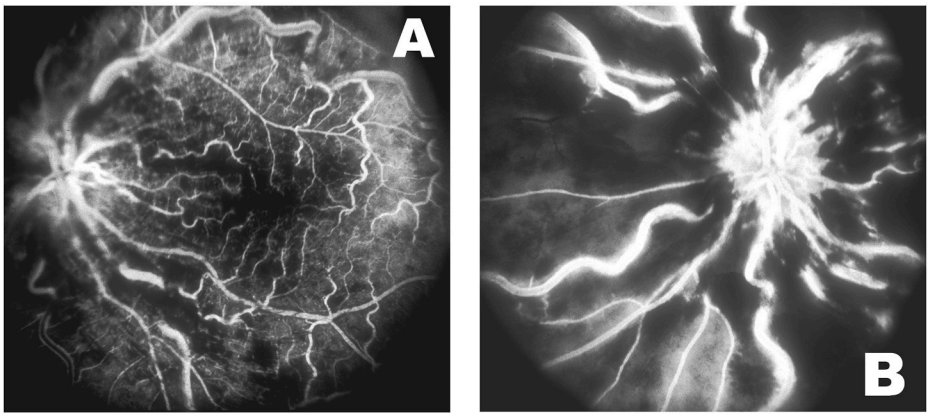


**Fig. 9.** Fluorescein fundus angiograms of left eye of a 55-year old man with ischemic CRVO. **(A)** At the initial visit, showed mostly intact retinal capillaries. **(B)** Shows extensive retinal capillary obliteration when seen 2¼ months later.

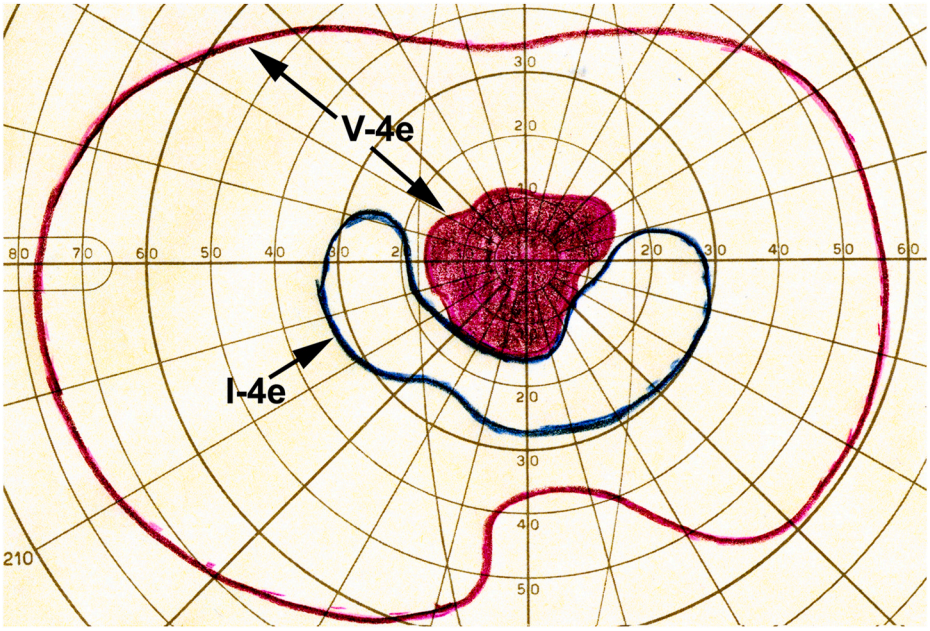


**Fig. 10.** Visual fields of left eye of a 60-year-old man with ischemic CRVO. It shows almost normal peripheral fields with V4e, with a large absolute central scotoma, and an inferior island field with I4e.

differentiating ischemic from nonischemic CRVO, as well as for predicting ocular NV. In the CVOS, this resulted in an inaccurate differentiation between ischemic and nonischemic CRVO in some cases. Thus, their baseline data (Baseline and early natural history report, 1993) suggest that they had a mixture of the two types of CRVO in both their categories - such a mixture has the potential for giving misleading information.

*7.2.3.2. Are the results of PRP therapy better than the natural history of anterior segment NV in untreated ischemic CRVO?*. In judging the outcome of any therapy, the first and most important aspect is to know the natural history of the disease. The authors of the CVOS (Central Vein Occlusion Study Group 1995) assumed that any ischemic CRVO eye with 2-o'clock of iris or angle NV is certain to develop NVG and therefore deserves prompt mandatory PRP. But this is a false assumption; it ignores the natural history of iris and angle NV. We studied that natural history in our prospective study (Hayreh and Zimmerman 2012b) on ocular NV in ischemic CRV0. The findings of that study are shown in Fig. 1. That shows that about one third of the eyes with iris NV and about one quarter with iris or angle NV never developed NVG on follow-up. Our criterion of NVG was persistent elevated IOP greater than 21 mm Hg. Iris NV may be worrisome and an indication for closer observation, but I have followed some ischemic CRVO eyes with iris or angle NV closely for years, not all of them progress to develop NVG; the iris and angle NV resolved spontaneously as the retinopathy resolved. The primary objective of PRP is to prevent development of NVG. In my experience, iris or angle NV on their own has no long-term deleterious complications - it is only if such an eye develops NVG that the eye suffers damage. Therefore, only an eye that shows signs of development of NVG on follow-up needs treatment. Much more importantly, by treating all patients with iris NV, and not randomizing them to "treatment" or "no treatment," the CVOS put a serious cloud over its use of iris NV as an outcome measure for the development of NVG, because, as discussed above, about one third of the eyes treated with PRP would never have developed NVG anyway (see Fig. 1), and were thereby subjected unnecessarily to the serious risk of developing marked and crippling peripheral visual field loss (Figs. 2–7) (Hayreh et al., 1990a). In our study on argon laser PRP in ischemic CRV0, although eyes with PRP showed a significantly ($P = 0.04$) less prevalent iris NV than the control group, there was no statistically significant difference between the two groups in angle NV and NVG.

Some may misunderstand my above NV comments about management of ischemic CRVO. The CVOS recommendation of "prompt PRP of eyes in which 2-o'clock iris/angle NV develops" to prevent "progression of iris or angle NV to NVG" has led to a widespread general belief that every eye with iris/angle NV develops NVG. My above comments simply show that belief is not valid. Our study showed that not every eye with ischemic CRVO, even if it develops iris/angle NV, develops NVG. That does not imply that ischemic CRVO does not require treatment even if it develops NVG. However, if an eye shows signs of development of NVG, then, of course, it should be treated appropriately to avoid subsequent devastating complications of NVG (see below the section "My Management Regimen for NVG in Ischemic CRVO").

*7.2.3.3. What are the side effects and complications of the laser therapy?*. Most importantly, no consideration was given in the CVOS design to obtaining information on the effect of PRP on peripheral visual fields in ischemic CRVO – that is where PRP is done. These eyes almost always have a large permanent central scotoma (Fig. 10) due to ischemic damage to the macular ganglion cells, resulting in poor central visual acuity. Like our study (Hayreh et al., 1990a), the CVOS (Central Vein Occlusion Study Group 1995) also showed no beneficial effect from PRP on visual acuity. Despite a large central scotoma, these eyes usually retain good "getting around" peripheral vision (Fig. 10), because their peripheral fields are preserved (similar to age-related macular degeneration), if the eye does not develop uncontrolled NVG (see Fig. 1). We (Hayreh et al., 1990a) found a statistically significant ($P \leq 0.03$) worsening of peripheral visual fields, with marked loss in eyes treated with PRP as compared with those in the control no laser group (Figs. 2–7). *In ischemic CRVO, normally there is a large central scotoma and almost always normal peripheral visual fields, as shown clearly by* Figs. 2A–7A and 10 *of our study* (Hayreh et al., 1990a). *This fact has important implication in the management of ischemic CRVO.* I have found almost a universally prevalent misconception among ophthalmologists that in ischemic CRVO there is a generalized loss of vision, including of peripheral vision.

There is a prevalent misconception that peripheral retinal capillary nonperfusion results in loss of function in that area. However, in my

studies in CRVO and BRVO over the years, I have found that, in spite of the loss of retinal capillaries in the peripheral retina, generally the peripheral visual fields are normal, indicating there is no loss of visual function. This is very well demonstrated by the intact peripheral visual field in pre-PRP ischemic CRVO in Figs. 2–7 and 10. This is because peripheral thin retina is still supplied by the choroidal circulation underneath. This misconception is created by the use of automated perimetry, which does not provide any information about the visual fields outside the central $30^0$, while Goldman perimetry provides information all the way to the periphery.

Following PRP, the large central scotoma combined with a severe loss of peripheral visual fields may virtually blind the eye (Figs. 2B–7B). Should we destroy most of an eye's remaining useful peripheral vision with PRP unless we are quite certain that, without treatment, every eye with iris and angle NV is destined for painful death? This study does not provide justification for that.

A study with such flaws in its basic design has the potential to provide serious misinformation that may retard rather than advance knowledge with regard to the role of PRP in ischemic CRVO. Although our study (Hayreh et al., 1990a) and that reported by CVOS (Central Vein Occlusion Study Group 1995) both deal with the role of argon laser PRP in ischemic CRVO, their results are very different because of the difference in the basic designs of the two studies.

As is customary, these concerns of mine were sent to the CVOS group for their comments. In their response (Clarkson et al., 1996), they made the following comments.

"Dr. Hayreh raises a number of excellent points, based on his extensive research and clinical studies over the past decades ..... We agree with Dr. Hayreh that our minimum criteria of 10 disc areas of retinal capillary nonperfusion for defining ischemic vein occlusion is a low risk for development of iris neovascularization (INV).... We also agree with Dr. Hayreh that when there is too much intraretinal hemorrhage to evaluate perfusion on the fluorescein angiogram, such eyes are likely to be nonperfused (ischemic CRVO).... ... We agree that INV never develops in many eyes with ischemic vein occlusion..... Dr. Hayreh is correct that we were not willing to follow the natural history of eyes in which INV was developing because of our fear that NVG would develop quickly; consequently, we do not have information about the natural history after INV develops in untreated eyes."

This discussion reveals that the CVOS study had serious flaws, which invalidate its conclusions. It is unfortunate that in spite of the fact that CVOS was a flawed study, it is still regarded by ophthalmologists as the gold standard for PRP in ishemic CRVO.

## 8. NVG in ischemic CRVO

NVG is the most dreaded, intractable and blinding complication of ischemic CRVO. I have discussed at length elsewhere its causes, pathogenesis, pathology, methods of early diagnosis and logical management (Hayreh 2007). There is a common notion among ophthalmologists that every eye with CRVO is at risk of developing NVG; that is not true at all. In general, the development of NVG in RVO depends upon the severity and extent (area) of retinal ischemia (Hayreh et al., 1983). NVG is a complication only of ischemic CRVO and not of nonischemic CRVO (Hayreh et al., 1983; Hayreh and Zimmerman 2012b.). As hemi-CRVO typically involves one hemisphere of the eye, the risk of developing NVG due to insufficient stimulus in ischemic hemi-CRVO is very low. Since 1996, several studies have implicated vascular endothelial growth factor (VEGF) as an important and the predominant factor in the pathogenesis of intraocular NV and NVG (Tolentino et al., 1996). In ischemic CRVO, there is persistent secretion of VEGF from ischemic retina into the vitreous cavity, and our study found a correlation between retinal vascular leakage and the development of ocular NV (Virdi and Hayreh 1982).

In NVG, iris and angle NV almost invariably develops before the intraocular pressure (IOP) rises. This is associated with the development of a fibrovascular membrane on the anterior surface of the iris and iridocorneal angle of the anterior chamber. Membrane development is followed by development of progressive anterior synechiae, angle closure, and precipitous rise of IOP, which may be of fairly acute onset.

Management of NVG is highly challenging, unpredictable, difficult and controversial. It involves several considerations, including the following: Most importantly, it is essential to have a high index of suspicion of its development in ischemic CRVO, which can lead to early diagnosis and treatment to prevent irreversible visual loss. Once NVG develops and the IOP is high, the major aspect of management is control of high IOP, which is almost invariably the main factor in irreversible and massive visual loss, rather than the original disease, which induced NVG.

Management of the high IOP in NVG includes medical therapies and surgical methods to lower and control high IOP in eyes with NVG; these include: anti-VEGF therapy, corticosteroid therapy, cycloablation, cyclophotocoagulation, filtering surgery, glaucoma drainage devices, and photodynamic therapy. If all fails and the eye is painful and blind, to make the eye feel comfortable, it is advisable to try first topical corticosteroids, cycloplegics, cyclodestruction and even alcohol injection. If all else fails, as a last resort one may have to consider enucleation. My policy is to try to avoid doing enucleation as far as possible, because even a blind eye is less bothersome in the long run (if cosmetically acceptable) than to maintain an artificial eye and socket. Some ophthalmologists advocate doing evisceration of such eyes.

### 8.1. Primary factor responsible for blindness in ischemic CRVO with NVG

As mentioned above, the most important consideration in the management of NVG in ischemic CRVO is high IOP, because it is the primary factor to cause marked loss of vision or even blindness in the vast majority of the NVG eyes, by producing glaucomatous optic neuropathy and anterior segment changes, and not the ischemic CRVO *per se*. Therefore, if NVG develops (the maximum risk of that is 39% - see Fig. 1), but the IOP is controlled satisfactorily by the various means available, the eye will maintain reasonably good peripheral visual fields and vision (Fig. 10) once the retinopathy burns itself out in due course. As the retinopathy regresses, the stimulus for NV diminishes, resulting in slow spontaneous regression of NV – *a fact widely ignored. The persistence of peripheral visual fields is functionally very useful for the patient's mobility and independence, in spite of poor visual acuity* (Fig. 10). By contrast, if every eye with ischemic CRVO is treated with PRP, the marked constriction and loss of the peripheral visual field (Figs. 2B–7B) caused by it, combined with the invariably pre-existing large, absolute central scotoma (Fig. 10), makes the eye almost blind. This is particularly unnecessary in the 61% of ischemic CRVO eyes which would never have developed NVG in the first place (see Fig. 1), and thus did not need PRP. Therefore, overall, PRP does more harm than good (Figs. 2–7), especially as it neither confers a statistically significant protection against NVG, nor always prevents development of ocular NV, nor offers any other significant benefit.

### 8.2. My Management Regimen for NVG in ischemic CRVO

As discussed above, NVG is a devastating, blinding complication of ischemic CRVO. From the above discussion, the question naturally arises: if I do not find any of the advocated treatments beneficial in ischemic CRVO, how do I manage my patients with NVG in ischemic CRVO? For a logical management of any disease, one has first to understand the basic issue involved and the available information which should act as guidelines. In ischemic CRVO, to reiterate what has been said above, we currently have the following definite information:

1. A maximum of 39% of ischemic CRVO patients are likely to develop NVG (contradicting the prevalent impression among

ophthalmologists that a vast majority of these eyes develop NVG); 61% are never going to develop it (Fig. 1) (Hayreh and Zimmerman 2012b).
2. Maximum risk of developing NVG is mainly during the first 7–8 months of the disease in about 35% (see Fig. 1). After that the risk falls dramatically, as is evident from Fig. 1. So the crucial period to monitor these patients closely is the first 7–8 months (Hayreh and Zimmerman 2012b).
3. The multicenter CRVO photocoagulation study showed that prophylactic PRP in ischemic CRVO does not prevent iris and angle NV (Central Vein Occlusion Study Group, 1995)
4. Our PRP study showed that eyes subjected to PRP usually suffer marked loss of peripheral visual fields (Figs. 2B–7B) (Hayreh et al., 1990a). Combined with the large pre-existing absolute central scotoma in these eyes, that peripheral visual field loss makes these eyes almost blind.
5. There is no convincing scientific evidence that PRP usually helps prevent development of NVG in ischemic CRVO, in spite of claims made to that effect (Central Vein Occlusion Study Group, 1995)
6. Most importantly, *the retinopathy runs a self-limited course*, and after a variable length of time it usually burns itself out and resolves spontaneously, with permanent residual retinal damage. Once that happens, the stimulus for NV disappears and consequently the anterior segment NV spontaneously starts to regress - a fact usually not appreciated in the management of these eyes. An understanding of this important fact must change our approach to the management of ischemic CRVO and associated anterior segment NV. We need to "baby-sit" these eyes during that period when they are at maximum risk of developing NVG, i.e. the first 7–8 months (Fig. 1). From my personal experience, I can safely say that "baby sitting" is generally not a pleasant experience for either the ophthalmologist or the anxious patient, but it is beneficial and vital in the long run.

In the light of these facts, one may follow the following regimen of management of these patients:

(a). I follow patients with ischemic CRVO every 2–3 weeks in my clinic for the first 7–8 months, to look for any evidence of anterior segment NV and rise of IOP as well as doing gonioscopy for angle NV. Every 2 months or so, I do a complete ophthalmic evaluation and visual field plotting with Goldman perimeter.

(b). If an eye develops moderate to marked anterior segment NV, I start topical steroid therapy, because there is evidence that steroid therapy inhibits angiogenesis and NV. (Warning: Topical steroids in steroid responders may cause the IOP to go high and that may be misdiagnosed as NVG.).

(c). If the IOP goes above 21 mmHg, I start topical ocular hypotensive therapy to lower the IOP. If need be, I may add oral carbonic anhydrase inhibitors also. Most of the time, this medical treatment regimen is enough to keep the IOP under satisfactory control.

(d). If the IOP goes very high and is not controlled by above medical regimen, then I do graduated cycloablation (by cyclocryotherapy or cyclo-photocoagulation with diode laser). When doing cyclocryotherapy, we first do that to one quadrant of the ciliary body, and if after a week the IOP is still high, then we do the same to the adjacent $90^0$, i.e. a total of $180^0$. In my experience this, combined with medical therapy, can control the IOP in the majority of eyes. Some require repeated cycloablation to keep the IOP under control. The universal impression that cycloablation invariably results in phthisis bulbi is based on aggressive $360^0$ application at one sitting. My study showed that a graduated cycloablation over a period of time, titrated according to the IOP, is generally not associated with phthisis bulbi. There are some cases where we have done a glaucoma tube shunt implant to manage elevated IOP in eyes with closed angle and very minimal or no NV.

With this treatment regimen, I have been able to tide many of these eyes over the first 7–8 months, or until the retinopathy starts to resolve and the stimulus for anterior segment NV to subside. After that these eyes start to settle down. So long as the IOP is maintained within reasonable limits by surgery or implantation of valve, the eyes maintain the residual peripheral vision. However, a few eyes very rapidly go into fulminant NVG and no amount of any treatment can control the IOP. In our PRP study (Hayreh et al., 1990a) I saw some eyes develop fulminant NVG in spite of early and extensive PRP of up to about 3,500 burns; they finally became totally blind and even developed phthisis bulbi.

(e). If the eyes do not develop NVG during the first 7–8 months, their risk thereafter is minimal (Fig. 1). Therefore, I follow them then every 3 months or so, depending upon the state of the eye. I have found that some of these eyes that do not develop NVG may develop disc or retinal NV at a much later stage (Fig. 1). If that happens, then I do advocate PRP, since by that time the retinal edema and hemorrhages are much less or even absent, and consequently PRP is not so destructive to the peripheral visual fields as during the early stages when there are extensive retinal hemorrhages and marked retinal edema – that is like burning a wet filter paper with laser.

## 9. Conclusion on role of PRP in ischemic CRVO

As is evident from the above discussion, there is no scientifically valid proof so far that PRP itself is safe and effective in the prevention or management of NVG in ischemic CRVO. In spite of that and ignoring the fact that PRP is highly destructive to the remaining peripheral visual fields in most of the ischemic CRVO cases, it is unfortunate that there are ophthalmologists who still advocate its use. Even worse, some non-ischemic CRVO eyes still get PRP.

## 10. Photocoagulation in ischemic hemi-CRVO

As discussed above, ocular NV occurs only in ischemic hemi-CRVO. Unfortunately, BRVO and hemi-CRVO have been combined in all the reported studies.

## 11. Photocoagulation in BRVO

Since 1968, a large number of publications have assessed the role of photocoagulation in the management of the two complications of BRVO: (1) macular and (2) ocular NV. Initially the xenon arc photocoagulator was used, but that was later replaced by a variety of lasers - argon, krypton red, diode and pulsed Nd:YAG. Most of the studies deal with the argon laser.

### *11.1. Grid pattern laser treatment for macular edema*

In 1984 the Branch Vein Occlusion Study (Branch Vein Occlusion Study Group, 1984) reported a multicenter, randomized, controlled clinical trial in 139 BRVO eyes (71 treated and 68 control), on the role of argon laser grid photocoagulation in macular edema secondary to BRVO, with photocoagulation over the area of capillary leakage seen on fluorescein angiography, to determine "Is argon laser photocoagulation useful in improving visual acuity in eyes with branch vein occlusion and macular edema reducing vision to 20/40 or worse?" Eyes were followed for a mean period of 3.1 years. In that study, a comparison of treated eyes with controls showed that the gain of at least two lines of visual acuity from baseline maintained for two consecutive visits was 65% in the treated group versus 37% in the control group - significantly ($P = 0.00049$) greater in treated eyes. Because of this improvement in visual acuity with argon laser photocoagulation of macular edema from BRVO, the authors recommended "laser photocoagulation for patients with macular edema associated with branch vein occlusion who meet the

eligibility criteria of their study". Visual acuity improvement in them is due to improvement of macular edema.

After that, several studies were published on this method of treatment of macular edema in BRVO, so that it became "standard care" for it; so much so that the various studies by the "SCORE" (standard care vs corticosteroid) Study Research Group for evaluation of intravitreal corticosteroid therapy used grid photocoagulation in macular edema as the control.

To put the above study findings in proper perspective, as discussed above, a prospective natural history study (Hayreh and Zimmerman 2015b) of 144 major BRVO eyes showed that macular edema spontaneously resolved in 33% within 12 months from onset, in 43% within 18 months, and in 51% within 24 months. As discussed above, the natural history of visual outcome in 216 BRVO (Hayreh and Zimmerman 2014) eyes with initial visual acuity of 20/60 or better was, that visual acuity improved or remained stable in 75% for major BRVO and in 86% for macular BRVO, compared with 65% in the treated group in the Branch Vein Occlusion Study (Branch Vein Occlusion Study Group, 1984). Parodi et al., (1999) in a study of 99 patients with macular BRVO, reported that grid laser treatment is not able to reduce the macular edema more than the natural evolution, and does not improve visual acuity.

With the advent of intravitreal anti-VEGF and intravitreal corticosteroid therapies for macular edema, the role of grid photocoagulation has faded markedly. The SCORE study (Scott et al., 2009) compared the effect of intravitreal triamcinolone with grid photocoagulation in BRVO eyes with macular edema and found that there was no difference in visual acuity between the two at 12 months; in view of the rates of adverse events of intravitreal triamcinolone (particularly elevated intraocular pressure and cataract), they recommended grid photocoagulation. However, grid photocoagulation for macular edema has its own complications, as discussed below.

I have found an unusual phenomenon in BRVO eyes treated with grid photocoagulation for macular edema. In spite of documented visual improvement following that procedure in clinical trials, the patients did not feel comfortable with the quality of vision in that eye. For example, if the fellow eye had slightly worse vision than the eye treated with grid photocoagulation, given a choice they preferred to use the fellow eye instead of the treated eye. This is because grid photocoagulation produced multiple microscotomas, giving the effect of looking through a pinhole disc – a phenomenon never described before.

### *11.2. Photocoagulation for ocular neovascularization in BRVO*

#### *11.2.1. First photocoagulation study*

In I986, the Branch Vein Occlusion Study (Branch Vein Occlusion Study Group, 1986), an argon laser multicenter, randomized, controlled clinical trial, reported its findings. This report addressed two questions: (1) "Can peripheral scatter argon laser photocoagulation prevent the development of neovascularization?", and (2) "Can peripheral scatter argon laser photocoagulation prevent vitreous hemorrhage?"

To answer the first question, 319 eyes were assigned randomly to either a treated or an untreated control groups. Comparing treated patients with control patients (average follow-up time, 3.7 years), the development of NV was significantly less in treated eyes ($P = 0.009$). To answer the second question, 82 eyes were assigned randomly to either a treated or untreated control group. Comparing treated patients with control patients (average follow-up time, 2.8 years), the development of vitreous hemorrhage was significantly less in treated eyes ($P = 0.005$). Although this study was not designed to determine whether peripheral scatter treatment should be applied before rather than after the development of NV, the data accumulated in this study suggested that peripheral scatter treatment should be applied after the development of NV rather than before. Because the occurrence of vitreous hemorrhage was lessened by peripheral scatter argon laser photocoagulation, the study recommended it for patients with BRVO who have developed NV and who meet the eligibility criteria of this study.

#### *11.2.2. Second photocoagulation study*

In 1993 we reported the results of our prospective and randomized study (Hayreh et al., 1993) dealing with argon laser scatter photocoagulation in the treatment of BRVO. The study was done in 271 eyes allocated to either treated (61 eyes) or untreated (210 eyes) groups. In this study, scatter argon laser photocoagulation was applied only to the involved sector in major BRVO and ischemic hemi-CRVO, unlike peripheral scatter argon laser photocoagulation in the Branch Vein Occlusion Study. Our study had the following objectives: does scatter argon laser photocoagulation to the involved sector in major BRVO and ischemic hemi-CRVO: (1) prevent development of retinal and/or optic disc NV and vitreous hemorrhage? (2) affects visual acuity, visual fields and macular retinal lesions?

After an average follow-up of 3.6 years, the study showed the following treatment results:

(1) It significantly reduced the risk of development of retinal NV and vitreous hemorrhage.
(2) In eyes with retinal and/or optic disc NV, the laser treatment significantly reduced the risk of vitreous hemorrhage as compared to the untreated eyes.
(3) It did not affect the visual acuity and macular retinal lesions.
(4) But it produced a significant worsening in the peripheral visual fields compared to the untreated eyes (Fig. 11).
(5) The way the laser treatment was given did not affect the macular microcystic edema, cystoid degeneration, scarring or retinal detachment.
(6) After adjusting for the severity of retinopathy and sector involvement, there was no statistically significant difference in the development of NV, vitreous hemorrhage or any other outcome, between eyes with ischemic hemi-CRVO and major BRVO.

In view of our findings, we recommended that argon laser photocoagulation treatment should be given only when NV is seen and not otherwise, because in the latter case, its detrimental effects may outweigh its beneficial ones. Thus, the findings of our study confirmed those of the Branch Vein Occlusion Study (Branch Vein Occlusion Study Group, 1986) that *photocoagulation treatment should be given only when NV is present*. However, our study (Hayreh et al., 1993) differed from the Branch Vein Occlusion Study (Branch Vein Occlusion Study Group, 1986) in that the latter study did not investigate the serious deleterious effect of photocoagulation on the visual field. Since in BRVO involvement of the superior retina is common, consequently the loss of the lower part of the visual field can produce marked disability and a significant worsening of visual fields with photocoagulation becomes a very important, clinically relevant finding. The prevalent practice of treating every BRVO patient with peripheral scatter laser photocoagulation is not justified in view of the high probability of visual field loss after treatment, when the risk of developing vitreous hemorrhage is only 14% (Hayreh et al., 1993). There was no significant difference in the number of laser burns between those eyes which developed NV and those eyes which did not. As discussed above, our prospective study (Hayreh and Zimmerman 2015b) in 214 consecutive eyes with BRVO showed that retinal NV developed in 9% within 12 months from onset, and in 15% within 36 months from onset; and optic disc NV in 8.3% within 12 months from onset and in 10.4% within 30 months from onset. Thus, these studies showed that only a small proportion of eyes with BRVO develop retinal or optic disc NV. On a risk/benefit ratio, if all these eyes are treated with photocoagulation, the majority of them would be treated unnecessarily and exposed to the unwarranted risk of visual field loss. Peripheral scatter laser therapy should therefore be done only if there is NV, to balance the beneficial effect of therapy in preventing vitreous hemorrhage against its detrimental effect on the visual fields.

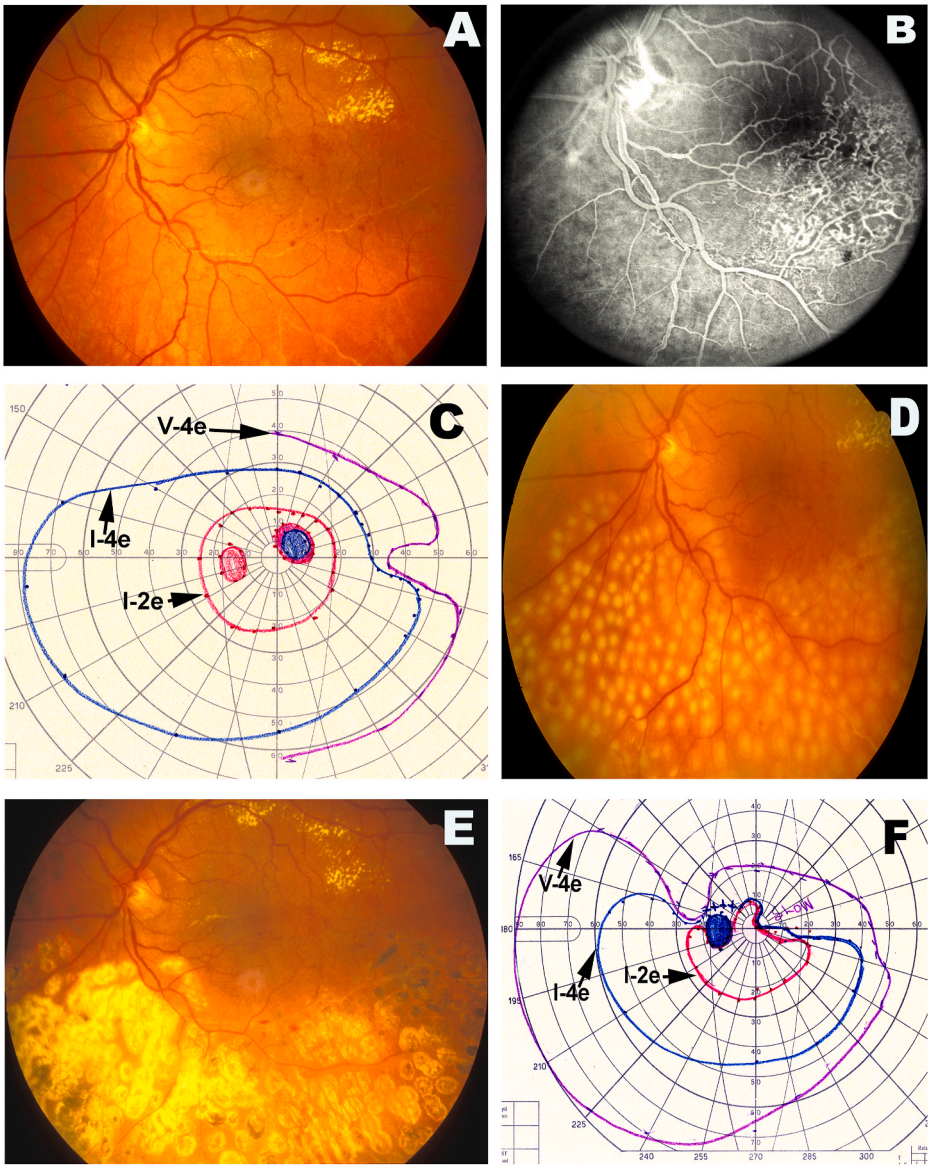


**Fig. 11.** Fundus photographs (**A,C,D**), fluorescein fundus angiogram (**B**), and visual field defects (**E,F**) of a 57-year old woman with left inferior temporal BRVO 5 years after the initial visit. At this visit, the eye had visual acuity of 20/50 and visual field shown in (**E**). The eye later on developed optic disc and retinal NV and had argon laser photocoagulation to the involved region.(**A**). Fundus photograph shows a few retinal hemorrhages, mild macular edema, sheathed involved retinal veins, retinal venous collaterals and lipid deposits in superior uninvolved macular retina.(**B**) Fluorescein fundus angiogram shows marked intraretinal microvascular abnormalities in the involved retina with focal retinal capillary obliteration. There was also extensive peripheral retinal capillary obliteration. There is optic disc and retinal NV. (**C**) Visual field with a Goldmann perimeter shortly before photocoagulation shows a nasal paracentral scotoma, a small temporal step and mild constriction of superior field. (**D**) Fundus photograph soon after the initial scattered argon laser photocoagulation; photocoagulation spared the macular region. There are lipid deposits in superior temporal region. (**E**) Fundus photograph 6 months after (**D**) shows extensive photocoagulation scars, a few punctate retinal hemorrhages, and lipid deposits in superior temporal region. (**F**) Visual field with a Goldmann perimeter 2 months after photocoagulation shows extensive visual field loss in the superior temporal region (compare the visual field before and after photocoagulation).

### *11.3. Photocoagulation by other than argon laser in BRVO*

As is evident from the studies discussed above, conventional suprathreshold retinal photocoagulation is a destructive procedure. To decrease chorioretinal damage, other types of laser photocoagulations have been tried.

#### *11.3.1. Krypton red laser (647 nm) photocoagulation*

Roseman and Olk (1987) used this in 23 eyes with BRVO, particularly in eyes with extensive intraretinal hemorrhage or in the presence of media opacities, such as vitreous hemorrhage or cataract. On a follow-up for 6–38 months, 89% of the 19 eyes treated for macular edema had complete resolution of their edema, one had reduction of its edema, and one was unchanged. All of five eyes treated for NV of the disc or retina had complete elimination of NV. The authors were unable to demonstrate any statistical correlation between final visual acuity and the following factors: duration of symptoms, cystoid macular edema, degree of paramacular nonperfusion, and contiguous intraretinal hemorrhage extending into the foveal avascular zone.

#### *11.3.2. Diode laser*

There are three reports of its use in BRVO. McHugh et al., (1989) reported regression of NV in six of eight eyes (75%) with BRVO. Friberg and Karatza (1997) in 14 BRVO eyes reported resolution of macular edema by 6 months in 92% of eyes, and 77% had stabilization of visual acuity. A study (Parodi et al., 2006) comparing the effectiveness of subthreshold grid laser treatment with an infrared micropulse diode laser with that of threshold grid laser treatment for macular edema secondary to BRVO found that resolution of macular edema and visual acuity improvement are similar to those obtained with conventional threshold grid laser treatment, but subthreshold grid laser treatment with an infrared micropulse diode laser is not associated with biomicroscopic and angiographic signs. Luttrull et al., (2012) also reported resolution of macular edema with this laser treatment.

#### *11.3.3. Pulsed Nd:YAG laser*

There is only one report of its use. Ulbig et al., (1998) retrospectively reviewed 21 eyes with a circumscribed premacular subhyaloid hemorrhage of various causes. These eyes were treated with a pulsed Nd:YAG laser to drain the entrapped blood into the vitreous. However, a macular hole and a retinal detachment were observed as complications.

## 12. Conclusions on photocoagulation

1. PRP in ischemic CRVO or sectoral photocoagulation in BRVO has a role in ocular NV, if there is already NV, and not as a prophylactic measure. The beneficial effect of photocoagulation for preventing vitreous hemorrhage or NVG must be balanced against its detrimental effect on the visual fields.
2. Since the discovery of the beneficial role of intravitreal anti-VEGF and corticosteroid therapies for macular edema in RVO, macular grid photocoagulation is no longer considered the treatment of choice for macular edema in BRVO.
3. My policy has been to discuss with the patient the pros and cons of photocoagulation treatment in RVO, the natural history of visual outcome in RVO, and financial costs of the procedure; and let the patient make his/her own choice, instead of simply prescribing one treatment, giving no other option to the patient.

## 13. Intravitreal anti-VEGF and corticosteroid therapy in RVO

Since the "grid pattern laser treatment for macular edema in BRVO" study (Branch Vein Occlusion Study Group, 1984), discussed above, the advent of intravitreal anti-VEGF and corticosteroid therapies has drastically changed the management of macular edema not only in BRVO but also in CRVO.

Many randomized clinical trials have shown that intravitreal anti-VEGF and corticosteroid therapies help to reduce macular edema in CRVO (SCORE Study Research Group 2009; 2012; 2015; Campochiaro et al., 2010; Pielen et al., 2017; Schmidt-Erfurth et al., 2019) and BRVO (SCORE Study Research Group 2009; 2012; 2015; Campochiaro et al., 2010; Robert et al., 2013; Suñer et al., 2013; Schmidt-Erfurth et al., 2019; Ang et al., 2020; Shalchi et al., 2020), thereby helping to improve visual acuity. While there is no doubt that these therapies improve macular edema, and thus improve visual acuity in the short term, there are important drawbacks in the use of anti-VEGF and corticosteroid therapies: they need frequent reinjections and more frequent control visits, to maintain the beneficial effect till the natural history takes over. Consequently, *it is basically a palliative treatment, and is not a curative treatment*. Furthermore, these therapies do have their own side-effects and complications. Corticosteroids are associated with increased potential ocular side effects (e.g., elevated intraocular pressure, cataracts). Moreover, the durations of the cited clinical trials are much shorter than the natural history of visual outcome in CRVO (Hayreh et al., 2011), hemi-CRVO (Hayreh and Zimmerman, 2012a) and BRVO (Hayreh and Zimmerman, 2014). Hence, these trials do not provide information about their long term beneficial effect on the course of the visual outcomes and the disease. I have found that these limitations and the expense of this therapy are usually not fully explained to patients, or, sometimes, even mentioned.

A meta-analysis (Ang et al., 2020) of 2530 eyes from 48 real-world studies of therapies for macular edema secondary to BRVO concluded that visual and anatomical gains achieved in the real-world for anti-VEGF therapy were not as impressive as claimed by randomized clinical trials, possibly due to reduced injection frequency in practice, and differences in baseline characteristics. There is an urgent need for consensus on the minimum efficacy, treatment burden and expense, and safety to be collected to strengthen the real-world evidence base.

### *13.1. Role of Anti-VEGF therapy in ocular neovascularization in RVO*

As discussed above, ocular NV is a serious complication in ischemic CRVO and BRVO. In the past photocoagulation was the advocated treatment. But with the advent of intravitreal anti-VEGF, it is pertinent to discuss briefly its role in ocular NV in RVO.

Most ocular NV disorders are caused by upregulation of VEGF, which, by linking tissue ischemia to angiogenesis, plays a critical role in the pathogenesis of ocular NV. Thus, disruption of VEGF is the most effective approach in the treatment of ocular NV. There is a huge volume of literature on the subject discussing its various aspects.

NVG is the most dreaded complication of ischemic CRVO. The role of anti-VEGF therapy has been studied by a large number of studies. In ischemic CRVO intravitreal bevacizumab leads to a rapid regression of iris and angle NV (Iliev et al., 2006; Wittström 2012) Despite significant clinical benefit with anti–VEGF therapy, the risk of NV complications was not ameliorated by VEGF blockade, but merely delayed (Brown et al., 2014). Although intravitreal injection of bevacizumab effectively reduces vascular permeability, newly formed vessels are still present in the iris and iridocorneal angle (Ishibashi et al., 2010). Thus, intravitreal anti-VEGF therapy delayed but did not prevent NVG in ischemic CRVO (Rong et al., 2019). Intracameral bevacizumab resulted in a rapid regression of the iris and angle NV, halting the progression of peripheral anterior synechial formation (Duch et al., 2009). A recent Cochrane Database Review analysis revealed that currently available evidence is uncertain regarding the long-term effectiveness of anti-VEGF medications, such as intravitreal ranibizumab or bevacizumab or aflibercept, as an adjunct to conventional treatment in lowering IOP in NVG (Simha et al., 2020).

### *13.2. Role of photocoagulation in combination with intravitreal Anti-VEGF\Corticosteroid in RVO*

It is relevant to discuss briefly the role of photocoagulation in RVO in combination with intravitreous anti-VEGF and corticosteroid therapies in macular edema.

#### *13.2.1. In BRVO*

Several small clinical trials showed that compared with standard grid laser, intravitreal anti-VEGF and corticosteroid therapies had more beneficial effects in visual acuity gain (Avitabile et al., 2005; Russo et al., 2009; Tan et al., 2014; Parodi et al., 2015; Tadayoni et al., 2016; Qian et al., 2017). A study of combined therapy had a substantial effect on reducing recurrent associated macular edema, but the effect on visual acuity was limited (Ogino et al., 2011). A combination therapy of intravitreal Ranibizumab and subthreshold micropulse photocoagulation for macular edema decreased the frequency of intravitreal ranibizumab injections while maintaining good visual acuity (Terashima et al., 2019). Another study showed that the combination of Ozurdex implant and macular grid laser is synergistic in increasing visual acuity and lengthening the time between injections after 4 months of treatment (Pichi et al., 2014).

A Report by the American Academy of Ophthalmology, while discussing therapies for macular edema associated with BRVO, concluded that the "Laser photocoagulation remains a safe and effective therapy, but VA results lag behind the results for anti-VEGF therapies" (Ehlers et al., 2017).

A study (Riese et al., 2008) claimed that macular edema can be effectively treated by a combination of intravitreal triamcinolone and subsequent laser photocoagulation. Another study (Parodi et al., 2008) showed that a combination of intravitreal triamcinolone and infrared micropulse diode treatment of macular edema in BRVO produced a significant visual acuity improvement, when compared with simple grid laser treatment.

#### *13.2.2. In CRVO*

A study (Pikkel et al., 2016) of 65 ischemic CRVO eyes reported that intravitreal injection of bevacizumab, laser photocoagulation, or a combined regimen caused similar benefits. In a study (Wang et al., 2019) of 112 CRVO, 50 cases of BRVO and 37 patients of HCRVO, followed up for 6 months, reported that intravitreal injection of ranibizumab combined with argon laser photocoagulation therapy had better safety and effectiveness in the treatment of different degrees of CRVO.

Thus, we have very limited information about role of photocoagulation in combination with intravitreal anti-VEGF\corticosteroid in

RVO.

## 14. Does photocoagulation still have a role in the management of RVO?

Retinal laser coagulation is still used in many university and other centers around the world in eyes with RVOs. In spite of a recent decrease in the use of photocoagulation for macular edema in RVO, it still pays an important part in ocular NV in RVO. The Canadian Expert Consensus (Berger et al., 2015) suggested that laser remains the therapy of choice when NV is secondary to RVO; adjunctive anti-VEGF therapy could be considered. Also, in eyes with macular edema due to RVO that respond poorly to anti-VEGF therapy or are incapable or reluctant to come for frequent for anti-VEGF injections, grid laser can be used combined with anti-VEGF therapy.

## 15. Conclusions and future directions

Retinal vein occlusion (RVO) is a common visually disabling disease. In spite of extensive studies over the years, yet there are many misconceptions (Hayreh 2005) and controversies about it and its management. Visual deterioration is most commonly due to macular edema and less often due to retinal ischemia. The development of NV, particularly NVG, has hazardous consequences for vision and even the eye itself. For an in-depth understanding of the role of photocoagulation in RVO, it is crucial to have basic scientific understanding of the following relevant issues: classification of RVO, ocular NV in RVO, and the natural histories of macular edema and visual outcome of RVO.

### *15.1. Prospective, randomised clinical trials*

These have been conducted about the role of photocoagulation in CRVO and BRVO (3 in ischemic CRVO and 3 in major BRVO), with differing study designs. Since study design determines the outcome of a study, their findings are controversial and contradictory; that has resulted in conflicting recommendations. In ischemic CRVO, PRP is highly destructive to the peripheral visual fields, resulting in loss of peripheral vision and severe visual disability, and not always of significant benefit for NVG. Since the discovery of the beneficial role of intravitreal anti-VEGF and corticosteroid therapies for macular edema in RVO, macular grid photocoagulation is no longer considered the treatment of choice for macular edema in BRVO and nonischemic CRVO. As for the question: "Does photocoagulation still have a role in the management of RVO?", in spite of a recent decrease in the use of photocoagulation for macular edema in RVO, it still pays an important part in ocular NV in RVO.

### *15.2. Visual field information*

This information provided by manual kinetic perimetry performed with a Goldmann perimeter is very different from that provided by the widely used current automated static threshold perimetries (Humphrey 30-2 or 24-2 SITA). Since automated perimetries do not provide full information about the visual field defect beyond $30^0$, that has serious implications:

It misses all the peripheral visual field defects, with serious functional consequences, because peripheral visual field is essential for "getting around" and driving.

It gives misleading information about the visual loss.

It has resulted in misinterpretation of the type of visual field defects.

However, newer perimeters, such as the Metrovision system, allows wider field of vision to be tested (e.g. 105° in the temporal side); but, so far that is not available for routine use in clinics. It is also most unfortunate that the abandonment of well-established Goldmann perimeter has resulted in all those problems.

### *15.3. Misconceptions*

There are the following major misconceptions about photocoagulation in RVO:

That PRP can be performed in ischemic CRVO without any deleterious visual side-effects. As discussed in section 7.2.2., that is not true. PRP in ischemic CRVO results in marked loss of peripheral visual fields, which are essential for "getting around". As discussed in section 11.1., grid photocoagulation for macular edema produces multiple microscotomas in the macula, which interfere with the central vision.

That every eye with CRVO is at risk of developing NV and NVG. Fig. 1 shows that these are complications of ischemic CRVO only, and NVG develops in only 34%.

That the natural history of CRVO does not involve any spontaneous visual improvement. As discussed above in section 5.1., this is not true.

### *15.4. Management of NVG*

In spite various modes of treatments being advocated for it over the years, it still remains unsettled. Further research is indicated to find a safe and effective mode of treatment for it.

### *15.5. Role of anti-VEGF therapy in NVG*

There is only one relevant study (Rong et al., 2019), which reported that anti-VEGF therapy delayed but did not prevent NVG. This mode of treatment for NV and NVG needs further exploration.

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