Fluorescein angiography versus ERG for predicting the prognosis in Central Retinal Vein Occlusion

Jörgen Larsson, Birgitta Bauer, Ulla Cavallin-Sjöberg and Sten Andréasson

Department of Ophthalmology, Lund University Hospital, Sweden

ABSTRACT.

Purpose: **It is not easy to predict which patients with a central retinal vein occlusion will develop rubeosis and which will not. We have compared two methods for doing so, fluorescein angiography and full-field electroretinogram (ERG). Our aim was to improve our possibilities for predicting rubeosis in patients with central vein occlusion.**

Methods: **32 patients with a central retinal vein occlusion with a duration of less than 14 days were included in the study. Fluorescein angiography and ERG were performed in all patients. The fluorescein angiograms were studied by two independent examiners in a masked mode. The patients were then followed for at least one year.**

Results: **Development of rubeosis in patients with central retinal vein occlusion could be predicted by fluorescein angiography in 82% of the patients and with ERG in 94% of the patients. The non-ischemic central retinal vein occlusions were identified in 62% by fluorescein angiography and in 100% with ERG. Fluorescein angiography misjudged 9 patients 28%, whereas ERG only misjudged 1 patient, 3%.**

Conclusion: **ERG seems to be a better method for predicting the prognosis in central retinal vein occlusion than fluorescein angiography.**

Key words: ERG – electroretinogram – fluorescein angiography – Central Retinal Vein Occlusion, CRVO – rubeosis.

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Fluorescein angiography has for many years been the standard method for distinguishing between the ischemic and the non-ischemic forms of central retinal vein occlusion (CRVO). This distinction is important because the two forms have a different prognosis. In the ischemic form, rubeosis develops in up to 70% and retinal neovascularization in 10–15% (Hayreh et al. 1983). Prophylactic panretinal photocoagulation in the ischemic cases has been proven to prevent neovascularization in CRVO (Laatikainen et al. 1976; Magargal et al. 1982; 1981), even though a recent study has shown that it is questionable whether the treatment should be done prophylactically or when rubeosis has already developed (The Central Vein Occlusion Study Group N Report 1995).

In fluorescein angiography the amount of retinal capillary dropout has been used as a measure of ischemia (Hayreh 1976; Hayreh et al. 1983; Laatikainen & Kohner 1976). Several problems arise when assessing the amount of capillary closure in CRVO with fluorescein angiography. Especially in early disease, large areas of retinal haemorrhages can make it difficult to visualize the ischemia. In old people, cataract or an insufficiently dilated pupil make it difficult to get pictures of a quality that permit an evaluation of the amount of retinal ischemia. There are also contraindications to fluorescein angiography, such as allergy (Yannuzzi et al. 1986). Further, it has been shown that the accuracy and reproducibility in assessing the amount of capillary dropout is rather poor (Welch & Augsburger 1987).

Karpe (1945) introduced clinical ERG as a possible prognostic marker in patients with CRVO. Since then, others have demonstrated that different parameters of the electroretinogram can be useful in distinguishing between the ischemic and the non-ischemic forms of CRVO (Breton et al. 1989; 1991; Hayreh et al. 1989; Johnson et al. 1988; Johnson & McPhee 1993; Kaye & Harding 1988; Matsui et al. 1994; Sabates et al. 1983; Severns & Johnson 1993; Vannas 1960).

Comparisons between fluorescein angiography and different parameters of the ERG have been done before and have shown correspondence between these two methods (Hayreh et al. 1989; Mangelschots et al. 1995; Matsui et al. 1994; Nilsson 1971). These investigations have mainly examined the amplitudes of the ERG, and in most studies the patients were included between 9 days and up to more than a year after the occurrence of CRVO. One study has shown that the interocular differences in the b-wave implicit time in the 30 Hz flicker ERG is a better predictor for rubeosis than fluorescein angiography (Morrell et al. 1991).

In order to improve our clinical standards, we decided to compare the ability of ERG and fluorescein angiography in predicting rubeosis. All patients had short disease duration, less than 2 weeks.

Patients and Methods

Patients

Thirty-two patients with CRVO were included in the study. Patients ranged in age from 40 to 85 (mean 49 years). Thirteen patients were women and 19 were men. The time between onset of the symptoms and examination was 1–13 days. Most of the patients were examined with ERG and fluorescein angiography on the same day, but in two patients the fluorescein angiography was done at the most 5 days after the ERG. The follow-up period ranged from 18 to 42 months.

Clinical examination

At their first visit, the patients were given an ordinary undilated slitlamp examination with gonioscopy. After dilation, biomicroscopy was also performed. The best corrected visual acuity was obtained, and the IOP was measured. The patients were seen every second week during the first 2 months and thereafter every month.

The same examinations were done at every visit. Special care was taken to detect early rubeosis, which was defined as at least one clock hour of iris neovascularization or any chamber angle neovascularization. Since rubeosis was the end point of this study, it was always confirmed by a retina specialist not taking part in the study in other respects and who had no information on the recent disease history of the patient. Patients developing rubeosis were treated with panretinal photocoagulation.

ERG

Full-field electroretinograms were recorded in a Nicolet analysis system as described previously (Andréasson et al. 1993). After dilation of the pupil with topical phenylephrine (10%) and cyclopentolate HCl (1%), a Burian-Allen bipolar contact lens ERG electrode was applied on the cornea together with a ground electrode on the forehead. The patient was dark adapted for 40 minutes before testing. Responses were obtained with a wide band filter (−3 dB at 1 Hz and 500 Hz), stimulating with single full-field flashes (100 μs) and with white light (7500 cd/m^2 and 36 000 cd/m^2). Cone responses were obtained with 30 Hz flickering white light (7500 cd/m^2) averaged from 20 sweeps. The luminance of the three different light stimuli was measured on the light reflected from the Ganzfeld sphere. Pupil size and media opacities were routinely checked, but did not seem to influence the ERG recording in these patients.

Fluorescein angiography

Fluorescein angiography was performed with 2ml of a 25% intravenous bolus injection of fluorescein sodium solution. Pictures were taken of the central fundus and of the midperiphery in all four quadrants, as was described in the Central Retinal Vein Occlusion Study (The Central Vein Occlusion Study Group N Report 1995).

The angiograms were independently interpreted in a masked mode by two specialists in medical retina. The disc area (DA) was used as reference area when evaluating the degree of ischemia. Like in the Central Vein Occlusion Study, less than 10 DA of capillary dropout was considered to be a non-ischemic occlusion (The Central Vein Occlusion Study Group N Report 1995). The angiograms were classified into 5 groups: 1. <10 DA of ischemia, 2. 10–20 DA of ischemia, 3. 20–40 DA of ischemia, 4. >40 DA of ischemia and 5. non classifiable due to extensive retinal haemorrhages or cataract.

Results

Of the 32 patients, 16 developed rubeosis during the follow-up period. They were treated with panretinal photocoagulation. Fluorescein angiography misjudged 9 patients (28%), whereas ERG only misjudged 1 patient, (3%).

Fluorescein angiography

In 18 (56%) of the 32 angiograms the two specialists made the same judgement, and of these 18, two were considered by both specialists as non-classifiable. In 3 cases one of the specialists considered the angiogram as non-classifiable, whereas the other specialist thought it possible to assess the degree of ischemia. In one case their interpretation differed by two scale steps, and in 10 cases their disagreement was one step (Fig. 1 and Table 1). When the two examiners differed in their interpretation in one scale step, the lower group was chosen and when they differed in two scale steps, the scale step in between was chosen. When one of the examiners considered the fluorescein angiography to be non-classifiable, the interpretation of the other one was chosen.

Electroretinography

We looked at the following ERG parameters: a and b-wave after white light single flash stimulation at two different intensities, the b/a ratio at these two different intensities, the amplitude and the implicit time in the 30 Hz flicker ERG. The b-wave implicit time in the 30 Hz

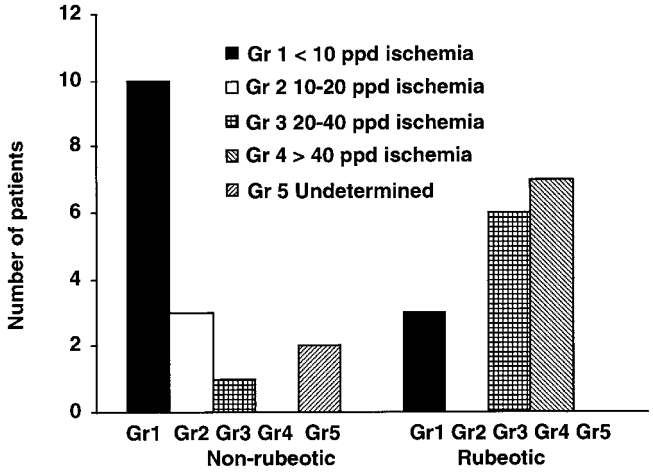

Fig 1. Demonstrating how the interpretation of the fluorescein angiographies correlates to the final outcome of the central retinal vein occlusions concerning rubeosis.

Table 1. Interobserver variability in interpretation of fluorescein angiograms.

	Examiner 1	Examiner 2
Gr 1 <10 ppd ischemia	11	8
Gr 2 10–20 ppd ischemia	5	4
Gr 3 20–40 ppd ischemia	4	8
Gr 4 >40 ppd ischemia	10	7
Gr 5 undetermined	2	5

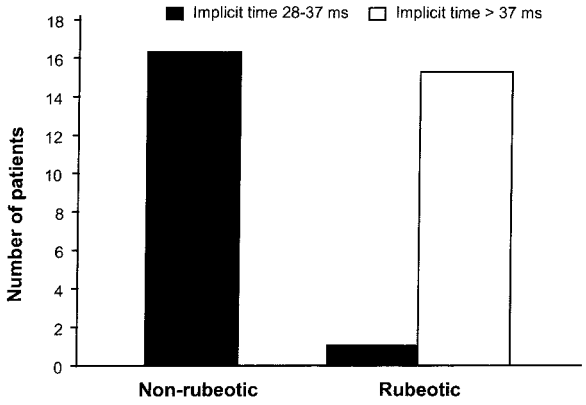

Fig 2. Demonstrating the correlation between the b-wave implicit time in the 30 Hz flicker ERG and the final outcome of the central retinal vein occlusion concerning rubeosis.

flicker ERG turned out to be the best ERG parameter for predicting rubeosis, as we have shown previously (Larsson et al. 1998).

In the 16 patients who developed rubeosis, the average b-wave implicit time in the 30 Hz flicker ERG was 39.5 ms (range 34.2–42.5). All patients but one had a b-wave implicit time of more than 37 ms (Fig. 2). The normal cone b-wave implicit time in the 30 Hz flicker ERG was 26.2–32.4 ms in 48 normal controls (Ponjavic et al. 1994).

In the non rubeotic patients, the average b-wave implicit time in the 30 Hz flicker ERG was 33.6 ms (range 28.2–37.0). No patient had an implicit time of more than 37 ms (Fig. 2). Development of rubeosis in patients with CRVO could be diagnosed by fluoreschein angiography in 82% of the patients and with ERG in 94% of them. The non-iscemic CRVO's were identified in 62% by fluorescein angiography and in 100% with ERG. Statistical analysis was performed using kappa statistics. The kappa analysis showed that the agreement between the final outcome of the CRVO's and the ERG had a Kappa value of 0.938, which is considered to be very good according to Altman (1991). The Kappa value for the agreement between the final outcome of the CRVO's and the fluorescein angiography was 0.438, which is considered to be moderate according to Altman (1991). Thus, the Kappa value shows that the ERG seems to be a better predictor than fluorescein angiography for the final outcome, concerning rubeosis in CRVO.

Fig. 3 and 4 show the fluorescein angiograms of two patients who later developed rubeosis. In patient 1 the fluorescein angiogram is hard to interpret, especially the field outside of the vessel arcades is blurred due to cataract and it is hard to assess the amount of ischemia. Patient 2 in Fig. 4 has abundant hemorrhages that make the angiogram hard to interpret, but no evident signs of ischemia are present.The ERG's of these two patients are shown in Fig. 5 compared to a normal ERG.

The b-wave implicit time in the 30 Hz flicker ERG turned out to be a better predictor for neovascular disease than the fluorescein angiography. In only one case did the ERG fail to identify the ischemia in a patient who later developed rubeosis. The fluorescein angiography performed 5 days later showed a capillary dropout of between 20–40 DA, and thus the CRVO was classified as ischemic. ERG was repeated one week after the fluorescein angiography, and now the b-wave implicit time in the 30 Hz flicker ERG was markedly delayed (40 ms). A possible explanation for this could be that the thrombosis had increased in size between the first ERG examination and the fluorescein angiography and thus compromised the retinal circulation more severely so that ischemia had developed.

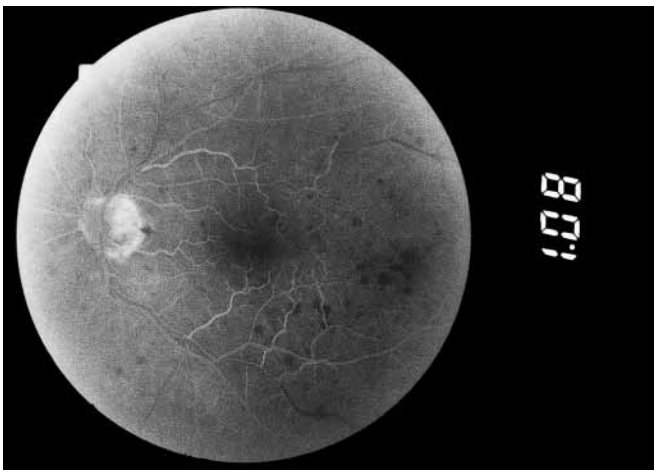

Fig 3. Patient 1: Fluorescein angiography of an 86-year-old man, 6 days after the onset of central retinal vein occlusion. The angiogram is not of very good quality, especially the field outside the vessel arcades is blurred due to cataract and it is hard to assess the amount of ischemia. Hemorrhages are sparse. The ERG (Fig. 5) shows a prolonged implicit time in the 30 Hz flicker ERG indicating ischemia. The patient developed rubeosis 4 weeks after these examinations.

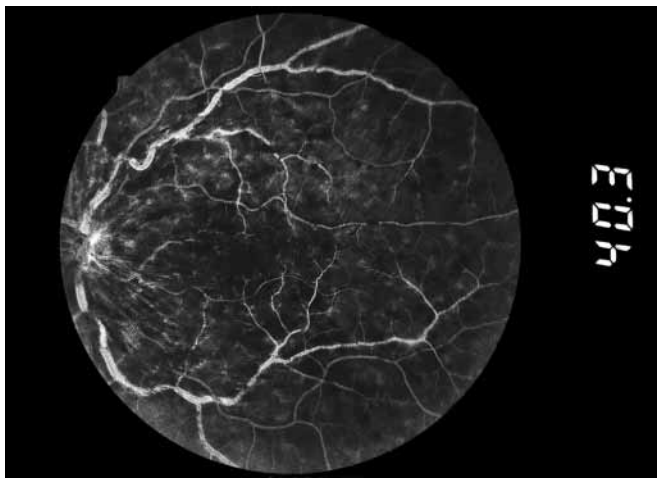

Fig. 4. Patient 2: Fluorescein angiography of a 58-year-old female 8 days after the onset of central retinal vein occlusion. Fluorescence is blocked by massive hemorrhages, and it is difficult to assess the degree of ischemia. The ERG (Fig. 5) shows a prolonged implicit time in the 30 Hz flicker ERG indicating ischemia, and the patient developed rubeosis 3 weeks after these examinations.

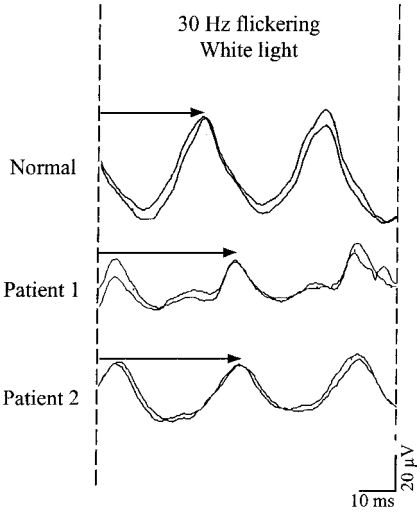

Fig 5. The arrows indicate the implicit time in the 30 Hz flicker ERG. Patient 1 as well as patient 2 show increased implicit time, indicating ischemia, and both patients developed rubeosis within a few weeks.

Discussion

Fluorescein angiography has for a long time been the standard method for assessing the degree of ischemia in CRVO, giving a classification into two different groups, the non-ischemic and the ischemic type (Hayreh et al. 1983). The ischemic type has a high rate of neovascular complications, which can be devastating for the eye, in particular when neovascular glaucoma develops. Panretinal photocoagulation can be used to prevent and treat these complications (Laatikainen et al. 1976; Magargal et al. 1982; 1981; The Central Vein Occlusion Study Group N Report 1995).

If you defer your treatment until the first signs of neovascularization, an ischemic picture on the fluorescein angiography will alert you to see the patient at fairly short intervals, so that panretinal photocoagulation can be performed at the first sign of rubeosis. The fluorescein angiogram is not always easy to interpret, especially early in the course of the disease, and the distinction between the non-ischemic and the ischemic form of the CRVO is often a problem. Interpretation of fluorescein angiograms has also been shown to vary between observers (Welch & Augsburger 1987).

In the fluorescein angiographies of this study, the two ophthalmologists made the same interpretation in 18 (56%) of the cases. In 10 cases they disagreed by one step on the scale and in four cases disagreement exceeded one step. This degree of variability is in agreement with earlier investigations (Welch & Augsburger 1987). Three of the patients later developing rubeosis were considered by both ophthalmologists as belonging to the non-ischemic group (group 1), whereas the ERG classified them as ischemic. No rubeosis developed either in four patients that were considered to be ischemic in the fluorescein angiography and belonging to group 2 and 3, or in two patients that were considered as non-classifiable by both ophthalmologists, whereas the ERG classified them as non-ischemic and at the end of the follow-up period their visual acuities were between 0.4 and 1.0. Thus, in these nine cases the fluorescein angiography failed to classify the CRVO's correctly. Especially in the cases that were considered as ischemic and finally ended with very good visual acuities, a prophylactic panretinal photocoagulation based on the results from the fluorescein angiography would not only have been unnecessary, but also possibly harmful for the function of these eyes.

One of the explanations as to why the ERG is a better predictor for rubeosis than fluorescein angiography could be that the full-field electroretinogram assesses the function of the whole retina. In contrast, only a restricted part of the retina is accessible in the fluorescein angiograms, so that it is possible to assess only less than 50% of the retinal area. Thus, an ischemia that is mainly located in the periphery could be missed by the fluorescein angiography, whereas it is possible to detect this peripheral ischemia by the ERG.

Neovascularization is considered to be triggered by hypoxic retinal cells that probably produce an angiogenetic factor (Breton et al. 1989; Hayreh 1983; Patz 1982), whereas the already dead retinal cells do not have this triggering effect. In the fluorescein angiography it is usually not possible to differ between hypoxic and already dead retinal tissue. Retinal cells that are ischemic, but alive, react slowly and give a long implicit time (Ikeda et al. 1992), making it easier to distinguish between hypoxic and dead retina. This may be a further explanation of why the ERG is a better predictor for rubeosis than fluorescein angiography.

Fluorescein angiography is a procedure that requires a photographer and a nurse or a doctor to inject the fluorescein, whereas many of the ERG examinations at our clinic are performed as standardized procedures by a specially trained nurse. The time for the ERG examination, once the patient is dark adapted, is no more than 10 minutes. In 4–5 % of the patients, nausea and vomiting occur as a reaction to the injection of fluorescein. Allergic reactions e.g. urticaria and even anaphylactic shocks have also been described (Yannuzzi et al. 1986). The ERG examination does not include any invasive procedures as does the fluorescein angiography, and the only side effects that are rarely seen is a vasovagal reaction and corneal abrasion due to the contact lens.

In conclusion, we have found that in patients with recent CRVO, the full-field ERG and especially the b-wave implicit time in the 30 Hz flicker ERG is a better predictor for prognosis than fluorescein angiography. We have also demonstrated that the fluorescein angiography, though not as good as the ERG, gives fairly good results even this early in the course of the disease. We also believe that the ERG procedure is the quicker of the two with fewer side effects. We therefore find it superior to fluorescein angiography in predicting the prognosis in CRVO.

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Corresponding author:
Jörgen Larsson, MD
Department of Ophthalmology
Lund University Hospital
221 85 Lund
Sweden
Tel. +46 46 17 20 74
Fax +46 46 211 50 74
E-mail: Jorgen.Larsson@oft.lu.se