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Vitreous fluorophotometry recordings in posterior segment disease

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Abstract. The results of vitreous fluorophotometry in a variety of retinal and systemic diseases are described, particularly in photoreceptor and retinal pigment epithelium dystrophies, in Best dystrophy, in choriocapillaris atrophy, in choroidemia and in inflammatory conditions, and in cystoid aphakic and non-aphakic macular edema. The patterns involved in breakdown of the blood-retinal barrier are defined for various diseases, and an attempt is made to characterize each disease type by a fluorophotometric "profile."

Introduction

Vitreous fluorophotometry is mainly a diagnostic technique, the only available method that can quantitate an alteration of the blood-retinal barrier (BRB). It appears also to be particularly suited for the early detection of functional changes in the BRB (Cunha-Vaz et al. 1975; Waltman et al. 1978) before lesions are visible in the retina using less defined methods of detection like ophthalmoscopy and fluorescein angiography.

The detection of an alteration in the BRB can also contribute significantly to the understanding of the pathophysiology of a variety of retinal diseases in which a breakdown of the BRB is suspected to play a major role. In this way diseases involving the retinal vessels and the retinal pigment epithelium are natural targets for the use of this technique.

Vitreous fluorophotometry (VF) recordings performed in a variety of retinal diseases, including retinitis pigmentosa, chorioretinal dystrophies, choroideremia, fundus flavimaculatus, pars planitis, optic nerve disease, circulatory deficiences, toxic neuropathy, cystoid macular edema, and diabetes mellitus (with and without retinopathy), will be reviwed and the findings correlated with the clinical picture.

This is the first attempt to define patterns of BRB breakdown, their characterization by vitreous fluorophotometry and their correlation with specific types of posterior segment disease.

Chorioretinal dystrophies

Photoreceptor dystrophies

A. Rod-cone (retinitis pigmentosa)

This disease serves as a paradigm to demonstrate the importance of VF and assessment of the BRB. Alterations in the VF recording can precede ophthalmoscopically visible fundus disease and electrophysiological changes in all genetic patterns.

Clinical features. Night blindness is the initial complaint. Fundus changes include black bone spicule or corpuscular-like retinal pigmentation (initiating within the mid-peripheral retina), attenuated retinal vessels and a waxy type of optic disk atrophy. This triad of findings, although characteristic, is not obligatory or pathognomonic. Some patients with retinitis pigmentosa do not ophthalmoscopically manifest pigment spicules. Others lack retinal vessels attenuation or optic disk atrophy. In most instances, both the autosomal recessive and X-linked recessive forms have nonrecordable or minimal EGR responses at an early stage of disease.

VF recordings. In a recent study, 15 patients with various types of retinitis pigmentosa were examined with vitreous fluorophotometry. All patients with retinitis pigmentosa showed abnomally high concentrations of fluorescein in the vitreous that reflected an abnormality of the BRB. The amount of fluorescein in the vitreous correlated with the extent of photoreceptor and retinal pigment epithelial disease, as well as with the presence of leakage from retinal capillaries. Furthermore, vitreous fluorophotometric measurements can show breakdown of the BRB in patients with retinitis pigmentosa who have no opthalmoscopically apparent abnormalities and only minor changes on the electroretinogram (ERG).

Two typical patterns of VF recordings are seen. In pattern type P, the leakage is predominantly from the posterior pole, whereas in pattern type M the leakage and alteration of the BRB is localized to the retinal midperiphery. The type M pattern is associated with particularly elevated levels of fluorescein accumulation in the vitreous and with values in the range of 10^{-7} g/ml in the mid-vitreous. When type M pattern is present or very high values of fluorescein leakage occur, VF examinations at 15 and 30 min are needed to differentiate the origin of the leakage and the relative participation of the BRB and blood-aqueous barrier (BAB). The nomenclature used to represent VF variables is reported elsewhere in this issue: PV – posterior vitreous; MV – middle vitreous; AV – anterior vitreous; L – lens; AC – anterior chamber; GPV – gradient of posterior vitreous; GAV – gradient of anterior vitreous; BRB Kin – blood-retinal barrier inward transfer rate; BRB Kout – bloot retinal barrier outward transfer rate; P – plasma.

If retinitis pigmentosa takes pattern P (Fig. 1), characteristic VF recordings are as follows:

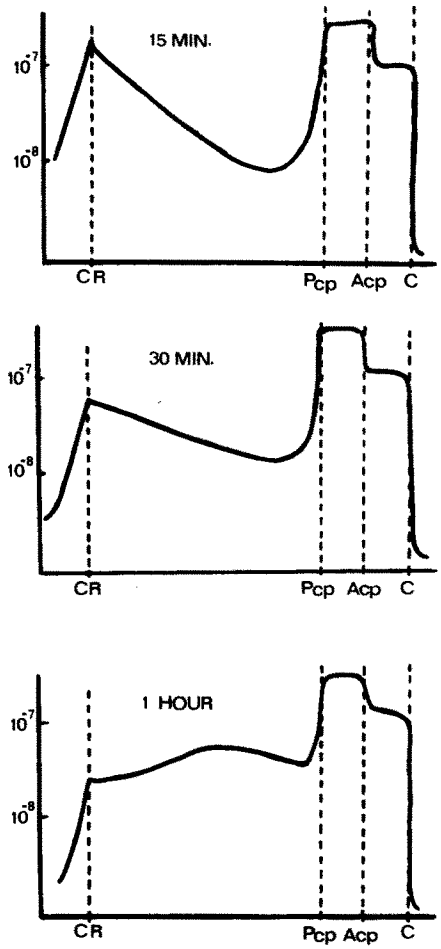

Fig. 1. Characteristic VF recordings in retinitis pigmentosa (pattern P) at 15 min, 30 min, and 1 h

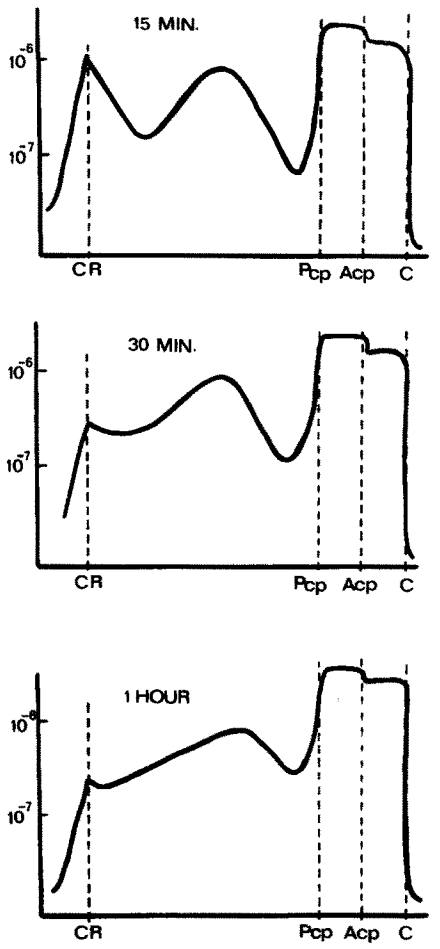

Fig. 2. Characteristic VF recordings in retinitis pigmentosa (pattern *M*) at 15 min, 30 min, and 1 h

1. PV higher than MV, higher than AV (15, 30 min, up to 1 h)
2. AC – normal range
3. GPV – negative (15, 30 min, up to 1 h)
4. GAV – negative
5. BRB Kin – increased
6. P – normal lens

If retinitis pigmentosa takes pattern M (Fig. 2), characteristic VF recordings are:

1. MV higher than PV, higher than AV (15 min and later); characteristic at 1 h
2. MV – increase starts early, 15–30 min
3. AC – normal range or increased
4. GPV – positive (1 h)
5. GAV – negative (1 h)
6. BRB Kin – highly increased
7. P – normal levels

Carriers of X-linked retinitis pigmentosa. The clinical features are fundus changes, which include high myopia, local areas of bone spicules, or a "tapetal reflex". Often there are no fundus abnormalities at all. The ERG recordings are generally normal in both amplitude and implicit times, although some cases with more extensive fundus involvement show subnormal ERG responses. Vitreous fluorophotometry examinations performed in a serie of seven female carriers of X-linked recessive retinitis pigmentosa showed an alteration in the BRB, even though the findings from fundus examinations and ERG recordings were sometimes normal.

For carriers of X-linked retinitis pigmentosa characteristic VF recordings at 1 h are:

1. PV higher than MV
2. PV values are between 1 to 2×10 g/ml
3. GPV – negative
4. AC – normal
5. BRB Kin – minimally increased
6. P – normal levels

B. Cone and cone-rod dystrophies

Clinical features. The acquired cone dystrophies are inherited as either a Mandelian autosomal dominant or autosomal recessive form of disease. The dominant form frequently manifests a "bull's eye" pattern within the macula with either normal or slightly attenuated retinal vessels. Sometimes a temporal disc pallor is visible. The autosomal

recessive form has a more diffuse central atrophy, often without a clear "bull's eye" appearance. Both groups have loss of central acuity, central scotoma, defective color perception, and photophobia.

VF. Examination reveals different degrees of alteration in the BRB, although a situation of relatively low leakage predominates. Of 19 patients with a variety of cone-rod dystrophies, 6 showed normal values and the other 13 showed a similar pattern, with the higher value at 1 h reaching 1×10 g/ml in the PV. There is therefore good correlation between alteration of BRB and more advanced fundus lesions.

In cone-rod dystrophies characteristic VF recordings at 1 h are:

1. PV > MV
2. Frequently MV > AV
3. AC – normal range
4. GPV – negative
5. BRB Kin – increased when pathology is more advanced
6. P – normal levels

Dystrophies of the pigment epithelium

A. Flecked retina

Clinical features. This syndrome includes the clinical features of (1) fundus flavimaculatus, (2) familial drusen, and (3) fundus albipunctatus. This group is characterized by yellowish – white flecks of varying size, shape and apparent depth, generally within the posterior pole. These conditions may be associated with a Stargardt type of atrophic macular dystrophy. The important emphasis in this syndrome is on the EOG which is abnormal in flecked retina diseases. An abnormal diffuse pigment epithelium appears to be implicated.

VF. In a recent study we were able to examine eight patients with fundus flavimaculatus (Stargardt's macular dystrophy). Although clinically and histologically lesions are noted at the level of the outer BRB (retinal pigment epithelium), this barrier was intact in all eight patients studied by our fluorophotometric technique. The configuration of the VF. recordings was characteristically normal and the values obtained within the normal range.

B. Best's (vitellirruptive) macular dystrophy

Clinical features. A diffuse functional abnormality of the pigment epithelium is involved here. The early stage of this dominant inherited disease has the classic "egg sunny side up" appearance. This lesion can either resorb (and later resecrete) or rupture, leading to a "scrambled egg" appearance which not infrequently is followed by a glial scar with pigment proliferation. The EOG is more markedly abnormal than in the flecked-retinal syndrome. Traditionally, the ERG is completely normal.

VF. We have examined so far only three patients. One patient had a normal VF recording and the two other patients had minimal changes in the BRB, with increased leakage localized to the posterior pole of the retina (PV MV, 1 h). Minimal leakage characterized by low values in PV and MV within normal limits at the 1 h examination.

Choroidal dystrophies

A. Choriocapillaris atrophy

Clinical features. Choriocapillaris atrophy can occur in the following forms: (1) central areolar, (2) central, (3) peripapillary, and (4) diffuse. The latter three categories may represent a continuum of the same disease and not seperate genetic diseases. Most frequently after age 40 these patients show a decrease in acuity and, not infrequently, a history of poor night vision; the ERG is subnormal in early stages, becoming extinguished with more advanced disease.

VF. A patient with early choroidal atrophy showed borderline values.

B. Gyrate atrophy

Clinical features. Patients with this autosomal recessive disease generally present within the first two decades complaining of poor night vision. The peripheral fundus has multiple discrete, irregular, atrophic patches of pigment epithelium, choriocapillaris and, later, a layer of choroidal vessels.

VF. Only one patient has been examined so far. The configuration of the VF recording was characteristic of a situation of high leakage, particularly marked in the mid-peripheral retina. Only the 1-h examination was performed. The right eye was more affected with more marked fundus lesions and showed a configuration similar to the M pattern of retinitis pigmentosa with MV PV, whereas the left eye showed lower levels of leakage and PV MV.

C. Choroideremia

Clinical features. The patients complain of poor night vision, which usually starts in the first decade of life. It is a X -linked chorioretinal dystrophy. The ERG is defective early, the responses being either minimal or nonrecordable.

VF. VF recordings have been performed in three patients with choroideremia; all of them showed an alteration of the BRB, with marked leakage of fluorescein into the vitreous cavity. The leakage appeared to be well distributed all over the posterior pole and midperiphery. At 1 h, PV MV AV. The gradient in the posterior vitreous (GPV) was negative and the gradient in the anterior vitreous (GAV) also negative.

Choroideremia carriers. The female carrier of choroideremia may show fundus changes although electrophysiologic studies are generally normal. VF studies in five carriers have shown a normal BRB in two of them. The other three had minimal changes, showing the characteristic picture of low leakage of the posterior pole (1-h examination).

Inflammatory conditions

We have observed a few isolated cases of different situations of intraocular inflammation, but because we have assembled VF recordings in 23 cases of peripheral uveitis or pars planitis we will use this condition as an example of VF changes in ocular inflammation.

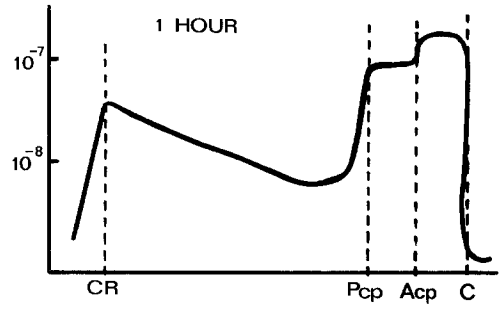

Fig. 3. Characteristic VF recordings in peripheral uveitis with pattern I

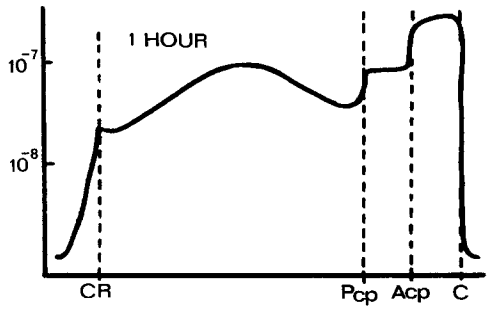

Fig. 4. Characteristic VF recordings in peripheral uveitis with pattern II

Peripheral uveitis

Clinical features. It is a chronic ocular inflammation that is characterized by blurred vision and the appearance of floaters. The patients tend to be adolescents and young adults. Many of these patients have a white, fluffy exsudate over the inferior peripheral retina and pars plana. Macular edema and retinal vasculitis are common findings.

VF. VF examination of 23 eyes with pars planitis have shown that the distribution of the fluorescein accumulation in the vitreous is generally uniform in the anterior vitreous without preference for the inferior side, as expected clinically. Only five of the 23 eyes showed more accumulation in the inferior vitreous. These were the eyes in which higher levels of fluorescein penetrated into the vitreous and had MV PV (at 1 h), indicating increased mid-peripheral leakage. The remaining eyes showed different degrees of leakage, but the leakage was more uniform all over the posterior pole, and at 1-h there was a gradient from the retina to the lens (pattern I, peripheral uveitis).

In peripheral uveitis with pattern I (Fig. 3) characteristic VF recordings are as follows:

1. PV > MV > AV
2. AC – elevated
3. GPV – negative
4. GAV – negative
5. BRB Kin – increased
6. P – normal levels

In peripheral uveitis with pattern II – high leakage (Fig. 4), characteristic VF recordings are:

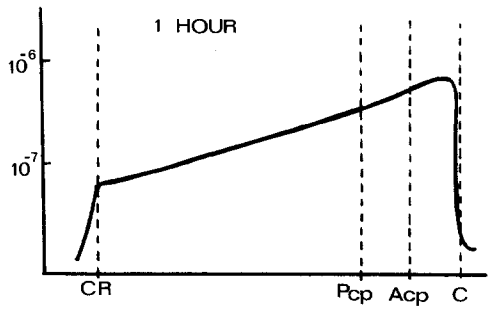

Fig. 5. Characteristics VF recordings in cystoid macular ederma (*CME*) with intracapsular extraction

1. MV > PV > AV (15 min to 1 h)
2. AC – eleveated
3. GPV – negative (15 min); GPV – positive (1 h)
4. GAV – negative
5. BRB Kin – highly increased
6. P – normal levels

Cystoid macular edema

Edema of the retina is a direct consequence of an alteration in the BRB. Cystoid macular edema is the involvement of the macular area by edematous fluid, which has been identified by its characteristic picture of fluorescein distribution as seen by angiography and slit-lamp biomicroscopy. The foveal reflex is absent. There is some forward bulging of the macular region, usually associated with translucent intraretinal cystoid spaces arranged concentrically around the foveola. The fluorescein angiographic pattern has been described as an initial leakage of dye from the retinal capillaries in the macular area in an irregular circular pattern. Finally, a remarkable and diagnostic dark stellate develops on the background of fluorescein staining.

Cystoid macular edema has become the most common and troublesome complication following cataract extraction, and it also occurs in retinal surgery, uveitis, ocular tumors, diabetes, and arteriosclerotic vascular disease. We will review, here, as an example, our observations on cystoid macular edema in surgical aphakia.

Surgical aphakia

VF. The alteration of the BRB associated with cystoid macular edema can be quantified using VF. The configuration of the VF recordings is different after intracapsular surgery or extracapsular surgery with intraocular lens implants, suggesting that this last method may be a better method to maintain a more effective diffusional barrier between the two ocular fluid compartments, vitreous and aqueous. VF values appear particularly valuable regarding follow-up and prognosis. Similarly, they correlate very well with the fluorescein angiographic picture.

Characteristic VF recordings in cystoid macular edema – intracapsular cataract extraction (Fig. 5) are:

1. AV is indirect continuity with AC (highly elevated).
2. AV > MV > PV (at 1 h).
3. GPV – positive.
4. GAV – positive.

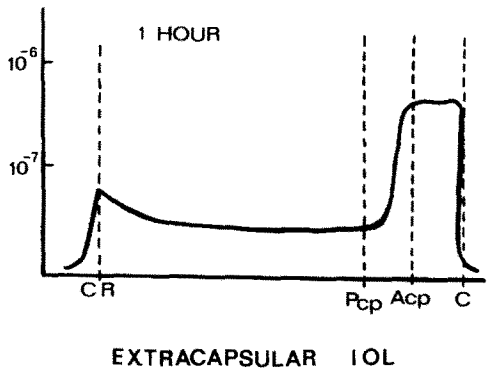

Fig. 6. Characteristic VF recordings in cystoid macular ederna (CME) with extracapsular extraction and intraocular lens implant (*IOL*)

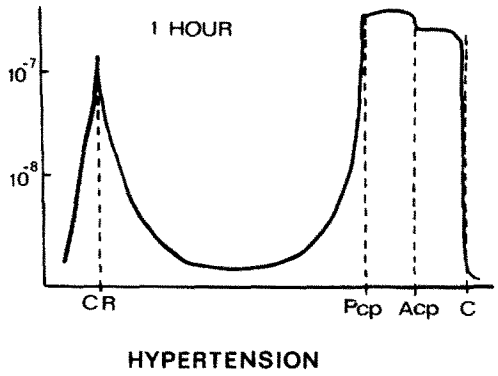

Fig. 7. Characteristic VF recordings in hypertension

5. BRB Kin – difficult to evaluate.
6. P – normal values.

Characteristic VF recordings in cystoid macular edema – extracapsular cataract extraction and intraocular lens implant (Fig. 6):
1. PV > MV > AV.
2. There is not direct continuity of AV with AC.
3. GPV – negative.
4. GAV – positive.
5. BRB Kin – increased.
6. P – normal values.

Toxic retinopathy

As an example, our findings in a case of thioridazine toxicity are presented.

Thioridazine (mellaril)

Clinical features. Patients receiving relatively high doses of thioridazine have reported decreased vision and night blindness. Both central and ring scotomas have been noted. In earlier stages, a pigmentary mottling appears in the macular and perimacular regions. Later extensive degeneration changes of the pigment epithelium, photoreceptors and choriocapillaris are seen.

VF. VF examination of one case showed alteration of the BRB with significant leakage of fluorescein into the vitreous. PV MV, AV MV, GPV was negative and GAV positive, sugestting that the leakage was mostly from the posterior pole and involving the BRB; AC values were normal; there was a slightly lowered plasma level (P).

Circulatory deficiences

We will use as representative our findings in 42 VF recordings performed in hypertensive patients.

Hypertension and arteriosclerosis

In patients with systemic hypertension and normal fundi, abnormal findings were observed on VF only when the blood pressure reached high levels. Otherwise, normal VF recordings were a frequent finding. As soon as minimal changes were apparent in the retina, then VF readings were consistently abnormal. The AC values were elevated and the simultaneous alteration of both barriers, the BRB and the BAB, gave a typical recording in which the configuration of the fluorescein concentration in the vitreous was characteristically symmetrical.

Characteristic VF recordings in hypertension (Fig. 7) are:
1. PV > MV
2. AV > MV
3. AV > PV
4. AC – elevated
5. GPV – negative
6. GAV – positive
7. BRB Kin – slightly increased (relates with blood pressure and retinopathy)
8. P – elevated

Optic nerve disease

Retrobulbar neuritis

Clinical features. Retrobulbar neuritis is defined as inflammation of the optic nerve head that is not detectable by ophthalmoscopic of fluorescein angiographic abnormality.

VF. In a series of six patient with acute retrobulbar neuritis, VF recordings were abnormal in one or both eyes of all six patients with acute retrobulbar neuritis. All six patients had normal optic disks and fluorescein angiography. The leakage was relatively minimal. The pattern of fluorescein leakage suggests an alteration of the BRB localized to the posterior pole. On the basis of the VF findings, this method appears useful as objective evidence of (1) acute retrobulbar neuritis, (2) involvement of the asymptomatic eye in acute retrobulbar neuritis, (4) a recurrence of acute retrobulbar neuritis, (5) alteration in the blood ocular barrier in patients with acute retrobulbar neuritis in multiple sclerosis, and (6) the effects of corticosteroids and other therapeutic agents in the treatment of acute retrobulbar neuritis.

The characteristics of VF recordings in retrobulbar neuritis (1 h) were:
1. PV > MV
2. AC – normal
3. GPV – negative

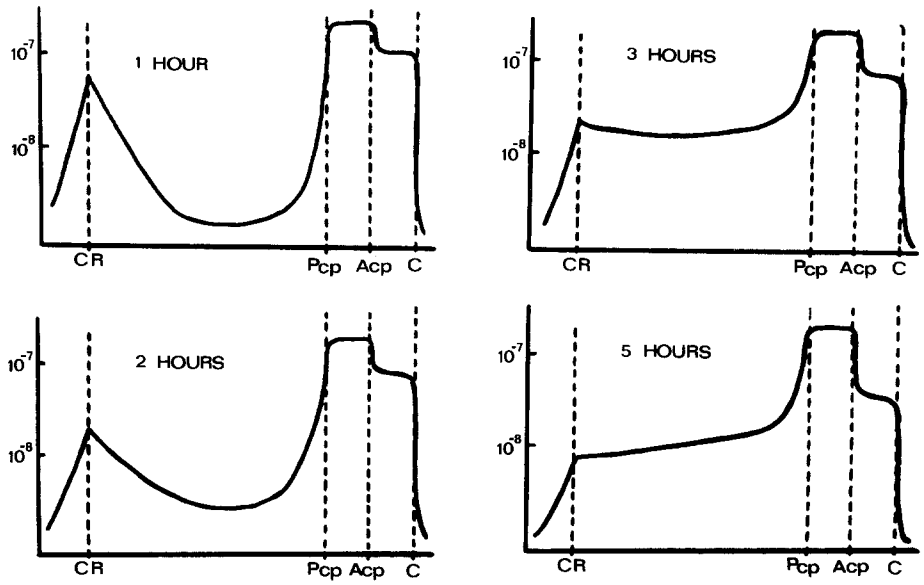

Fig. 8. Characteristic VF recordings in diabetes with no retinopathy

4. GAV – positive
5. BRB Kin – slightly increased
6. P – normal values

We have also had the opportunity of examining cases of disc edema, optic atrophy associated with retobulbar neuritis, and obstructive neuropathy. It was possible to find elevated posterior vitreous fluorophotometry values in these cases, indicating that VF has an important role in diagnosing inflammatory, obstructive and infiltrative optic neuropathies, when conventional fluorescein angiography is normal.

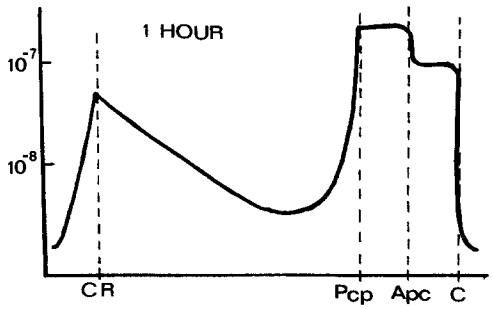

Fig. 9. Characteristic VF recordings in diabetes with background retinopathy

Diabetes mellitus

Retinopathy is the major cause of visual loss in diabetes mellitus (84%).

Diabetic retinopathy

Clinical features. The retinal involvement in diabetes includes three different phases: an initial, preretinopathy stage, followed by a nonproliferative and a proliferative phase. In the preretinopathy stage there are no visible changes in the retina either ophthalmoscopically or with fluorescein angiography. Nonproliferative diabetic retinopathy is characterized by vascular changes in the retinal capillary bed, with formation of microaneurysms, lipid exudates and small intraretinal hemorrhages. Edema and/or ischemia of the macula may be the major cause of reduced visual acuity. Proliferative retinopathy is characterized by the development of new retinal vassels anywhere in the fundus, with apparently a predilection for the optic disc and the superior temporal quadrant of the retina.

VF. The technique of vitreous fluorophotmetry has opened up new perspectives in our understanding of retinal involvement in diabetes. VF demonstrates an alteration of the BRB in the preretinopathy stage before fluorescein angiography and ophthalmoscopy show any apparent abnormalities (Fig. 8).

Characteristic VF recordings in diabetes with preretinopathy (1 h) are:
1. PV > MV
2. AV > MV
3. AC – elevated
4. GPV – negative
5. GAV – positive
6. BRB Kin – increased
7. P – normal or decreased (insulin-dependent)

When there is retinopathy, both background and proliferative, leakage of fluorescein is apparent even with a much less sensitive method like fluorescein angiography. VF becomes important in these phases of diabetic retinopathy as a quantitative method of evaluation of the fluorescein leakage which is particularly useful for following the progress of the disease and examining the effects of therapy.

Characteristic VF recordings at 1 h in diabetes with background retinopathy (Fig. 9):

1. PV > MV
2. MV > AV
3. AC – elevated
4. GPV – negative
5. GAV – negative
6. BRB Kin – highly increased
7. P – normal or decreased (insulin-dependent)

The configuration of VF recordings in proliferative diabetic retinopathy is variable, depending on the location of the new vessels and their extension into the vitreous. The levels of leakage are much higher than in the previously referred to phases of diabetic retinopathy. Their usefulness is limited to follow-up, particularly after treatment.

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