Electrophysiological Evaluation of the Macular Cone System: Focal Electroretinography and Visual Evoked Potentials After Photostress

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In this article, the methodologies and clinical applications of two electrophysiological tests, the focal electroretinogram (FERG) and the visual evoked potentials (VEPs) after photostress, are described. These techniques provide somewhat complementary results about macular function because they tap the activity of different neural substrates along the pathway of the cone system and allow evaluation of the macular function under steady-state (ie, the FERG) or dynamic (ie, the VEPs after photostress) conditions. The results obtained in patients with different macular pathologies indicate that while the FERG provides direct information about the extent and sites of macular dysfunction, the VEPs after photostress represent an objective, although not specific, index of the dynamic properties of macular performance after exposure to intense light stimulation. The combined use of both techniques appears to be promising for gaining further insights into the diagnosis and pathophysiology of macular diseases.

A VARIETY of refined psychophysical techniques (see, for example, Weleber and Elsner[1]) has been developed in the clinical setting to evaluate the function of the macular cone system: color matching techniques, absolute cone thresholds, cone sensitivity to sinusoidal flicker modulated at different temporal frequencies (ie, the De Lange function), perimetric cone sensitivity tested by microperimetric techniques, and recovery of visual acuity after photostress. Recently, electrophysiological tests have been receiving increasing attention, either because they are objective and direct probes of macular cone function, or for their value in understanding the pathophysiology of different disorders. In this article, the methodologies and clinical applications of two electrophysiological tests, namely the focal electroretinogram (FERG) and the visual evoked potentials (VEP) after photostress, will be described. These techniques provide somewhat complementary results about macular function. Indeed, they tap the activity of different neural substrates along the pathway of cone system (ie, from the macular area to visual cortex). In addition, they allow evaluation of macular function in "steady-state" conditions (ie, the FERG), or in a "dynamic" status (ie, VEP after photostress) because of the recovery of the system after exposure to a bleaching light.

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FOCAL ELECTRORETINOGRAPHY

An objective electrophysiological test, such as the electroretinogram (ERG), which provides information about the function of localized retinal areas (FERG), is of obvious interest in both physiological and clinical research. The FERG is primarily used to evaluate macular or foveal cone function. The number of cone photoreceptors located within the central 10 degrees represents about 7% of the total cone population.[2] Therefore, the ERG responses generated by macular cones represent less than 10% of the total cone contribution to the full-field photopic ERG, which may not be sensitive enough to detect a dysfunction limited to the macular region. Several specific techniques have been developed over the past 20 years to record and isolate FERG responses. These methodological efforts have dealt mainly with two problems: first, the reduced amplitude and signal-to-noise ratio of the FERG signals, and second, the effect of modulation of the stray-light outside the stimulated retinal area. Regarding the first problem, the low amplitude of FERG signals requires the use of advanced signal analysis techniques, such as Fourier analysis and cross-correlation coupled with automated artifact rejection, to reliably isolate the responses. Regarding the second problem, the stimulation of areas outside that of interest can significantly contaminate the FERG, altering the response characteristics specific for a particular retinal region. In a classic experiment, Asher[3] and Boynton and Riggs[4] showed that a small spot of light, when

presented in the dark to the optic disk, which is functionally silent because of lack of photoreceptors, elicited an ERG with an amplitude that was slightly larger than that evoked when the same spot was oriented on the fovea. This was determined by the stray-light stimulation of areas surrounding the stimulus. The effect of stray-light modulation can be minimized by keeping the peripheral retina light-adapted at a constant level by a steady background.[5] It has been shown[6] that, if the stimulus luminance is kept sufficiently low relative to the adapting background and does not exceed the levels of response saturation, the stray-light modulation contributes only to a minimal fraction (1%) of the FERG response. Another approach used to minimize the stray-light modulation is represented by the use of bars or checkerboards (pattern stimuli) whose luminance is modulated in counterphase at a constant mean luminance.[7] Under these stimulus conditions, the mean flux of luminance remains constant over time, so that no response can be elicited from the areas surrounding the region directly stimulated. The ERG evoked by pattern stimuli, although focal in nature, has different generators and physiological properties with respect to the luminance FERG.[8,9] In this article, which focuses on methodological and clinical aspects of the FERG, the pattern ERG will not be treated in detail, but only in some selected applications for comparative purposes with the FERG.

Methodological Procedures

Stimulation techniques. The FERG is usually generated by a test stimulus of variable angular subtense (3 to 10 degrees) presented on a steady, light-adapting background.[10] In the studies of Biersdorf,[11] the stimulus consisted of a Grass photostimulator placed in a field opening of 4 degrees on the rear of a Ganzfeld bowl. Ganzfeld background intensity was able to saturate rods and minimize stray light. The focal stimulus was optically filtered through a diffuser and a long-wavelength filter. It was presented, at three different stimulation intensities, in the foveal region (central fixation) and in the region corresponding to the optic disk (eccentric fixation, 15 degrees temporal). The amplitude ratio between the foveal and the optic disk response (the latter is supposed to provide an estimate of the residual stray-light effect) was used as a clinical measure. This had the advantage of minimizing interindividual variability in pupil size and stray-light modulation. Another light source used as a stimulus consisted of an array of light-emitting diodes (LEDs) presented through a diffusing filter[12] in a light-adapting Ganzfeld. LED stimuli allow the investigator to explore easily a wide range of stimulus conditions in terms of temporal frequency, intensity, and modulation depth, given the linear properties of this light source under electronic analog or digital control. A new stimulus configuration that has been recently developed[13] is that based on a multi-input system, where many flickering stimuli, modulated according to a pseudo-random binary sequence, are presented simultaneously at different retinal locations. The binary sequence of individual stimuli is such that every stimulus sequence is slightly delayed respective to the others. The signals generated by every stimulus can then be extracted from the mass response by a cross-correlation technique. This approach has proven to be effective in providing a topographical analysis of retinal function with a spatial resolution up to 1.5 degrees within the central 30 degrees of eccentricity.

A limitation of the above techniques is that they can be used only in cooperative subjects with stable and central fixation. Therefore, several methods have been developed that allow the examiner to directly visualize the stimulus when it is focused on the retinal region of interest. Hirose et al[14] used a modified, infrared fundus camera to monitor stimulus location in the macular region. The optics of the fundus camera were modified so that the intensity of both stimulus and background could be independently controlled. Sandberg and Ariel[15] introduced into clinical use another stimulator, built into a hand-held direct ophthalmoscope. By this apparatus, a 42-Hz flickering stimulus of 3 or 4 degrees, could be presented in Maxwellian view in the center of an adapting surround of 10 degrees. The signal acquisition could be electronically interrupted whenever the eye movements or eccentric fixation of the tested eye preclude a steady location of the stimulus on the retinal region of interest.

Recording Techniques. Aside from conventional averaging, frequency domain analyses based on Fast Fourier Transform, Discrete Fourier Transform,[16] digital filtering, and narrow-band selective filtering (lock-in amplifiers[17]) have been applied to steady-state FERG responses evoked by flickering stimuli. These mathematical approaches, which allow isolation of the response's harmonic compo-

nents of interest, provide a superior signal-to-noise ratio and an unambigous estimation of amplitude and phase characteristics of the signals, independent of the waveform properties. Lock-in amplifiers have been used for real-time retrieval of FERGs collected at different temporal frequencies as a function of stimulus modulation depth, thus providing an objective determination of the De Lange function at retinal level.[12]

Recently,[13] cross-correlation analysis has been applied to isolate retinal responses generated by a multi-input stimulus in which every stimulus was modulated according to a specific pseudorandom binary sequence. This methodological approach is based on the assumption that the retinal system behaves, at least in part, linearly. Therefore, from the response component linearly correlated with the stimulus sequence (ie, the so-called first-order kernel[13]), the temporal impulse response of a given retinal location can be accurately described. Cross-correlation analysis of the responses provides a favorable signal-to-noise ratio and can be implemented in an FERG testing system.

FERG Response Components and Their Retinal Generators

The FERG is usually recorded in response to either on-off, low-frequency modulation, or sinusoidal, high-frequency (flicker) modulation of a uniform field. The FERG to on-off stimuli (Fig 1) consists of three main components: an a-wave followed by a b-wave at stimulus onset, and a positive d-wave at stimulus offset. The a-wave represents the leading edge of a larger negative component, called PIII, which is partially obscured by the b-wave intrusion. The similarity between the components of the on-off FERG and those of the full-field ERG evoked by on-off stimulation strongly suggests that both responses share common retinal generators. The a-wave of the on response is presumed to be generated from photoreceptors and off bipolars,[18] the b-wave mostly from on-bipolars, and the d-wave from photoreceptors and off bipolars. The FERG to sinusoidal flicker (Fig 2) has an approximately sinusoidal waveform that is dominated by a component at the same frequency as the stimulus (fundamental component or first harmonic). However, with relatively small stimulus fields (<10 degrees) modulated at low temporal frequencies (10 Hz or less), a component at twice the stimulation frequency (second harmonic) gives

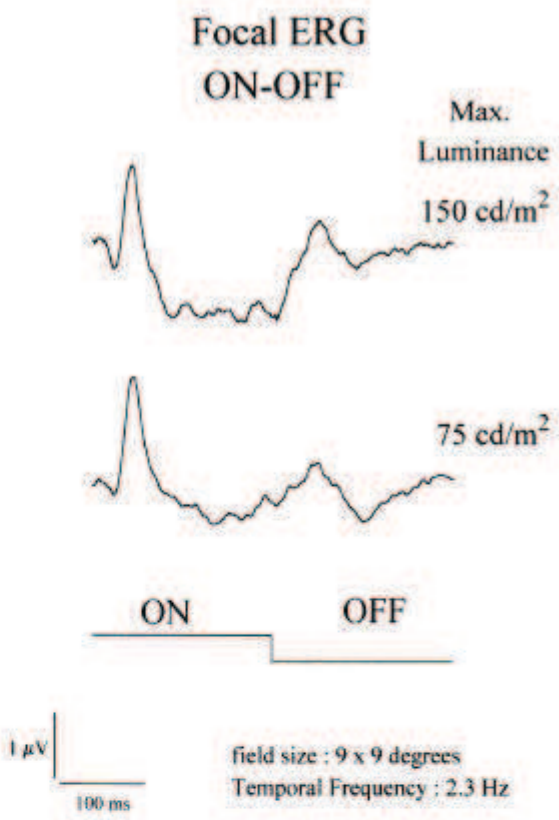

Fig 1. Examples of normal FERG to on-off stimulation.

also a significant contribution to the response waveform.[19-22] Pharmacological experiments have suggested[18] that the fundamental component of the flicker ERG is mainly generated by postreceptoral retinal elements, probably both on and off bipolars. However, other clinical[21] and experimental[23] results suggest that photoreceptors may also give a contribution to the response. Wherever the exact response generators are located, there is now little doubt that the FERG fundamental is mostly generated by outer retinal layers (including both photoreceptors and bipolar cells), because the response is unaffected by retrograde ganglion cell degeneration following optic nerve transection.[24] By contrast, the FERG second harmonic has been shown both in experimental[23] and clinical[21] studies to have an important contribution from generators located in the innermost retinal layers, although they somewhat differ from the generators of pattern ERG.[21] Taken together, the fundamental and second harmonic of the FERG to sinusoidal flicker can provide complementary information about the function of outer and inner retinal layers within the

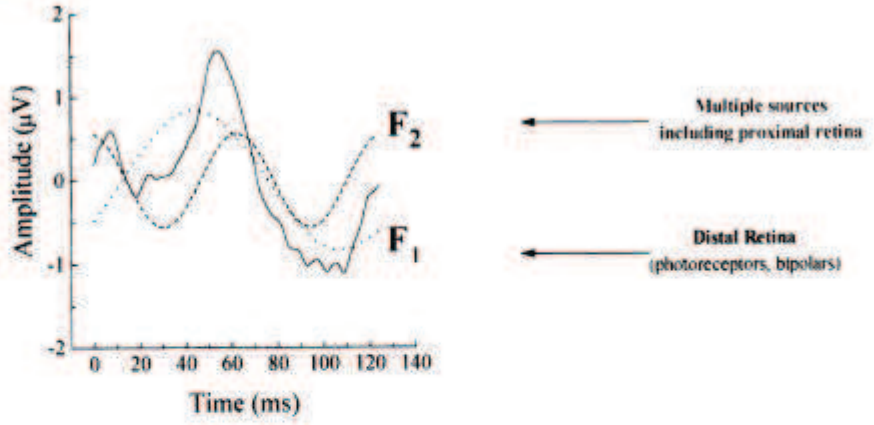

Fig 2. FERG to 8 Hz sinusoidal flicker stimulation.

same, localized retinal region. The linear component of each focal ERG derived with the multifocal technique consists mainly of a negative-positive-negative complex, in which the peak latencies of the individual waves resemble those of the conventional ERG. This linear component has been shown to provide information from the outer retinal layer. Hood et al[25] found a close correlation between the first-order kernel response component and the Ganzfeld ERG in parametric studies.

Clinical Applications of the FERG

The FERG has been largely used to evaluate age-related changes in normal macular function as well as functional abnormalities associated with retinal diseases. FERG amplitude decreases significantly as a function of normal aging. Evaluating foveal (4 degrees) and parafoveal responses in a large sample of normal subjects, Birch and Fish[26] found that foveal but not parafoveal FERG amplitude was negatively correlated with age of subjects, suggesting a selective effect of aging on macular cone function. Similar results have been reported by Bagolini et al.[27] The authors also estimated that, after correction for changes in pupil size with age, FERG amplitude reduction was of the order of 6% per decade in the age range 20 to 80 years. It is worth noting that this FERG age coefficient is comparable with that reported for other electrophysiological (Ganzfeld photopic ERG), psychophysical (visual acuity, cone thresholds) and anatomical (cone density, neuronal density in the central nervous system) parameters. FERG amplitude and implicit time are affected to a variable extent in diseases of macular cones resulting from either macular dystrophies or diffuse retinal degenerations. The foveal (4 degrees) FERG has been reported to be altered in both amplitude and implicit time in Stargardt's disease.[28-30] Significant abnormalities have been reported even in eyes with relatively preserved visual acuity (0.6 to 1.0). Biersdorf[11] estimated that, in eyes with Stargardt's disease with a visual acuity >0.6, the probability of having an abnormal FERG (in amplitude and/or implicit time) was about 64%. Based on their results, Sandberg et al[29] suggested that in early stages of disease the foveal cones are reduced in number with a shortened outer segment. Seiple et al[31] evaluated the FERG to sinusoidal flicker stimuli as a function of temporal frequency. They reported that FERG losses were more marked at low (10 Hz) and high (50 Hz) as compared with intermediate (30 to 40 Hz) temporal frequencies. This pattern of loss was quite consistent across patients and was independent of visual acuity. Multifocal ERG has been applied in Stargardt's disease by Kretshmann et al.[32] They found that the area of dysfunction detected by multifocal ERG was usually larger than expected from psychophysical measurements and morphological alterations. In early stages of disease, a foveal dysfunction was documented, even in patients without fundus changes and good visual acuity. FERG alterations in Best's vitelliform dystrophy have been reported to be milder than those found in Stargardt's disease.[10,31,33-35] Horiguchi et al,[35] however, reported profound abnormalities in the FERG to on-off stimuli (5 degrees) in two patients with normal visual acuity. Seiple et al,[31] in a patient with a visual acuity of 20/60 (0.3), found that FERG amplitude was larger than that of Stargardt's disease patients with comparable acuities.

Several studies[28,31,36,37] investigated the FERG in retinitis pigmentosa. Sandberg et al[36] and Biersdorf[28]

found a fairly good correlation between FERG amplitude and visual acuity of individual patients. Sandberg et al[36] did not find significant changes in the response implicit time, while Biersdorf[28] reported temporal abnormalities in 31% of patients. Seiple et al[12,31,37] reported that, in patients with preserved visual acuity, FERG losses were restricted to high temporal frequencies. By reducing the modulation depth, however, significant losses became apparent also at intermediate and low temporal frequencies, suggesting an early abnormality in cone contrast sensitivity. FERG contrast sensitivity losses were indeed qualitatively similar to flicker sensitivity losses determined psychophysically.[37] On the basis of the FERG and psychophysical results, it has been suggested[37] that macular dysfunction in retinitis pigmentosa can be ascribed to a reduction in the number of macular cones, with normal properties of the remaining photoreceptors. Multifocal ERG has been recently investigated in retinitis pigmentosa by Seeliger et al.[38,39] Eccentricity-dependent changes were found in both amplitude and implicit time, with increasing amplitude losses and time delays toward retinal periphery. Because the multifocal ERG can differentiate between affected and unaffected retinal areas,[32] it appears that this technique can add to the diagnostic information of individual patients with retinitis pigmentosa.

In age-related maculopathy, some investigators[10,26] reported a relatively poor FERG sensitivity, the response being altered consistently only in patients with acuities lower than 0.5. However, in fellow eyes of patients with the unilateral exudative form, Sandberg et al[40] found a significant increase in the FERG (4 degree) implicit time without amplitude abnormalities. More recently, Remulla et al[41] reported a significant association of FERG delays and choroidal perfusion defects in fellow eyes of patients with unilateral exudative maculopathy. It is still unclear whether these FERG abnormalities may be, like psychophysical flicker sensitivity losses, of predictive value for the development of the exudative form in patients in early stages of disease. In full-thickness macular holes, Birch et al,[42] evaluating FERG to 3 degrees stimuli, reported that significant FERG amplitude reductions were detectable only in eyes with lesions larger that 300 μm in size (about 1 degree). Further increases in the size of the hole were paralleled by a decrease in response amplitude. In a prospective study of patients with unilateral macular holes, Birch et al[42] found that a FERG abnormality in the unaffected fellow eye of an individual patient was significantly associated with the subsequent development of a clinically evident full-thickness hole. It therefore appears that the FERG may be of potential predictive value in detecting the future development of a macular hole in patients with unilateral disease.

Patients with central serous chorioretinopathy were investigated by Miyake et al[43] using the FERG to on-off stimuli (10 degrees). In eyes with macular serous detachment, a reduction in amplitude of all FERG components (a-waves, b-waves, and oscillatory potentials) was observed. However, losses in b-wave and oscillatory potentials amplitudes were significantly more marked than those of the a-wave, suggesting a postreceptoral dysfunction that was additive to that of photoreceptors. Two to five months after the resolution of macular detachment, all FERG components recovered in amplitude. However, the recovery was quantitatively lower for the oscillatory potentials than for the other components. This finding suggests that a subclinical dysfunction of inner macular layers could persist even in eyes with an apparently full recovery in central visual function.

Three distinct patterns of FERG abnormalities, each of them related to a different stage of pathology and visual acuity loss, were identified by Miyake et al[43] in aphakic cystoid macular edema. The first pattern consisted of a selective loss of the oscillatory potentials; the second, of a loss of the b-wave and oscillatory potentials with normal a-waves, and the third, of a nonselective loss of all FERG components. These patterns likely reflect different levels of retinal dysfunction extending from inner to outer retinal layers and could provide prognostic cues regarding functional recovery during the course of disease.

FERG abnormalities have also been reported in disorders affecting more selectively inner macular layers, even though, in general, the FERG is relatively less sensitive than the pattern ERG to inner retinal pathologies. In x-linked retinoschisis, FERG b-wave and oscillatory potentials abnormalities, with a normal a-wave, have been reported by Miyake et al[44] in eyes without concomitant abnormalities of the retinal pigment epithelium. An involvement of the latter was instead associated with a loss of amplitude of all FERG components. FERG abnormalities were more evident for stimuli

restricted to the foveal region as compared with those including the parafovea. In inner lamellar macular holes, Falsini et al[45] reported a selective abnormality of the FERG (9 degrees) second harmonic. This differed from that found in eyes with full-thickness holes, which always displayed a loss of both FERG fundamental and second harmonic. Selective abnormalities of the FERG (ie, FERG second harmonic) and/or multifocal ERG have been reported in glaucoma,[46-49] multiple sclerosis,[46,50] diabetes,[51,52] and optic nerve compression,[46] suggesting that the response can sometimes be a useful complement to the pattern ERG in disease affecting the inner retina.

VEPs AFTER PHOTOSTRESS

The mechanism of vision depends on the state of adaptation of the photoreceptors: the bleaching of a portion of the retina alters the adaptation process with the consequent formation of a scotoma; the return to the normal condition depends on the integrity of the complex retinal pigmented epithelium-photoreceptors, functionally crucial for the resyntesis of macular pigment.

In the clinical evaluation of the central retina, Baillart[53] suggested to measure the period of recovery in visual acuity after dazzling of the macular region with an ophthalmoscope. This test, called the macular photostress test (MPST), was indicated as an index of the "functional macular reserve."[53] In a clinical setting, the MPST has been applied in the past in normal subjects[54-56] and in patients with maculopathies,[57-60] diabetic retinopathy,[57,61,62] or glaucoma.[63] The test has proven to be sufficiently reliable and clinically useful for detecting early dysfunction.

An objective method for evaluating the recovery of macular function after bleaching is that based on VEPs, which represent mainly the response of primary visual cortex elicited by visual stimuli. Lovasik[64] and Franchi et al[65] first studied the effects of macular dazzling on the pattern-evoked VEPs. This method, called "VEP after photostress," has been proposed as an index of the macular function.[65]

Photostress induces transient VEP changes consisting of an increase in response latency and a decrease in amplitude. When serial VEP recordings are obtained at discrete time intervals (ie, every 20 seconds) after bleaching, the recovery of VEP waveform can be evaluated. The time needed for the VEP to recover to the prebleach baseline status (ie, the recovery time after photostress) ranges in normal subjects between 68 and 78 seconds.[66]

Methodological Procedures

The three fundamental steps in performing the VEP after photostress test are: (1) recording of basal VEP, (2) dazzling of the central retina, and (3) recording of VEPs after dazzling and evaluation of the recovery time after photostress.

Recording of "basal VEP." The subjects under examination are seated in a semidarkened room, acoustically isolated, in front of the display, which is surrounded by a uniform field of a luminance of 5 cd/m^2. Before the experiment, each subject has been adapted to the ambient room light for 10 minutes, with natural pupil (diameter of about 5 mm). The stimulation is monocular, after full occlusion of the fellow eye.

The visual stimuli consist of checkerboard patterns (contrast 70%: mean luminance 100 cd/m^2) generated on a TV monitor and reversed in contrast at the rate of two reversals/s. At the viewing distance of 114 cm, the single check edge subtends 15 minutes of visual arc. The screen of the monitor subtends 18 degrees, and to maintain stable fixation, a red small target (0.5 degrees) is placed in the center of stimulation field.

Cup-shaped electrodes of Ag/AgCl are fixed with collodion in the following positions: active electrode in Oz, reference electrode in Fpz; ground in left arm. The interelectrode resistance is kept below 3 kΩ. VEP signals are amplified (gain 20000), filtered (band pass 1 to 100 Hz), sampled with 12-bit resolution, and averaged with automatic artifact rejection.

The recording session begins with a preliminary experiment in which at least two VEPs are recorded (analysis time 500 ms, averaging over 100 stimulus periods), and the loss in recording time caused by artifacts is noted. The resulting waveforms are stored and superimposed to check for the repeatability of the results. The VEP response is characterized by several waves with three peaks of negative-positive-negative polarity, respectively. In normal subjects, these peaks have the following times to peak (peak latency): 75, 100, and 145 ms. After this preliminary trial, the basal VEPs are recorded by reducing the average to 40 events per trial. Responses are accepted only if no more than two sweeps are discarded because of artifacts. The basal

VEP waveform is kept on display on the computer screen. Six consecutive records are taken every 20 seconds, and the corresponding records are compared with the basal response to check intratest reproducibility.

Dazzling of the central retina. Photostress is induced for a duration of 30 seconds by means of a circular diffusing surface (the bulb of a 200-W lamp). Subject fixates at the center of the circular surface from a distance of 20 cm. The bleaching lamp usually produces a central relative scotoma of 6 degrees in diameter. During the photostress procedure, the pupil diameter is usually about 2 mm.

Recording of VEP after dazzling and evaluation of the recovery time after photostress. Immediately after the end of photostress, fixation is shifted to the pattern stimulus, and recording of VEPs is started. The small red target is perceived by all subjects notwithstanding the presence of scotoma. Several records are taken for successive periods of 20 seconds each and stored on the computer screen. The recordings are performed until the VEP waveform is superimposable on the basal record, and the corresponding time is considered as recovery time after photostress (RT).

In each subject tested, the signal-to-noise ratio (SNR) is estimated by recording noise response while the monitor is screened by using a piece of cardboard. We accept VEP after photostress responses as only those with a SNR > 2.

Clinical Applications of VEP after Photostress

The standard curve responses of VEP recordings after photostress (changes in P100 peak latency and in N75-P100 peak amplitude) in normal subjects are shown in Fig 3. At 20 seconds after photostress, an increase in P100 peak latency and a decrease in N75-P100 peak amplitude is observed. At 40 and 60 seconds after photostress, the P100 peak latencies are shorter than the 20-second value, but still longer than in the basal P100 peak latency. The N75-P100 peak amplitude increases from the value observed at 20 seconds, but without reaching the basal value. In normal subjects, the VEPs are superimposable to the basal VEPs (RT) at 72.8 ± 1.6 seconds.

In the analysis of VEP after photostress, the following parameters are usually considered: the mean increment (MI) in P100 peak latency (latency MI), the mean percentage decrease (MPD) in

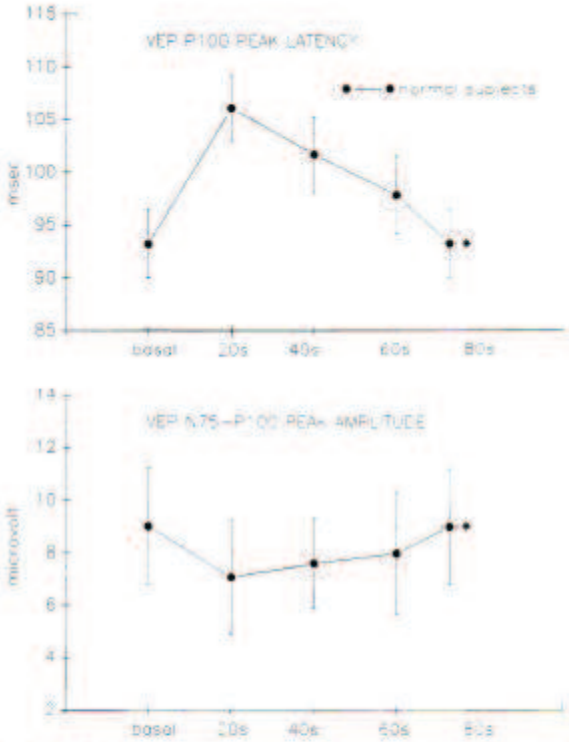

Fig 3. Graphic representation of mean values of the VEP P100 peak latency and N75-P100 peak amplitude observed in normal subjects in the basal condition and 20, 40, 60, and 80 seconds after photostress. Error bars represent one standard deviation of the mean. The mean recovery time after photostress (*) is 72.8 ± 1.6 seconds.

N75-P100 amplitude (amplitude MPD) observed at 20, 40, and 60 seconds after dazzling, and the RT.

Patients with different pathological conditions display after photostress a response curve similar to that of controls. Examples of VEPs after photostress recorded in a normal subject and in individual patients are shown in Fig 4.

Subjects with maculophathies. In patients with different maculopathies (age-related, Stargardt's disease, Best's disease, cone dystrophy [Parisi, 1998, unpublished data]) the basal VEP showed a delay in P100 latency and a reduction in N75-P100 amplitude.

After photostress, all patients showed higher MLI and more marked MPAD than in control subjects. In addition, an RT longer than in controls (mean 114 ± 2 s) was observed.

Ocular hypertension (OHT) and primary open angle glaucoma (POAG). OHT and POAG patients showed a delay in basal VEP P100 latency with respect to control subjects, whereas basal VEP N75-P100 amplitudes were reduced in POAG

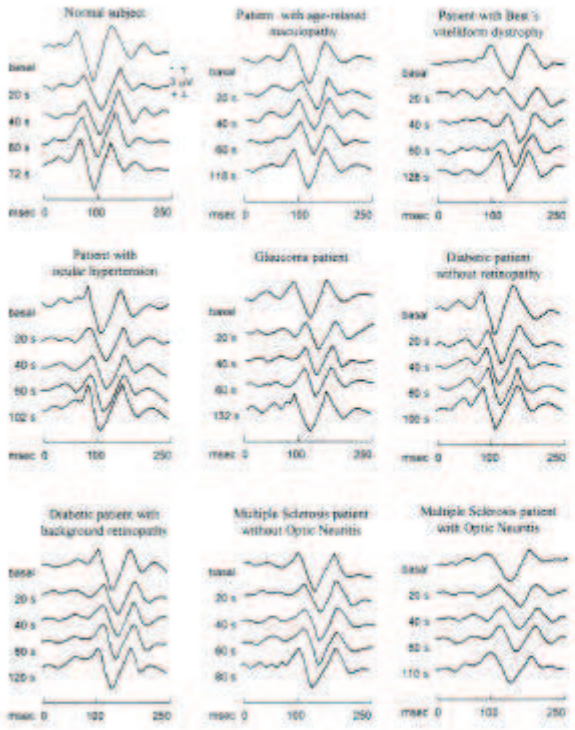

Fig 4. Examples of VEP recorded in basal condition and 20, 40, and 60 seconds after photostress in a normal subject and in patients with different pathologies. Note that in each recording series, the last VEP waveform is superimposable on the basal record and the corresponding time is considered as RT.

patients only. The VEP response after photostress was impaired in both OHT and POAG patients: in fact, higher MLI, more marked MPAD, and longer mean RT (OHT: 95.1 ± 6.5 seconds; POAG: 113.2 ± 11.8 seconds) were observed in patients as compared with control subjects.[66]

Artificially increased intraocular pressure (IOP) was obtained in normal subjects by using a Baillart ophthalmodynamometer to evaluate the effects of acutely raised IOP on the VEP after photostress: IOP was increased up to a value equal to half the systolic arterial pressure. The results showed that transient IOP elevation induces changes on the VEP response after photostress that are similar to those observed in OHT and POAG patients: higher MLI, more marked MPAD, and longer RT (114.2 ± 5.1 seconds), when compared with a condition of normal IOP, were found.[67]

Diabetes: newly-diagnosed, without retinopathy and with retinopathy. Diabetic patients newly diagnosed (mean duration of disease less than 6 months), without retinopathy (duration of disease between 1 and 20 years and no fluoroangiographic signs of retinopathy) and with background retinopathy (Klein level 3 to 5), had basal VEPs with P100 latency delayed and N75-P100 amplitude reduced with respect to the values observed in age-matched controls.[68-73]

The VEP responses after photostress in newly diagnosed diabetics were similar to those of controls (RT: 73.6 ± 1.2 seconds), whereas impaired responses were observed in diabetics with or without retinopathy. In diabetic patients with and without retinopathy, higher MLI, more marked MPAD, and delayed RT (no retinopathy patients: 88.17 ± 10.48 seconds; retinopathic patients: 113.33 ± 12.9 seconds) when compared with those of controls were found. No correlations between duration of disease and MLI, MPAD, and RT were observed.[68-71]

Multiple sclerosis: with (MSON) or without optic neuritis (MSWO). In MSON and MSWO patients, basal VEP P100 latencies and N75-P100 amplitudes were delayed and reduced, respectively, when compared with those of age-matched controls. VEP recorded after photostress in MSWO patients showed MLI, MPAD, and RT (71.2 ± 4.7 seconds) similar to those of controls, whereas MSON patients had higher MLI, more marked MPAD, and longer RT (97.8 ± 5.1 s) when compared with control values.[74]

Carotid occlusive disease. VEPs after photostress have been investigated in carotid occlusive disease by Bianchini et al[75] and Franchi et al.[76] It was found that an improvement of the response amplitude after photostress paralleled the restoration of cerebral blood flow after endoarterectomy.

CONCLUSIVE REMARKS

The VEP recovery to its basal state after photostress has been related to the resynthesis of photopigment,[65] and because a longer RT was observed in patients with carotid occlusive disease,[75,76] an adequate ocular blood flow appears to be essential for this process. Furthermore, the process seems to be not only related to the function of the outer retina, because the integrity of inner retinal layers may also play a role. Support for this suggestion comes from the evidence that a longer RT can be observed in glaucoma,[66,67] diabetes,[68-71] and multiple sclerosis,[74] which are known to be associated, at least in their early stages, with a selective impairment of the inner retina.

Although FERG may provide direct information about the extent and the sites of macular dysfunction, the VEP after photostress represents an objective, although not specific, index of the dynamic properties of macular performance after exposure to intense light stimulation. For both techniques, some of the fields of clinical application (eg, different genetic subtypes of retinal dystrophies, hereditary or some acquired optic neuropathies) have not yet been explored in detail. In this context, the combined use of both focal electroretinography and VEP after photostress appears to be promising for gaining further insights into the diagnosis and pathophysiology of macular dysfunction.

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