Macular Function in Eyes with Open-Angle Glaucoma Evaluated by Multifocal Electroretinogram

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PURPOSE. To evaluate macular function in patients with open-angle glaucoma (OAG) by means of multifocal electroretinogram (mfERG).

METHODS. Twenty-four OAG patients (mean age 54.6 ± 9.1 years) and 14 age-similar controls were enrolled. OAG patients had intraocular pressure (IOP) less than 18 mm Hg with topical medical treatment, 24-2 visual field (Humphrey Field Analyzer [HFA]) with mean deviation (MD) between –2 and –12 dB, and corrected pattern standard deviation (CPSD) between +2 and +10 dB and no history or presence of cataract and/or macular disease. MfERGs in response to 61 M-stimuli presented to the central 20° of the visual field were assessed in OAG patients (24 eyes) and in controls (14 eyes). Ring (R) analysis was performed every five retinal eccentricities in areas between the fovea and midperiphery: 0° to 2.5° (R1), 2.5° to 5° (R2), 5° to 10° (R3), 10° to 15° (R4), and 15° to 20° (R5). MfERG response amplitude density of the N1-P1 components (N1-P1 RAD, nV/deg²) and P1 implicit time (P1 IT, ms) of the first-order binary kernel were measured for each ring.

RESULTS. OAG patients showed a significant (P < 0.01) decrease in N1-P1 RADs and an increase in P1 IT in both R1 and R2 with respect to controls. The reduction in N1-P1 RADs was significantly (P < 0.01) correlated with HFA MD and CPSD. No other significant differences between OAG and controls were found.

CONCLUSIONS. OAG patients show macular dysfunction detectable by the mfERG technique. Since the mfERG N1-P1 component is thought to be generated by preganglionic elements (photoreceptors and OFF bipolar cells), our data support the functional impairment of the neural generators of the macular region in patients with glaucoma. (Invest Ophthalmol Vis Sci. 2012;53:6973–6980) DOI:10.1167/iovs.12-10256

Macular function can be evaluated electrophysiologically in a steady-state condition by recording of focal ERG (FERG), or in a dynamic status by recording of visual evoked potentials (VEPs) after photostress.1–9 Both techniques have been used to study macular function in patients affected by open-angle glaucoma (OAG).10,11 In OAG patients, FERG and VEP abnormalities have been described.10,12 In particular, Machida et al.11 saw an abnormality in the ERG that was ascribed to ganglion cells.

Two concerns exist about OAG macular damage and the electrophysiologic evaluation. First, in OAG patients, pattern ERG (PERG) recordings showed an impairment of the ganglion cells and their fibers,13,14 while FERG recordings suggested a dysfunction of preganglionic elements secondary to the pressure damage.12,15,16 Second, a focal stimulus, testing local regions, has been used to study the retinal damage in OAG.17 PERG and FERG responses, however, cannot provide a measure of pathologic changes in different retinal areas or a topographical assessment of retinal activity. The multifocal ERG (mfERG), instead, can examine the retina giving a clear indication of central and peripheral electrical responses.18 The multifocal technique allows detection of the bioelectric responses obtained from localized retinal areas and in particular from the macular region, which are driven largely by the preganglionic components, for the greatest cone cell density.19 Moreover, while FERG allows the electrophysiologic evaluation of preganglionic elements in response to luminance stimuli presented in a restricted part of the central retina (4–9 retinal degrees),1,2,20 the mfERG technique is useful for assessing responses of several different retinal areas enclosed between 1° and 20° of eccentricity from the fovea.21–23 In fact, while the FERG recording collects the contribution from the entire macular region, mfERG ring analysis allows separating selective measures of bioelectric responses obtained from localized macular areas.22,23 This means that recording mfERG, testing visual acuity, and performing automated visual field analysis make it possible to explore the entire central retina and, through appropriate data analysis, to receive selective information regarding the function of localized retinal regions.22–24

A kernel analysis applied to mfERG responses can be used to assess nonlinear functions of the visual system.25 Since the first-order kernel of mfERG originates primarily in the preganglionic elements (photoreceptors and bipolar cells),26 and several studies have reported altered mfERG in OAG and in ocular hypertension,27–32 the present authors believed it would be interesting to clarify whether a dysfunction of the preganglionic elements may occur in OAG.

The aim of the present study was to evaluate the function of the preganglionic elements of the macular region by means of mfERG recordings with respect to the more peripheral retinal areas in OAG patients.

METHODS

Patients

Fourteen eyes of 14 normal control subjects (range: 40–70 years, mean age 51.7 ± 6.0 years) and 24 eyes of 24 patients (range: 42–72 years,
The research followed the tenets of the Declaration of Helsinki. The protocol was approved by the local institutional review and ethical boards. Upon recruitment, informed consent was obtained from each subject enrolled in the study.

**MfERG Recordings**

VERIS Clinic 4.9 (Electro-Diagnostic Imaging, San Mateo, CA) was used for the mFERG assessment by our previously published method.22–24

The multifocal stimulus, consisting of 61 scaled hexagons, was displayed on a high-resolution, black-and-white monitor (size, 30 cm width and 30 cm height) with a frame rate of 75 Hz. The array of hexagons subtended 20° of the visual field. Each hexagon was independently alternated between black (1 cd/m²) and white (200 cd/m²) according to a binary m-sequence. This resulted in a contrast of 99%. The luminance of the monitor screen and the central fixation cross (used as target) was 100 cd/m². The m-sequence had 215 elements, and total recording time was approximately 4 minutes. Total recording time was divided into eight segments. Between segments, the subject was allowed to rest for a few seconds. Focusing lenses were used when necessary. In order to maintain a stable fixation, a small red target (0.5°), which was perceived by all subjects tested, was placed in the center of the stimulation field. At every mfERG examination, each patient positively reported that he or she could clearly perceive the cross fixation target. A camera provided an image of the eye, which was displayed on the computer screen so that fixation could be continuously monitored.

In all OAG tested subjects (OAG patients and controls), mERGs were binocularly recorded in eyes with pupils maximally dilated to 7 to 8 mm after application of 1% tropicamide drops. Pupil diameter was measured by an observer (GG) by means of a ruler and a magnifying lens and stored for each tested eye. The cornea was anesthetized with 1% dicaine. mERGs were recorded bipolarly between an active electrode (contact electrode Dawson-Trick-Litzkow [DTL]) and a reference electrode (Ag/AgCl electrode placed on the ipsilateral temple). A small Ag/AgCl skin ground electrode was placed at the center of the forehead. Interelectrode resistance was less than 5 KΩms. A binocular mFERG recording was preferred to help subjects have a stable target fixation. Eyes that exhaustively met the inclusion criteria were selected from each patient. When both eyes could be selected, the eye with the highest R1 to R5 N1-P1 response amplitude densities (RADS) was considered for statistical analysis (see below) according to the criteria used in our previously published work.23

The signal was amplified (gain 100,000) and filtered (band pass 1–100 Hz) by BM 6000 (Biomedica Mangoni, Pisa, Italy). After automatic rejection of artifacts (by VERIS Clinic 4.9 software), the first-order kernel response, K1, was examined. We analyzed the averaged response obtained from five concentric annular retinal regions (rings) centered on the fovea: from 0° to 2.5° (ring 1, R1), from 2.5° to 5° (ring 2, R2), from 5° to 10° (ring 3, R3), from 10° to 15° (ring 4, R4), and from 15° to 20° (ring 5, R5). For each obtained averaged response we evaluated the amplitude densities between the first positive peak, N1, and the first positive peak, P1 (N1-P1 RAD, expressed in nV/deg²), and the implicit time of the first positive peak (P1 IT).

The MfERG ring analysis was selected to differentiate changes in the bioelectrical responses of the central macular region with respect to the more peripheral retinal areas.

**Signal-to-Noise Ratio**

MfERG signal-to-noise ratio (SNR) was estimated following the methodology discussed by Hood and Greenstein.22 Briefly, a noise window equal in length to the period within which the response was analyzed was set as part of the record, but it was included in a temporal window that was assumed to contain little or no response. Signal temporal window for the mFERG was 0 to 80 ms. SNR was defined as the ratio of the root mean square (RMS) signal plus noise (measured in the signal temporal window) of a given record to the mean RMS of all
noise windows (61 for the mfERG). A SNR $\geq 3$ was accepted for mfERG measurements. A recordable response had to have a SNR $\geq 3$.

### Statistics

For all parameters, a 95% confidence limit was obtained from age-

<table>
<thead>
<tr>
<th>OAG Patients</th>
<th>A</th>
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<th>HFA CPSD</th>
<th>HFA FT</th>
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<td>OAG 24</td>
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<td>-5.26</td>
<td>2.62</td>
<td>34</td>
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### RESULTS

The clinical characteristics of OAG enrolled eyes, including demographic, perimetric, and electrophysiological data, are reported in Table 1.

Figure 1 shows examples of mfERG recordings (all traces and ring traces) and relative HFA performed on one control eye and on three different OAG eyes.

Table 2 reports the mean data and statistical analysis of age, as well as all perimetric and electrophysiological values observed in control and OAG eyes. The number of normal or abnormal values for HFA FT, MD, and CPSD, and mfERG N1-P1 RADs and P1 ITs detected in the OAG group is also reported.

Considering the individual outcomes, two OAG eyes presented HFA FT abnormal values. In ring 1, 19 and 20 eyes were abnormal for N1-P1 RADs and P1 ITs, respectively. In ring 2, normal values for N1-P1 RADs and P1 ITs were found in 21 and 18 eyes, respectively. In the more peripheral rings (R3, R4, and R5), all OAG eyes showed normal N1-P1 RADs and P1 ITs.

In Figures 2 and 3, individual values of N1-P1 RAD and P1 IT recorded in OAG eyes from ring 1 and ring 2 are plotted as a function of corresponding mean values of HFA MD and CPSD, respectively.

In ring 1 and ring 2, the reduced N1-P1 RADs were significantly ($P < 0.01$) correlated with the HFA MD and CPSD. No statistically significant correlations ($P < 0.01$) were found between P1 ITs and perimetric (HFA MD and CPSD) parameters or between HFA FT and N1-P1 RADs or P1 ITs.

In the more peripheral rings (R3, R4, and R5), no statistically significant correlations ($P > 0.01$) were found between perimetric (HFA FT, MD, and CPSD) and electrophysiological (N1-P1 RADs or P1 ITs) data.

On average, in OAG eyes, mfERG N1-P1 RADs and P1 IT values differed significantly ($P < 0.01$) from controls exclusively in ring 1 (0–2.5°) and ring 2 (2.5–5°). No significant ($P > 0.01$) differences between OAG and control eyes in FT, and in
the mfERG parameters (N1-P1 RADs and P1 ITs) in the more peripheral rings (R3, R4, and R5), were observed.

**DISCUSSION**

Our aim was to assess the function of the preganglionic elements of the macular region in OAG patients by evaluating electrophysiological (mfERG) responses.

With respect to controls, in the OAG eyes with IOP values <18 mm Hg with topic beta-blocker monotherapy, a significant reduction of mfERG N1-P1 RADs was detected exclusively in R1 and R2 (0–5 central degrees), as well as a significant increase of P1 ITs. This may suggest a dysfunction selectively localized in the macular area. Because of our careful observation of control subjects and OAG patients during the mfERG recording (see our very stringent inclusion criteria), we believe that the observed abnormalities cannot be ascribed to losses of fixation or to the presence of early cataract or maculopathy. Our results are in agreement with previous suggestions obtained by psychophysical (color vision and contrast sensitivity) and other electrophysiological (VEPs after photostress, FERG, and PERG) measurements showing macular impairment in glaucoma patients.\[10,11,15,17,43\] Since the cited electrophysiological techniques (VEPs after photostress, FERG, and PERG) cannot provide a measure of functional changes in localized retinal areas within the macular region, we analyzed the mfERG responses that are able to provide information about the function of preganglionic elements from areas enclosed between 0° and 20° of eccentricity from the fovea.\[18\]

In fact, according to a framework proposed by Hood,\[26\] a disease that acts largely at the photoreceptoral level will decrease the amplitude of the mfERG, while damage of the
inner retina (i.e., amacrine cells, ganglion cells, and their connections) and the optic nerve head can only alter the mfERG waveform, producing small changes in amplitude. Because damage of the ganglion cells or optic nerve does not decrease the mfERG amplitude, an abnormal mfERG provides strong evidence for preganglionic dysfunction.

In particular, the outer and partially inner retinal layers have been debated as the most probable generators of the mfERG first-order kernel responses. Hood et al. also described the first-order kernel as originating from photoreceptors and bipolar cells, in a study of the blockage of signal transmission to ON bipolars in nonhuman primates, as a working model of the human mfERG. Accordingly, we studied the first-order kernel of mfERG responses selectively, also following previous studies reporting that deficits of the outer retinal components in glaucomatous eyes are specifically reflected in disorders of

The RADs and ITs were derived from five concentric annular retinal regions (rings) centered on the fovea. We analyzed the N1-P1 RADs derived from 0° to 2.5° (R1), from 2.5° to 5° (R2), from 5° to 10° (R3), from 10° to 15° (R4), and from 15° to 20° (R5). ANOVA was one-way analysis of variance between groups, \( F_{1,37} \). N, number of eyes; Nr, number of eyes inside the normal limits; Ab, number of eyes outside the normal limits. Normal limits were obtained from control subjects by calculation of mean values +2 SD for IT and CPSD and mean values –2 SD for MD, FT, and RADs.

### Table 2: Mean Values ± SD of Age (years), HFA 24-2 MD (dB), CPSD (dB), and FT (dB), and mfERG RAD (nV/deg²) and mfERG P1 IT (ms) Values Observed in Control Eyes (C) and OAG Eyes

<table>
<thead>
<tr>
<th></th>
<th>C, ( N = 14 )</th>
<th>OAG, ( N = 24 )</th>
<th>( F_{1,37} )</th>
<th>( P )</th>
<th>Nr</th>
<th>Ab</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>51.7 ± 6.0</td>
<td>54.6 ± 9.13</td>
<td>1.12</td>
<td>0.296</td>
<td></td>
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<tr>
<td>HFA MD</td>
<td>-0.554 ± 0.928</td>
<td>-4.842 ± 2.38</td>
<td>41.1</td>
<td>&lt;0.001</td>
<td>0</td>
<td>24</td>
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<tr>
<td>HFA CPSD</td>
<td>1.30 ± 0.17</td>
<td>4.19 ± 2.44</td>
<td>19.36</td>
<td>&lt;0.001</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>HFA FT</td>
<td>35.6 ± 1.74</td>
<td>34.3 ± 2.18</td>
<td>3.67</td>
<td>0.0632</td>
<td>22</td>
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<tr>
<td>R1 RAD</td>
<td>118.3 ± 15.80</td>
<td>71.6 ± 27.06</td>
<td>34.65</td>
<td>&lt;0.001</td>
<td>5</td>
<td>19</td>
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<tr>
<td>R1 IT</td>
<td>50.2 ± 1.55</td>
<td>35.8 ± 2.74</td>
<td>47.91</td>
<td>&lt;0.001</td>
<td>4</td>
<td>20</td>
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<tr>
<td>R2 RAD</td>
<td>47.5 ± 3.80</td>
<td>33.8 ± 9.81</td>
<td>24.45</td>
<td>&lt;0.001</td>
<td>3</td>
<td>21</td>
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<tr>
<td>R2 IT</td>
<td>30.7 ± 1.47</td>
<td>34.7 ± 2.01</td>
<td>42.09</td>
<td>&lt;0.001</td>
<td>6</td>
<td>18</td>
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<tr>
<td>R3 RAD</td>
<td>22.8 ± 4.33</td>
<td>22.0 ± 6.19</td>
<td>0.18</td>
<td>0.675</td>
<td>24</td>
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<tr>
<td>R3 IT</td>
<td>35.2 ± 2.47</td>
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<td>5.40</td>
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<tr>
<td>R4 RAD</td>
<td>20.2 ± 6.54</td>
<td>15.3 ± 4.23</td>
<td>5.35</td>
<td>0.027</td>
<td>24</td>
<td>0</td>
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<tr>
<td>R4 IT</td>
<td>52.8 ± 2.96</td>
<td>34.6 ± 2.05</td>
<td>4.90</td>
<td>0.035</td>
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<td>R5 RAD</td>
<td>16.5 ± 3.33</td>
<td>14.1 ± 9.98</td>
<td>4.42</td>
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<td>R5 IT</td>
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<td>38.9 ± 3.06</td>
<td>0.99</td>
<td>0.327</td>
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</table>

**Figure 2.** Individual mfERG N1-P1 response amplitude densities (RADs) and P1 implicit time recorded in the central 0° to 2.5° (ring 1) plotted against the corresponding values of MD and CPSD of the Humphrey 24-2 visual field in OAG eyes. Pearson’s test was used for the linear regression.
the first-order kernel. A general depression of the first-order kernel in OAG eyes has also been found by Vaegan and Buckland, who suggested a uniform reduction in mfERG responses related to choriocapillary perfusion deficit and microcirculatory damage. This is in agreement with histological studies in postmortem human eyes, which describe a lower density of capillaries of the choriocapillaris in the macular choroid of OAG patients when compared to control eyes.

Our remarkable finding consisted of an impairment localized in the 5 central degrees with a functional sparing of those preganglionic elements enclosed between 5 and 20 central degrees. This suggests a selective dysfunction of the foveal cell population. Nevertheless, this impairment is not sufficient to lead to a loss in sensitivity. In fact, only two of our OAG patients showed a reduction in the HFA FT, which was not statistically different between OAG and control subjects.

The observed dysfunction of the innermost area of the macular region is supported by recent findings suggesting morphological changes of the integrity of the cone outer segments in OAG patients with central visual defects. These structural abnormalities, which are potentially due to underlying decreased choroidal blood flow in the macula, were documented via reduced directional reflectance of foveal cone photoreceptors. Additionally, histological studies by Nork et al. have described signs of photoreceptoral swelling, not loss, in human outer retinas from OAG eyes, suggesting that changes of cone morphology are due to chronically elevated intraocular pressure. The authors proposed a mechanism of cone ischemia due to reduced choroidal blood flow in OAG eyes, leading to a reduced reuptake of glutamate. The high levels of extracellular glutamate would eventually result in secondary overstimulation and loss of second-order neurons and retinal ganglion cells. In this regard, Pelzel et al. described a reduction in the expression of red/green and blue cone opsin in monkey retinas with chronic ocular hypertension by means of a quantitative mRNA analysis and in situ hybridization studies. However, they did not observe a rodopsin mRNA loss, thus concluding that ocular hypertension leading to glaucoma selectively affects cone photoreceptors of the outer retina. Nevertheless, these studies did not provide direct information about morphological changes exclusively localized in the foveal region. In the past, there was an extensive debate surrounding this argument. In fact, previous histological studies conducted on human glaucomatous eyes reported either photoreceptor preservation or photoreceptor loss. Also electrophysiological reports vary greatly. Studies conducted with full field/flash ERG in glaucoma have shown changes in scotopic and/or photopic responses, thereby suggesting generalized photoreceptor damage; however, a more recent study in experimental glaucoma reported normal photopic amplitude parameters. In addition, the regional retinal functional impairment in glaucoma has been argued for years. Previous mfERG and multifocal pattern ERG studies reported limited success in localizing inner retinal layer damage in OAG, and only recent evidence has shown regional outer retinal dysfunction in the central 24° in advanced glaucoma. Therefore, at present, the mechanisms inducing the dysfunction of foveal photoreceptors in OAG still remain unclear.

We used two rather overlapping methods to explore the same area (the mfERG was derived from the central 20°, and the HFA explored the central 24°), but we did not aim to compare results provided by psychophysical (HFA 24-2) and electrophysiological (mfERG) techniques. In fact, in our study, we correlated the reduction of the N1-P1 mfERG amplitudes and the increase of P1 IT detected in the two more central

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**Figure 3.** Individual mfERG N1-P1 response amplitude densities (RADs) and P1 implicit time recorded in the central 2.5° to 5° (ring 2) plotted against the corresponding values of MD and CPSD of the Humphrey 24-2 visual field in OAG eyes. Pearson's test was used for the linear regression.
rings (R1–R2) with the generally used perimetric indices of glaucomatous damage (HFA MD and CPSD),\textsuperscript{63} exclusively to assess whether the dysfunction observed in the macular area could be related to the grade of severity of OAG disease. We found a significant correlation between HFA MD and CPSD parameters and the NI-PI mfERG RADS. This suggests that the grade of severity of OAG disease may influence the observed macular dysfunction. By contrast, changes in HFA MD and CPSD did not correlate significantly with the increase of mfERG P1 IT. The lack of significant correlation between the perimetric and the mfERG IT values can be explained by lower intragroup variability in the analysis of IT values: IT SD values were lower than 8% of the mean values, while RADS SD values were greater, with approximately 30%.

In the more external rings (R3–R5, 5–20°), we did not find any statistically significant differences in RADS and ITs between OAG and control eyes. Nevertheless, notwithstanding any statistically significant differences in RADs and ITs were greater, with approximately 30%.

In conclusion, our findings lead us to believe that in OAG patients, a dysfunction of the preganglionic elements localized in the foveal area may occur and is detectable by mfERG recordings. Different quantitative changes in this dysfunction may appear at different stages of the glaucoma disease, thus perhaps reflecting a complexity of pathophysiologic mechanisms.\textsuperscript{20,65}

\section*{Acknowledgments}

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\section*{References}


