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Correlation between Goldmann perimetry and maximal electroretinogram response in retinitis pigmentosa

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Abstract. To evaluate the relationship between Goldmann perimetry and maximal electroretinographic responses in patients with retinitis pigmentosa, analyses were performed on 220 affected subjects and separately on two subgroups with autosomal dominant (n = 35) and autosomal recessive (n = 29) inheritance. Electroretinograms were recorded averaging 100 iterations elicited with a 20-lux/s, 0.5-Hz white flash ganzfeld stimulation. The peripheral isopters of the visual fields were delimited with I4e, IIIe and V4e targets, measured on conventional perimetry charts with a light pen and expressed in square centimeters. Unlike most previously published reports, this investigation showed a definite correlation ($p = 0.0001$) between maximal electroretinographic response amplitude and visual field areas. This correlation was more evident for I4e and IIIe isopters ($r = 0.89$ and 0.87, respectively) than for V4e isopter ($r = 0.69$). This phenomenon appears to be related to distortion occurring on standard isometric charts and to spatial summation effects in the peripheral field. Such correlations held for both the autosomal dominant and autosomal recessive subgroups. It appears that, if enough accuracy is provided, maximal electroretinographic responses and Goldmann visual fields are both good measures of the remaining functioning retina in nonsyndromic retinitis pigmentosa, irrespective of inheritance models and dystrophic patterns.

Abbreviations: ADRP – autosomal dominant retinitis pigmentosa, ARRP – autosomal recessive retinitis pigmentosa, RP – retinitis pigmentosa, VF – visual field.

Introduction

The examination of a patient affected with retinitis pigmentosa (RP) is mainly based on the combination of psychophysical variables (e.g., visual acuity, visual field, dark adaptation) and objective measurements. Within the latter group, the electroretinogram (ERG) provides essential information on the amount and quality of functioning retina left. Different relationships of ERG to visual field (VF) measures have been reported. Most studies have emphasized the existence of a substantial correlation between these two methods when

performed under identical selective conditions, i.e., comparing photopic and scotopic results separately [1–4]. Conversely, the frequent occurrence of a substantial discrepancy between maximal ERG responses and Goldmann perimetry has been reported [1, 3, 5–9]. According to these studies, it is not surprising to have barely recordable signals from patients with relatively well-maintained VF outer isopters.

Previous studies on smaller samples of patients strongly suggested a definite correlation between ERG and VF areas [10, 11]. It was therefore the purpose of this investigation to evaluate in a larger sample of patients with RP whether visual field testing and ERG, as they can be routinely performed by every ophthalmologist, could be correlated or whether they rather varied independent of one another and, if so, to what extent. In addition, the same relationship was verified for subgroups of patients identified on the basis of inheritance, to assess possible differences related to genetically determined factors.

Subjects and methods

A group of 220 consecutive patients with typical RP were randomly selected from our case material for this investigation to avoid interference by selection bias (i.e., irrespective of age, gender, inheritance, stage of the disease, ongoing therapeutical trials or other possible biasing characteristic). The diagnosis of RP was based on the clinical, genetic and instrumental criteria established by Marmor *et al.* [12]. The age of the sample ranged from 10 to 84 years (average, 39 ± 15.6 [standard deviation]). ERG and clinical data were consistent in all cases with a rod-cone degenerative pattern (inclusion criterion). Patients who showed a definite cone-rod pattern or who were affected with RP syndromic forms (i.e., Usher or Laurence-Moon-Bardet-Biedl syndrome) were not included in this investigation (exclusion criteria).

On the basis of the inheritance pattern, two further groups were extrapolated. Group 1 consisted of 35 patients with autosomal dominant RP (ADRP), with a mean age of 33.8 ± 14.5 years (range, 12–62 years). All subjects showed a diffuse pattern of degeneration, with neither sectoral pigmentation nor altitudinal or quadrantic VF defects; this was consistent with type 1 ADRP, according to Fishman and coworkers' clinical diagnostic criteria [13]. Group 2 was made up of 29 patients with autosomal recessive RP (ARRP), with an average age of 37.2 ± 14.8 years (range, 10–70 years). Sporadic cases and patients whose inheritance pattern was not yet clearly identified were not taken into account for these separate analyses, nor were data from patients with X-linked recessive RP, since the small number of cases in this subset did not allow a reliable statistical evaluation.

Maximal ERG responses [14] were recorded according to our low-noise methods, elsewhere described in greater detail [15, 16]. In brief, 100 iterations elicited with a 10-μs standard flash from a dark-adapted eye (after full pupillary dilation and dark adaptation for 20 min) with a full-field 20-lux/s 0.5 Hz flash stimulation were recorded and off-line averaged to evaluate the retinal response. Henkes-type corneal electrodes, connected to a mechanical, continuously controlled suction pump, were employed to record the tracings. In case of extreme reduction of the signal, a differential derivation system was used (electrode on the patched fellow eye used as a reference) resulting in a substantial increase in the signal-to-noise ratio [15, 16].

ERG variables, i.e., amplitude of the signal and a-wave and b-wave peak times, were determined according to standard criteria [14]. ERG b-wave amplitudes were expressed and statistically analyzed both as raw data (in microvolts) and after conversion to log units, while peak times were determined in milliseconds.

For VF testing, we used a Goldmann kinetic perimeter under low photopic conditions (12.4 asb). Peripheral isopters were determined with the I4e, III4e and V4e targets. VF areas were measured on a conventional perimetry chart with a light pen and expressed in square centimeters. Scotomas within each isopter were subtracted from the total area. Analyses were also performed on log-converted data.

Results were correlated to ERG variables referring to the VF area of each of the tested targets. In view of the symmetry of the majority of the findings, only one eye for each patient was taken into account to ensure independent observations, although this is not mandatory in studies on RP [17]. In the few cases that showed a substantial asymmetry, therefore, both eyes were evaluated. Statistical analyses were performed by means of an Apple Macintosh II computer (Cupertino, CA) with the Stat View^{TM} SE+Graphics program (Abacus Concepts Inc., Berkeley, CA). Simple regression curves and R coefficient values were determined. Statistical significance was expressed in terms of p values. Correlations were considered statistically significant at 0.05 or less.

Results

Each ERG variable was evaluated as a function of the residual VF area. The simple regression curves for ERG b-wave amplitude versus VF area from the group studied as a whole are illustrated in Figures 1–3, and statistical data are summarized in Table 1. In detail, ERG maximal responses and I4e isopter areas showed an R coefficient of 0.89, equivalent to a p value of 0.0001 (Fig. 1) The ERG and the III4e areas were correlated to the 0.0001 level with an R

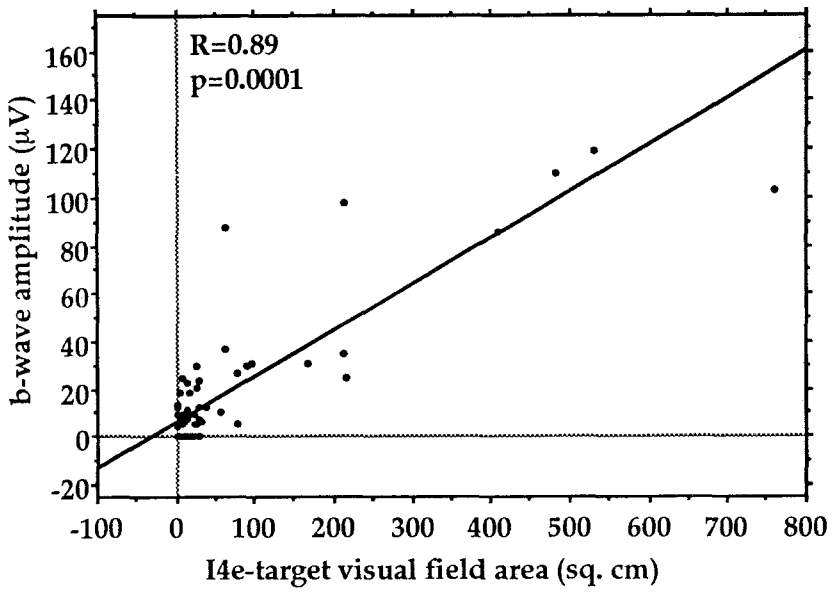

Fig. 1. Regression analysis for ERG b-wave residual amplitude as a function of VF area as determined with the I4e target. Point overlap in the graph is not shown to allow better resolution.

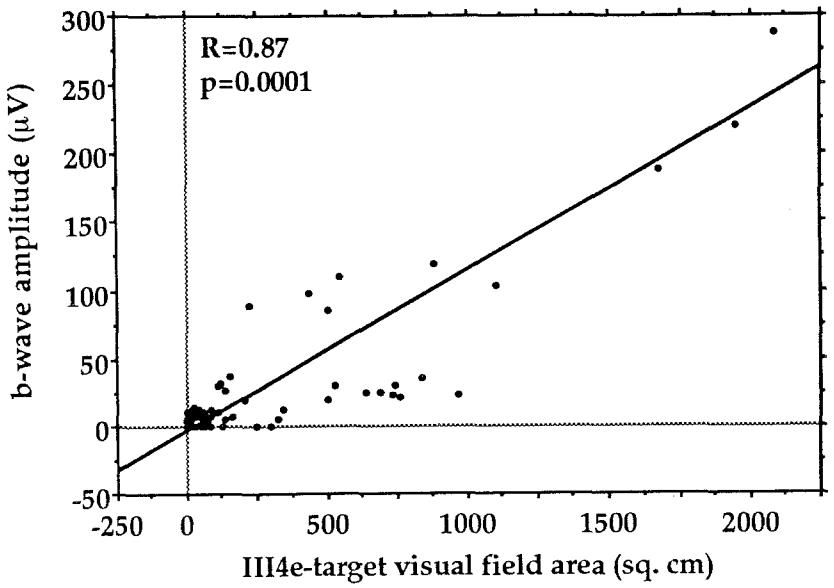

Fig. 2. Regression analysis for ERG b-wave residual amplitude as a function of VF area as determined with the III4e target. Point overlap is not shown.

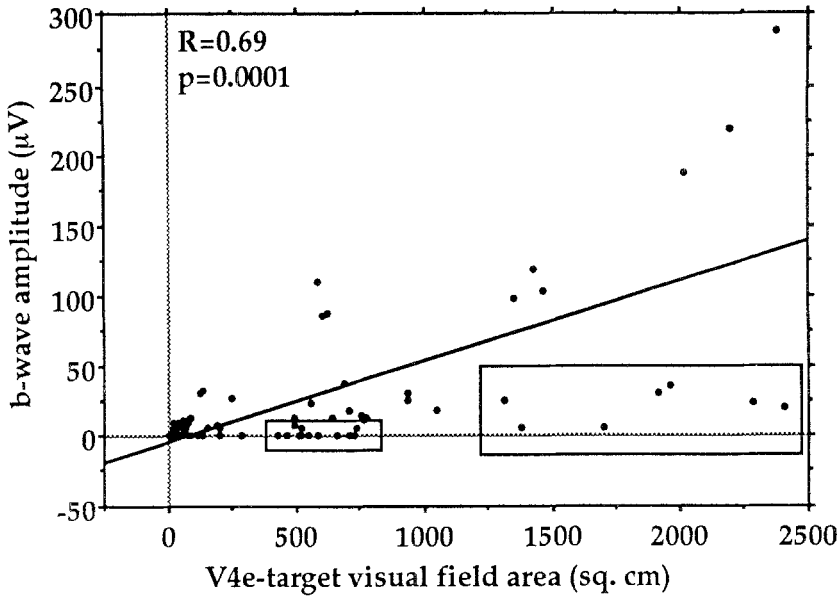

Fig. 3. Regression analysis for ERG b-wave residual amplitude as a function of VF area as determined with the V4e target. Point overlap is not shown. In the lower part of the graph, the two boxes highlight cases with far peripheral islands on the visual field chart showing poor correlation to ERG amplitude (see text for more detailed discussion and Fig. 6).

Table 1. Summary of statistical data

		b-wave vs. I4e		b-wave vs. III4e		b-wave vs. V4e	
	Comparison	R value	p value	R value	p value	R value	p value
Rod-cone RP (n = 220)	μV vs. cm^2	0.890	0.0001	0.870	0.0001	0.690	0.0001
	Log-log analysis	0.810	0.0001	0.770	0.0001	0.650	0.0001
Group 1: ADRP (n = 35)	μV vs. cm^2	0.991	0.0001	0.845	0.0001	0.200	NS
	Log-log analysis	0.860	0.0003	0.750	0.005	0.144	NS
Group 2: ARRP (n = 29)	μv vs. cm^2	0.967	0.0001	0.796	0.0001	0.664	0.0096
	Log-log analysis	0.804	0.0001	0.744	0.0001	0.728	0.0001

NS = not significant.

value of 0.87 (Fig. 2). Despite a lower degree of correlation between b-wave amplitude and V4e areas (R = 0.69), the significance remained unchanged (p = 0.0001) (Fig. 3). If the values were converted to log units, little change in correlation coefficients and p values was found (Table 1). Simple regression curves were also calculated for ERG peak times as a function of VF area.

Unlike ERG amplitude, neither one of these variables (a- and b-wave peak time) showed a significant correlation with VF areas.

The same statistical analyses were performed on the above-described subgroups identified on the basis of the inheritance model (Table 1). For group 1 (ADRP), a close correlation was found between both I4e and III4e targets and ERG amplitude (R = 0.991 and 0.845, respectively) at the 0.0001 level of significance. The log-log conversion yielded slightly lower degrees of correlation (R = 0.86 and 0.75, respectively) and a lower significance. No correlation was found for the V4e stimulus in either case. For group 2 (ARRP), correlations held for each target, decreasing along with the increasing size of the stimulus (R = 0.967, 0.796 and 0.664 for I4e, III4e and V4e targets, respectively), with a substantial statistical significance in each instance (p = 0.0001 for I4e and III4e and 0.0096 for V4e). Conversion into log units affected these findings minimally (Table 1). Also in this case, no correlation was found for ERG wave peak times as a function of VF area.

Discussion

Data from this investigation are substantially different from what has been reported in most previously published reports. In 1961 Armington and coworkers [18] first suggested some relationship between ERG and VF measures, when they found an approximately linear relationship of ERG log sensitivity to the log area of intact retina on a limited sample of patients with RP. However, several subsequent studies on large groups of patients did not support the possibility that the amplitude of the ERG is related to the residual functioning retina as estimated by VF testing. In fact, it was a common belief that a correlation between VF extension and ERG amplitude could be demonstrated only when photopic and scotopic measurements were compared separately [1–4], whereas no such relationship was observed with the maximal ERG responses [1, 3, 5–7]. Similarly, Massof *et al.* [7] were unable to find a correlation between R_{max} and VF areas.

Few recent studies supported the possible existence of a correlation between the ERG and VF. A relationship between ERG recording and VF results was suggested by De Rouck *et al.* in 1986 [19], who studied patients with ADRP and ARRP and noted a decreasing percentage of recordable ERGs as VFs became narrower. However, no clear correlation between ERG amplitude and VF results was reported. More recently, Fahle and coworkers [20] found a close correlation between ERG amplitude and VF diameters in a group of 116 patients affected with different forms of RP (including 18 cases of cone-rod dystrophy), with regression coefficients between 0.4 and 0.67 and significance of 0.0001. Another strong piece of evidence was presented by Heckenlively

[17], who demonstrated a close correlation between maximal ERG b-wave and field size in a study of 73 patients with cone-rod dystrophy ($R = 0.4759$, $p < 0.001$), despite some dispersion of the data in his scatterplots. Of interest, he noted a higher degree of correlation between VF and ERG findings when analyzing fields with rod-cone-like scotomas.

The striking similarity of the findings of Fahle *et al.* and Heckenlively to the results of our previous studies [10, 11] prompted us to extend the investigations to a larger and well-defined group of patients with RP, excluding cone-rod cases and syndromic forms from the evaluation. In addition, we separately analyzed data from patients with ADRP and ARRP, to identify possible differences related to the inheritance pattern.

Results presented here show a close correlation between ERG signals and VF extension in a large sample of patients with rod-cone RP. Simple regression lines, in fact, illustrate that the amplitude of the ERG signal elicited from a patient with RP tends to increase along with the extension of the peripheral isopters of Goldmann VF testing, although some exceptions were observed (Figs. 1–3). This trend was also supported by strong statistical significance ($p = 0.0001$ in every instance).

The above correlations were more evident for I4e and III4e isopters ($R = 0.89$ and 0.87, respectively) than for the V4e isopter ($R = 0.69$ for the group as a whole, and no correlation for the ADRP group), where a bigger scatter and some cases of underestimation of the functioning retina by ERG testing were observed (see also boxed areas in Fig. 3). This can be related to the distortion that occurs in the projection of VF areas larger than 55° on conventional isometric perimetry charts [21, 22]. A spatial summation effect must also be considered when large targets such as V4e are used, making measurements increasingly inaccurate and, ultimately, larger than the actual size of functioning retina. In fact, it is known that planimetric distortion occurs when perimetric data from stimuli presented in spherical polar coordinates are plotted in planar coordinates [22]. Various corrections of these cartographic errors have been suggested. One of the most complete is the classic study by Drasdo and Fowler [21], who also developed a nonlinear perimetric chart for an actual quantification of the retinal areas. Further improvements were achieved by Kirkham and Meyer in 1981 [23] and, more recently, by Dagnelie [22], who developed a method for the conversion of planimetric data into solid angles and retinal areas.

It is highly feasible that, considering some of the above physical and mathematical correcting factors, the correlation of our data could have been strengthened also for the larger target. This suspicion is increased by the observation that patients with mild to moderate ring scotomas to large stimuli showed well-preserved ERGs and good correlation between b-wave ampli-

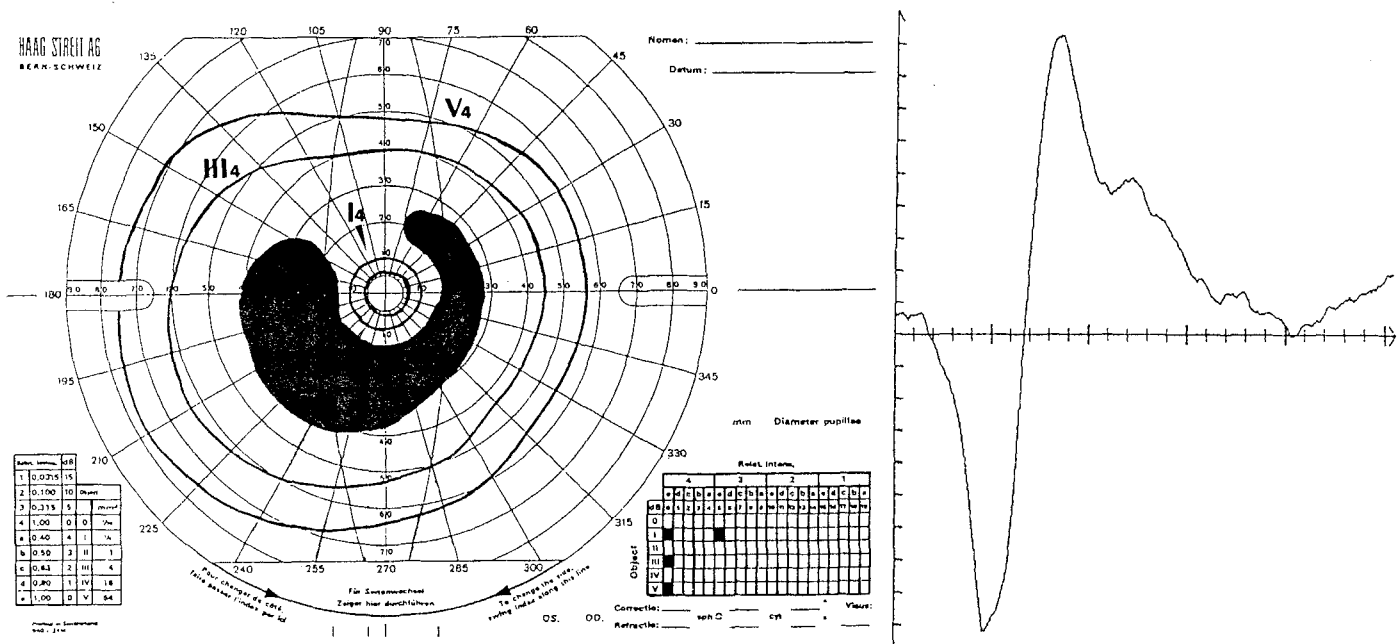

Fig. 4. An example of cases with mild to moderate ring scotomas to large targets showing well-preserved ERGs. In such instances a good correlation between ERG b-wave amplitude and visual field area was found also for the V4e target. For ERG calibrations, the vertical ruler measures 5 μV per unit; the horizontal ruler measures 50 ms per major unit (large tickmark).

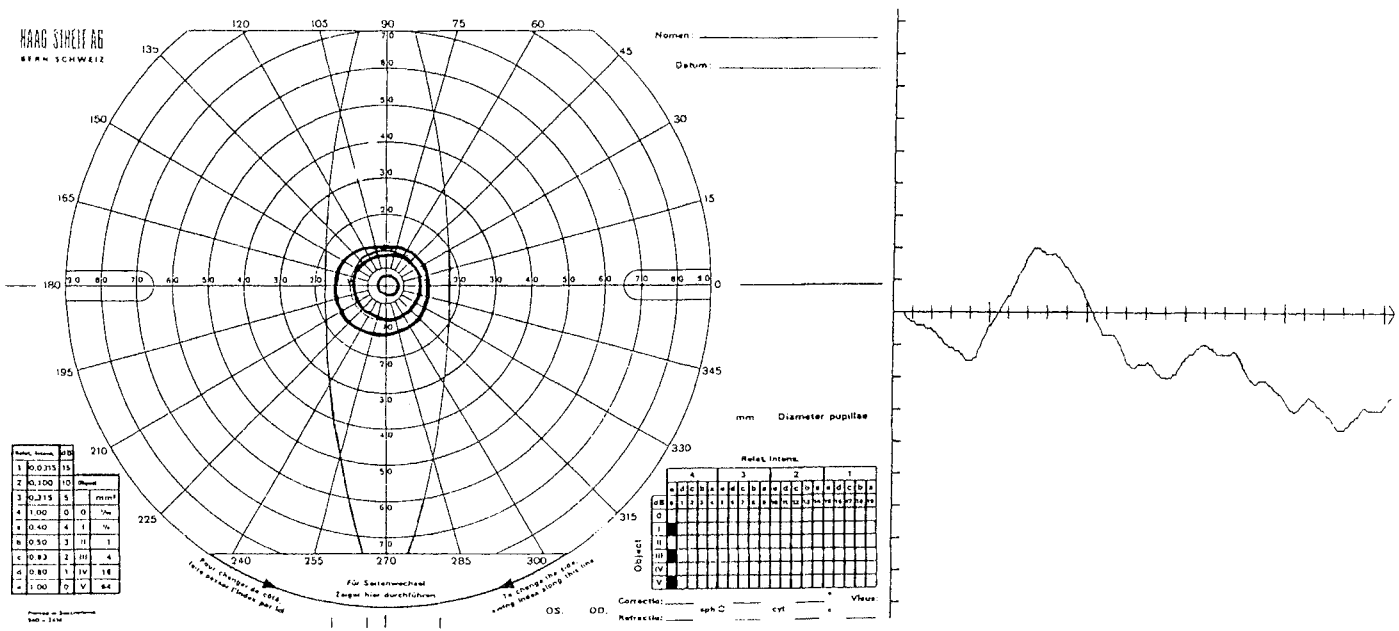

Fig. 5. An example of severe concentric narrowing of the VF with severely attenuated ERG signal. In these cases an almost linear correlation between VF area and ERG b-wave amplitude was also found for each target. For ERG calibrations, the vertical ruler measures 2.5 μV per unit; the horizontal ruler measures 50 ms per major unit (large tickmark).

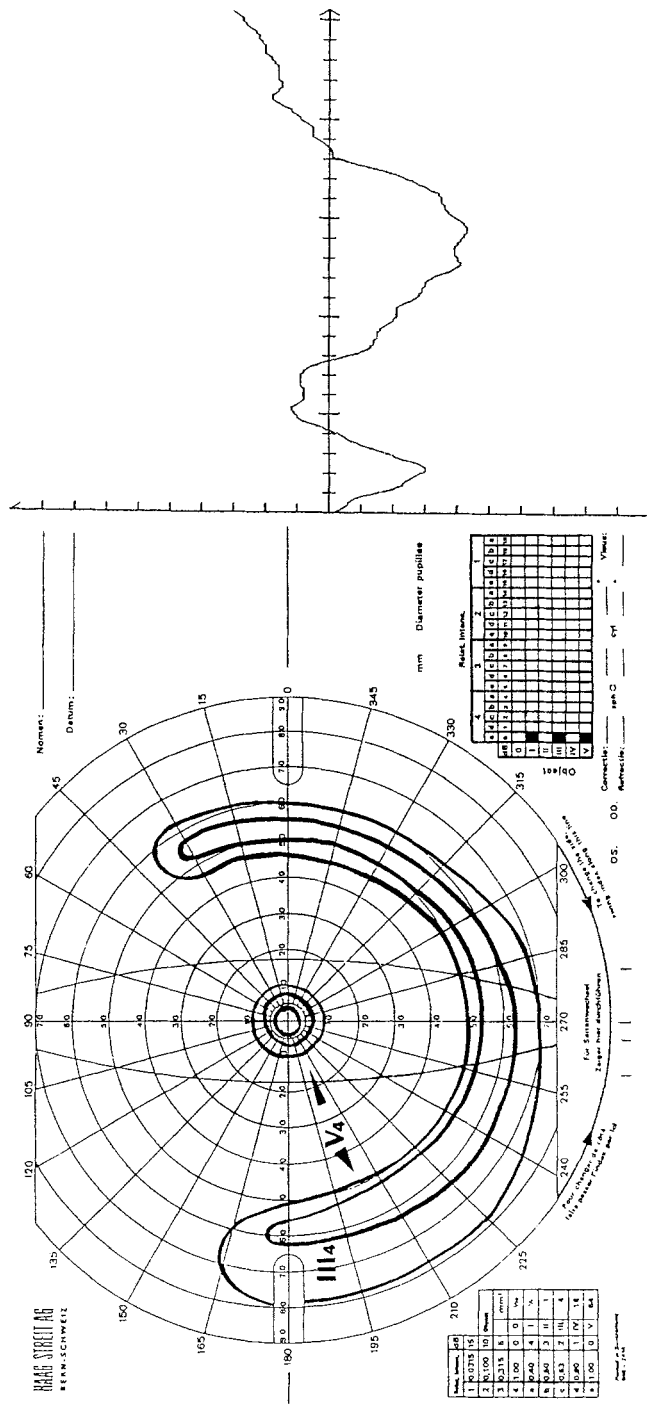

Fig. 6. In cases with far-peripheral islands of vision, falling mostly beyond the central 55° ring, a correlation between the V4e target area and the residual amplitude of ERG b-wave was lacking. For ERG calibrations, the vertical ruler measures 2.5 μV per unit; the horizontal ruler measures 50 ms per major unit (large tickmark).

tude and the V4e target (Fig. 4). Similarly, patients with severe concentric narrowing of the VF had severely attenuated ERG signals, still showing an almost linear correlation (Fig. 5), while this was lacking for the V4e target in those cases in which far-peripheral islands of vision had been detected (measures from these patients are highlighted by the boxes in the lower portion of Fig. 3). In fact, in such cases the islands fell mostly beyond the central 55° ring (Fig. 6), which is indicated as a distortionless limit for the conventional planimetric charts [21, 22]; it is worth noting that a 400% distortion occurs in the 80° to 90° ring if related to the actual receptive retinal area [21]. Therefore, fields like the one shown in Fig. 6 do not predict good maximal ERG response amplitudes and should better not be regarded as well-preserved ones, to avoid claiming a false discrepancy between the two tests in such cases.

These results are confirmed for patients with ADRP and ARRP evaluated as separate groups. This suggests that the correlation between ERG b-wave amplitude and VF residual area depends on physiologic and functional mechanisms that are apart from genetic differences within the disease, at least as far as we consider rod-cone nonsyndromic forms alone. In agreement with the study by Fahle *et al.* [20], this investigation further demonstrated that ERG and VF are closely correlated in most cases, not only for cone-rod [17] but also for rod-cone patterns. Since both rods and cones contribute to the maximal ERG response elicited with the stimulus conditions used in this study [14, 16], it is not surprising that the correlation holds irrespective of which is the most affected population of photoreceptors, expressing only the extent of functioning retina left.

Discrepancies between the two tests in previously published reports could be related to measurement methods rather than actual lack of correlation. Particularly, low-noise recording systems are mandatory both to allow ERG detection in cases with small fields left and to ensure precise measurements for signals in the 20-μV range, which represent a large part of the signals in RP [16]. A noisy system, or recording techniques inadequate for patients with RP (e.g., single-flash technique), might preclude fulfilling both the above needs.

Moreover, VF quantification plays a key role, because inadvertent inaccuracy or approximation can further exaggerate the distortion that already occurs on the perimetric charts. This point becomes increasingly important if peripheral islands have to be measured; for instance, the use of the horizontal diameter of the field as a criterion [5] may not ensure enough accuracy and probably should be avoided at least in these cases. It is also possible that the correlation coefficients found by Fahle *et al.* [20] could have been even higher if, in place of the average between horizontal and vertical diameters, VF areas had been measured. Determination of percentages of normal (either diameters

or areas) does not seem the most appropriate approach either, since normal fields fall completely in the maximal distortion band and show substantial variability in that area. VF areas are probably the best measure to be used, and the use of a light pen proved to be reliable enough to ensure the results achieved in this study. Should these facilities be unavailable, the method proposed by Heckenlively [17] seems to provide a reliable alternative, although it did not prevent a high scatter in his plots.

The target to refer to might also be crucial. For larger fields, especially if they retain peripheral islands of vision, the size of the III Goldmann target (4 mm^2) should probably not be exceeded to avoid substantial overestimation of residual functioning retinal areas by spatial summation effect. For best correlation of maximal ERG responses to VFs, the III target could be suggested as the most appropriate one also when areas of very small fields are measured. In these cases, in fact, the I4e target might not even be detected at all or might be too small to be reliably measured with a light pen; conversely, the V4e target might once again overestimate the retinal area and be slightly less accurate than the III4e. A further investigation currently in progress seems to confirm these latter assumptions and probably suggests that the 30-Hz cone ERG might show the highest correlation to VF area for very small fields (unpublished data), as already alleged by Arden and coworkers [1]. Finally, conversion of amplitudes and areas in log units does not seem to provide more accuracy and therefore does not appear to be as essential as measurement methods to ensure good correlation between ERG and VF.

In summary, this investigation may not be considered conclusive about the long-lasting problem of comparing different functional variables in RP, such as VFs and ERGs. However, it confirms that ERG is a measure of the retinal status reliable enough for long-term follow-up studies and that appropriate testing procedures are needed to avoid apparent discrepancies between psychophysical measures and objective electrophysiologic data. This issue is becoming of increasing relevance, now that essential steps are made toward the identification of possible cures for retinal degenerations, and the need for reliable and precise testing methods has to be met. It will also be of interest to verify whether this correlation holds for other types of retinal degenerations, particularly in syndromic conditions where retinopathy seems to behave substantially differently from typical RP [24].

Acknowledgements

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