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Rarebit perimetry and frequency doubling technology in patients with ocular hypertension

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PURPOSE. *To test the capability of rarebit perimetry (RP), a recent non-conventional perimetric technique, in detecting early functional damage in subjects with ocular hypertension (OHT) and to compare RP findings with those obtained by frequency-doubling technology (FDT) perimetry.*

METHODS. *Thirty patients with OHT were matched with 30 healthy subjects. All were tested with RP and FDT. Frequency-doubling technology mean deviation (MD) and pattern standard deviation (PSD), as well as RP mean hit rate (MHR), of the two groups were analyzed. The agreement between the two techniques was tested by Kappa analysis.*

RESULTS. *In the OHT group the mean (SD) FDT MD was 0.5 (2.1), the mean (SD) FDT PSD was 4.2 (1.6), and the mean (SD) RP MHR was 81.4 (6.7). In the control group, corresponding values were mean (SD) FDT MD 1.1 (1.4), mean (SD) FDT PSD 3.0 (0.3), mean (SD) RP MHR 96.2 (2.0). The differences between the two groups were not significant for the studied indexes. Eleven (36.6%) out of the 30 OHT eyes had abnormal RP results; 12 (40.0%) eyes had abnormal FDT results. Five (16.6%) eyes had abnormal RP and FDT findings. Only 1 eye (3.3%) in the control group had abnormal RP results and 3 eyes (10.0%) had abnormal FDT results. RP and FDT showed a moderate agreement (Kappa = 0.43; 95% CI: 0.42 to 0.51).*

CONCLUSIONS. *RP and FDT showed VF defects not shown in standard automated perimetry in the OHT group. This may be indicative of an increased risk in developing glaucoma, even if a gold standard for detecting subtle defects is not currently available. RP has the additional advantage of not requiring any expensive device to be used. The poor agreement between these techniques in identifying eyes with early damage warrants further investigations. Large longitudinal studies are needed before defining the role of RP in early glaucoma diagnosis. (Eur J Ophthalmol 2008; 18: 205-11)*

KEY WORDS. *Standard automated perimetry, Early glaucoma diagnosis, Frequency doubling technology, Ocular hypertension, Rarebit perimetry*

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INTRODUCTION

In recent years a number of new perimetric techniques have been introduced, in an attempt to overcome standard automated perimetry (SAP) limitations (1). Some have become popular and can be performed with commercially available instruments: short-wavelength automated perimetry (SWAP) (2, 3), frequency-doubling technology (FDT) perimetry (4-19), high-pass resolution perimetry (HRP) (20, 21). The main goal of these techniques is the early detection of glaucomatous damage, owing to the possibility of selectively stimulating a specific subpopulation of ganglion cells. Frisén has recently introduced a new perimetric method, rarebit perimetry (RP) (22-26).

Although RP was not specifically designed for early glaucoma diagnosis, since it tests the integrity of the neural matrix by means of sparse targets (high-contrast microdots carrying a minimum of information: rare bits) and does not seem to be selective for any subpopulation of

The results of this study were partially presented as a poster at the 16th International Perimetric Society Meeting; Barcelona, Spain; July 2004

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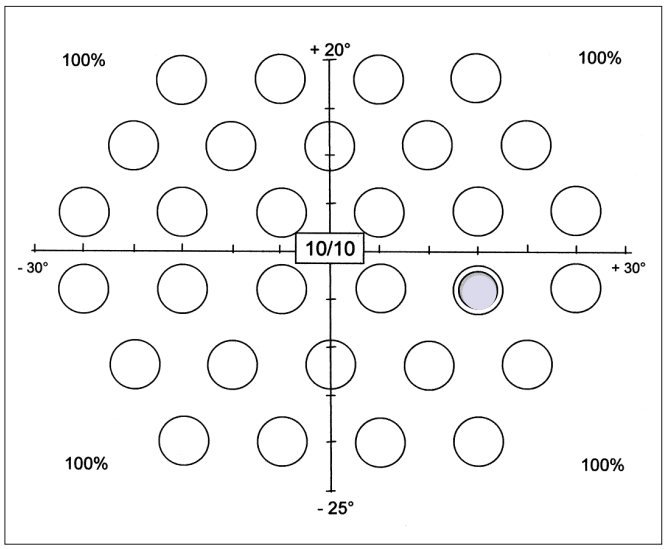

Fig. 1 - *The pattern of the rabbit test (30 circular areas).*

ganglion cells, it has potential sensitivity to subtle defects, which might represent an advantage for detection of early glaucomatous visual field damage. The aims of this study are to test the capability of RP to detect early visual field defects in subjects with ocular hypertension and to compare RP findings with those obtained by FDT, a technique that has already proved its effectiveness in detecting early glaucoma functional damage.

METHODS

Thirty subjects with OHT underwent RP (software available free of charge from lars.frisen@neuro.gu.se) and FDT perimetry (Welch Allyn, Skaneateles, NY, and Carl Zeiss Meditec, Dublin, CA, USA) N-30 threshold test. They all had intraocular pressure (IOP) greater than or equal to 21 mm Hg on no treatment, on at least two occasions; normal white-on-white automated perimetry findings; normal-appearing optic nerve head (ONH) and retinal nerve fiber layer (RNFL); and central corneal thickness (CCT) ≤550 µm.

All subjects were recruited among patients of the perimetric service of our institution and had two or more previous normal SAP results obtained with a Humphrey 750 II VFA (Carl Zeiss Meditec) central 30-2 threshold test, SITA (Swedish Interactive Threshold Algorithm) strategy. Thirty healthy volunteers were recruited from our staff and from normal subjects attending our outpatient clinic. They had IOP less than 21 on at least two occasions, normal SAP (performed at least twice), normal ONH and RNFL findings. All subjects underwent a complete ophthalmologic examination. Subjects with myopia or hyperopia >5 diopters or astigmatism >2 diopters were excluded, as well as subjects with any general or ocular disease other than OHT that could have an influence on perimetric results. Only one eye of each subject was randomly selected. Each subject underwent three perimetric sessions, at 1-week interval. All subjects underwent SAP, FDT, and RP testing in the first session. FDT and RP were repeated twice in the second and third session, with at least a half hour interval between tests. Repeated tests were performed to reduce the learning effect. Only the last test results were considered in the analysis. Before testing, an informed consent was obtained for all study participants, according to the guidelines of the Declaration of Helsinki. Both patients with OHT and normal subjects had at least three standard threshold visual field tests, each classified as normal. According to Anderson and Patella (27) at least one of the following criteria had to be present to classify SAP results as abnormal: 1) a cluster of ≥3 points in the pattern deviation probability plot, located in areas typically observed in glaucoma, having a probability level of <5%, with at least one point having a probability level of <1%; none of the points could be edge points unless they were located immediately above or below the nasal horizontal meridian; 2) PSD probability level of <5%; 3) glaucoma hemifield test outside normal limits. Reliability criteria included false-positive and false-negative responses of <33% and fixation losses of <20.

Rarebit perimetry

This technique does not require any specific device, as it simply runs on a standard personal computer (PC). A liquid crystal display (LCD) functions as the perimeter's screen, on which targets represented by bright, high-contrast, briefly-exposed (200 ms) microdots appear on a dark background. Targets have a 0.5 minimum angle of resolution and are presented one or two at a time. They are presented randomly within 30 5° circular areas (Fig. 1). The results are presented in a particular graphical form. It consists of partially filled (i.e., only a proportional rate of targets was seen) or fulfilled (i.e., no targets at all were seen) circles, while an empty circle means that 100% of targets were perceived within that area (Fig. 2). According

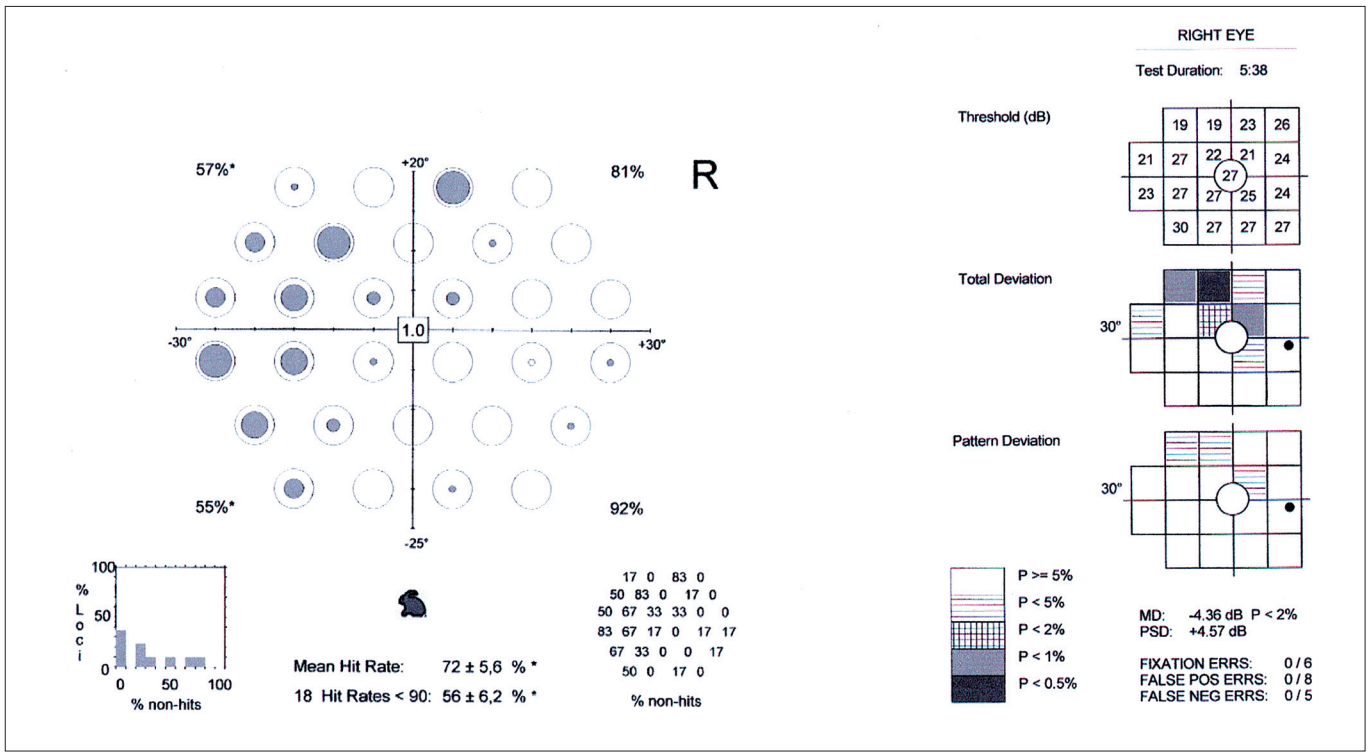

Fig. 2 - *A pathologic rarebit perimetry finding (left) and the corresponding frequency-doubling technology results (right) in a patient with ocular hypertension. Both techniques revealed abnormal results in this case. This finding was observed in 5 (16.6%) out of the 30 examined eyes.*

to Frisén's normative data (22), healthy subjects respond to at least 96% of probes. The plot provides, among some other indices, an index named mean hit rate (MHR), indicating the rate of proper responses. When visual field damage is present, a lower hit rate is expected. In agreement with Brusini et al (25), we considered RP findings abnormal in the presence of at least one of the following conditions: MHR <80%; more than 15 areas with a hit rate of less than 90%; at least two areas with a hit rate of less than 50%; at least one area with a hit rate 30% or less. Automatic tests of fixation accuracy are not made in RP, but one of the test areas is placed so as to partially overlap with the blind spot, in the expectation that good fixation causes a substantial fraction of probes to be missed in this location. In addition to the examiner's judgment, we considered RP results reliable in the presence of three or less errors, according to Frisén (22), but taking also into account the percentage of misses in the blind spot area. In the current study, version 3.0 was used, as it was the only version available at that time. An updated enhanced version 4.0, however, has recently been introduced.

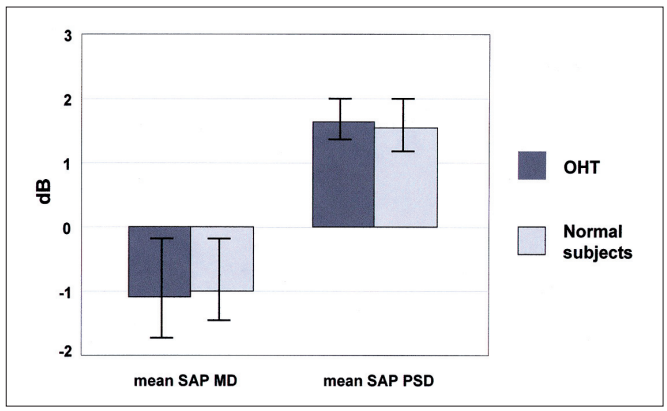

Fig. 3 - *Comparison between the two groups (patients with ocular hypertension and normal subjects) for mean values of standard automated perimetry mean deviation and pattern standard deviation. Differences were not statistically significant.*

Frequency doubling technology perimetry

FDT utilizes wide, square stimuli, that consist of sinusoidal gratings of low spatial frequency (0.25 cycles/degree) undergoing counter phase flicker at high temporal

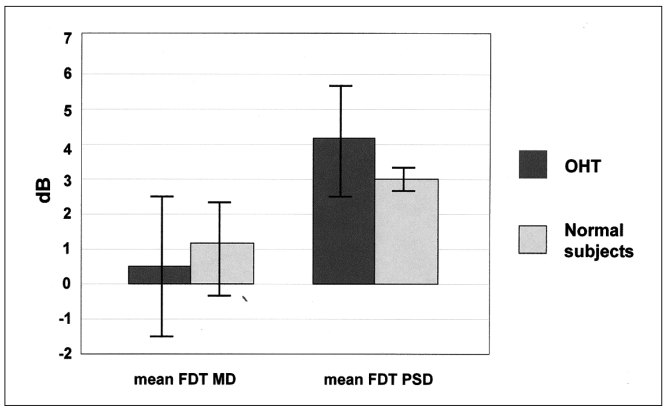

Fig. 4 - *Comparison between the two groups (patients with ocular hypertension and normal subjects) for mean values of frequency-doubling technology mean deviation and pattern standard deviation. Differences were not statistically significant.*

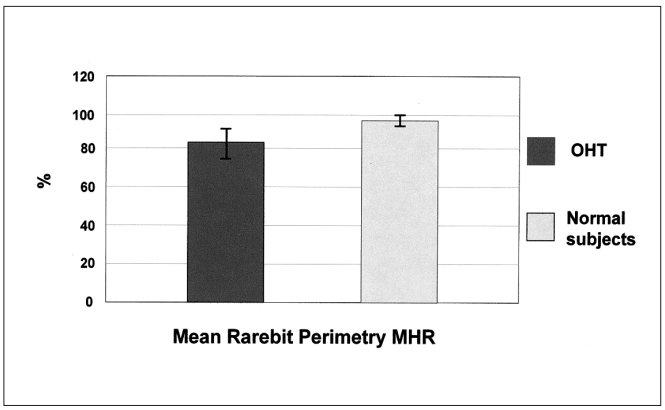

Fig. 5 - *Comparison between the two groups (patients with ocular hypertension and normal subjects) for mean values of rarebit perimetry mean hit rate index. Differences were not statistically significant.*

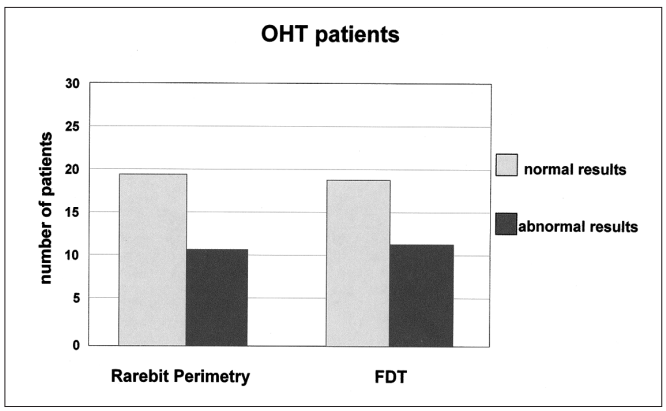

Fig. 6 - *Number of normal and abnormal tests as identified by rarebit perimetry and frequency-doubling technology, respectively, in the ocular hypertension group.*

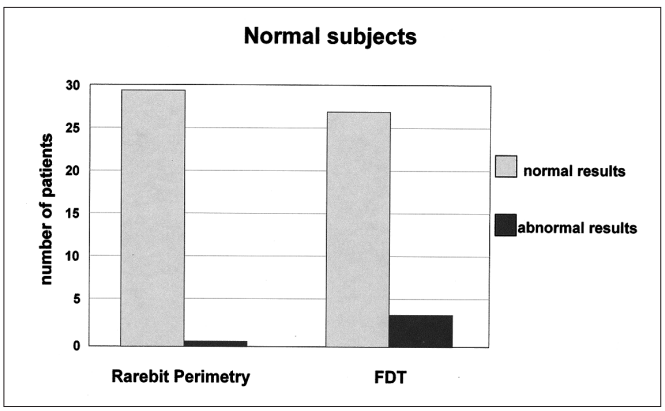

Fig. 7 - *Number of normal and abnormal tests as identified by rarebit perimetry and frequency-doubling technology, respectively, in the normal subjects group.*

frequency (25 Hz), projected on a dim background. The N-30 program was utilized in this study. According to Medeiros et al (17), we considered FDT results abnormal in the presence of PSD <5% and/or at least two areas with p<5% on the pattern deviation plot. Fixation errors, false positives, and false negatives are provided for the evaluation of reliability. For evaluating cooperation, we adopted the criteria reported in the instrument primer (wrong responses not to exceed 30%).

ONH and RNFL normal appearance were evaluated by one of us (M.I.) with fundus biomicroscopy using a 78 D lens. The presence of any of the following findings was to be excluded: ONH cupping, diffuse or focal rim thinning, hemorrhages, RNFL generalized or focal defects indicative of glaucoma. In addition, RNFL thickness (RNFLT) evaluation included a confocal laser scanning laser polarimetry with variable corneal compensator, using a 780 nm polarized light source (GDx-VCC–software version 5.3.1, Laser Diagnostic Technologies Inc., San Diego, CA, USA). On the basis of the parameters provided by the software, patients were considered normal when the nerve fiber indicator (NFI) was less than 30.

CCT was measured with a Pocket II Precision Pachymeter (Quantel Medical Inc., MT).

The mean values of the indices MD and PSD of FDT, as well as the mean value of the MHR of RP of the two groups (OHT patients and healthy subjects), were analyzed by Student t-test when the distribution of data was

normal and by Mann-Whitney test when the distribution of the data was not normal. A $p<0.05$ was considered statistically significant. The agreement between the two techniques was tested by Kappa analysis.

RESULTS

Mean (SD) age was 42 (7) (range 26–61) in the OHT group and 40 (9) (range 22–59) in the control group. There was no statistically significant difference between the two groups (Student *t* test; p=0.71). The mean (SD) SAP MD was –1.08 (0.79), the mean (SD) SAP PSD was 1.63 (0.27), the mean (SD) FDT MD was 0.5 (2.1), the mean (SD) FDT PSD was 4.2 (1.6), and the mean (SD) RP MHR was 81.4 (6.7) in the OHT group. The corresponding values of control group were the following: mean (SD) SAP MD –1.04 (0.68), mean (SD) SAP PSD 1.60 (0.31), mean (SD) FDT MD 1.1 (1.4), mean (SD) FDT PSD 3.0 (0.3), mean (SD) RP MHR 96.2 (2.0). The differences between the two groups were not significant for all studied indexes (Figs. 3-5). According to the abnormality criteria we adopted, 11 (36.6%) out of the 30 OHT eyes had abnormal RP results; 12 (40.0%) eyes had abnormal FDT results (Fig. 6); 5 (16.6%) eyes had abnormal RP and FDT findings. Only 1 eye (3.3%) in the control group had abnormal RP results and 3 eyes (10.0%) had abnormal FDT results (Fig. 7). RP and FDT showed a moderate agreement (Kappa = 0.43; 95% CI: 0.42 to 0.51) (28). Mean (SD) CCT was 532 (8) µm (range 510-548 µm) in the OHT group and 561 (22) µm (range 515-607) in the control group (a cutoff level was adopted for CCT only for OHT patients).

DISCUSSION

This study compares the role of two unconventional perimetric techniques, RP and FDT, in detecting early functional damage in OHT eyes. In recent years, a number of methods have been proposed whose goal was early detection of functional damage due to glaucoma. According to some studies, the loss of neurons must exceed 25 to 50% before abnormal results can be detected by SAP (29-34). To overcome the limitations of conventional white-on-white perimetry, many innovative methods were proposed and several have achieved some popularity, owing to their sensitivity and ease of use. FDT perimetry is probably, at present, the most widely utilized among all unconventional perimetric techniques. The comparison of RP with FDT had the purpose to verify the efficacy of the new method proposed by Frisén. FDT may be considered a selective technique, since the perception of the targets it uses is thought to be processed by M cells, representing about 20% of the total ganglion cells population. Several authors believe that M cells are the first cells to be selectively damaged in early glaucoma (35-38). However, this assumption is not shared by all (39, 40). The selective sampling of retinal cells with FDT may be effective at detecting early change due to reduced redundancy, as stated by Johnson (41). A gold standard does not exist to differentiate subjects with early defects from those with benign OHT who will probably never develop glaucoma. In contrast with most unconventional techniques, Frisén's RP was not specifically designed for early glaucoma diagnosis, since this method simply represents the attempt of testing the integrity of the neural matrix. The specific function analyzed by RP is unknown. The midget ganglion cells, which represent the largest contingent of all ganglion cells, seem to be mainly involved (22). However, even in the absence of selectivity for any ganglion cell subpopulations that are primarily involved in glaucoma damage, RP's potential sensitivity to very subtle defects and the probable absence of any redundancy effect are promising for early glaucoma diagnosis. On the basis of these premises, some authors have tested RP efficacy for early glaucoma diagnosis. A recent study by Brusini et al (25) concludes that RP appeared to be a rapid, comfortable, and easily accessible perimetric test showing a high sensitivity and specificity in detecting early glaucomatous visual field defects. Another study by Martin and Wanger (24) compared RP and FDT in normal subjects and patients with glaucoma. These authors found that information from the RP and FDT perimetry was almost completely overlapping. Moreover, they report that RP perimetry was preferred by the patients and seemed to have a larger dynamic range than FDT and conclude that RP hit rate is apparently a straightforward and efficient measure of visual field function. Another article by Martin (26) described the outcome of visual field examination performed with RP and FDT in children and young adults. The author reports that reliable RP examinations were carried out in 76% of the younger group (6.5 to 12 years) and 90% of the older group (14 to 20 years); corresponding values for FDT were 57% and 90%, respectively. The author concluded that RP seems useful for visual field examination in children aged 7 years and over and that the

test was also preferred by the tested subjects. The usefulness of both RP and FDT has also been demonstrated in case of pathologic conditions other than glaucoma, particularly in neuro-ophthalmologic disorders (42-46). Our study is in agreement with the literature, except the fact that we did not find the fairly complete equivalence between RP and FDT reported by Martin. The agreement observed between RP and FDT results is only moderate. An explanation may be that the two techniques test different visual functions; a further possibility could be that different individuals have different subsets of cells or fibers initially affected by glaucoma. We have found a good reproducibility of RP in normal subjects (unpublished data). RP is lacking an automatic test of fixation accuracy. The fixation target is moved during the test, stimulating patient's attention, while one of the test areas overlaps the blind spot to control for fixation. Only for OHT patients, we used a cutoff value (≤550 μm) for CCT in our inclusion criteria, with the aim to avoid an overestimation of IOP values, caused by thicker corneas. This likely reduced, but did not eliminate, false positive IOPs (47). This inclusion criterion also explains why average CCT values seem different from the expected values in the two groups, since OHT patients showed thinner corneas. With regards to functional tests, we chose the last test results for statistical analysis. An alternative approach might consist of having repeated tests confirming a defect, as opposed to applying a strict order of which test results to consider. However, the aim of our choice was to reduce the learning effect. The size of our sample is not sufficient to draw definitive conclusions. RP is a simple, fast, inexpensive recent perimetric technique. Some of its theoretical aspects make it a promising method for detecting early functional damage. Large longitudinal studies are needed before defining its role in early glaucoma diagnosis. Further research is warranted in order to identify subjects who are developing true early defects and to differentiate them from subjects who show false positive results, as might have happened in some of our subjects.

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