Original Article

Association between hyperacuity defects and retinal microstructure in polypoidal choroidal vasculopathy

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Purpose: To improve our understanding of hyperacuity defects measured with preferential hyperacuity perimetry (PHP) by correlating PHP findings with the retinal microstructural changes visible on spectral-domain optical coherence tomography (OCT) in patients with polypoidal choroidal vasculopathy (PCV). **Materials and Methods:** Twenty-eight eyes of 28 patients with PCV were retrospectively reviewed. All patients underwent a complete ophthalmologic examination, including best-corrected visual acuity (logMAR) testing, PHP, and OCT. The functional 'PHP test score' and 'total volume of hyperacuity defect zone' were also analyzed. **Results:** Patients were classified based on the hyperacuity defect by PHP, as follows: Hyperacuity defect (n = 17 eyes) group and hyperacuity intact (n = 11 eyes) group. The mean best-corrected visual acuity in the hyperacuity intact group (0.46 ± 0.39) was better than that in the hyperacuity defect group (0.82 ± 0.37) (P = 0.014). The presence of serous retinal detachment and retinal pigment epithelial detachment did not differ significantly between groups (P = 0.120 and P = 0.689, respectively). A disrupted photoreceptor layer was more common in the hyperacuity defect group compared with the hyperacuity intact group (P = 0.0001). Among 17 eyes with a hyperacuity defect, 9 eyes showing intra-retinal pathology (intra-retinal cyst or hard exudates) and had a significantly higher PHP test score and larger total volume of the hyperacuity defect zone than 8 eyes without intra-retinal pathology (P = 0.006 and P = 0.021, respectively). **Conclusion:** A hyperacuity defect in PCV was associated with photoreceptor disarrangement. Furthermore, PCV lesions on the inner retina that invaded the photoreceptor layer were associated with a more severe hyperacuity defect.

Key words: Polypoidal choroidal vasculopathy, preferential hyperacuity perimetry, spectral-domain optical coherence tomography

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Polypoidal choroidal vasculopathy (PCV) is a choroidal vascular disease characterized by an inner choroidal vascular network ending in an aneurysmal bulge or outward projection visible clinically as a reddish-orange, spheroid, polyp-like structure.[1,2] PCV can lead to multiple recurrent episodes of serous retinal detachment and retinal pigment epithelial detachment (PED).

Preferential hyperacuity perimetry (PHP, ForeseePHP, NotalVision, Tel Aviv, Israel) is a technology that is based on the phenomenon of hyperacuity, which is defined as the ability to perceive a difference in the relative spatial location of two or more visual stimuli.[3] This psychophysical testing technique is useful for measuring metamorphopsia.[3-6] PHP in addition to the Amsler grid can be used as a reliable tool for diagnosing central visual field defects in patients with macular disease.[7] PHP has also been suggested for testing for retinal toxicity due to hydroxychloroquine.[8]

The basic anatomic changes by which PHP detects hyperacuity defects in age-related macular degeneration can be explained by a choroidal neovascularization (CNV)-induced increase in the elevation of the retinal pigment epithelium (RPE), which induces the photoreceptors to shift their position. In addition, metamorphopsia is also related to separation and crowding of the retinal receptors and the resultant minification and magnification.

Spectral-domain optical coherence tomography (OCT) allows for the improved delineation of retinal features.[9,10] We hypothesized that the integrity of the retinal microstructure may be essential for preserving visual function, including hyperacuity. The purpose of the present study was to improve our understanding of hyperacuity defects measured with PHP by correlating the PHP findings with retinal microstructural changes visible on OCT in patients with PCV.

Materials and Methods

We performed a retrospective study of 28 eyes from 28 patients with PCV who were diagnosed between March 2009 and January 2010. Approval for this retrospective review was obtained from the Institutional Review Board of our institution. PCV was diagnosed based on the indocyanine green angiography (ICGA) findings for the choroidal vasculature, branching vascular networks, and abnormal polypoidal vascular lesions. The polypoidal lesions were either a single polyp or a cluster of multiple polyps. A diagnosis of PCV was also applied to eyes with only polypoidal dilatations and poorly visualized branching vascular networks. A Heidelberg Retina Angiograph system (Heidelberg Engineering, Heidelberg, Germany) with a confocal scanning laser ophthalmoscope was used for ICGA examination. In most cases, orange-red colored nodules were observed during the dilated fundus examination.

All patients received a complete ocular examination, including best-corrected visual acuity (BCVA) testing, dilated

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fundus examination with slit-lamp biomicroscopy, color fundus photography, digital fluorescein angiography, ICGA, and PHP. BCVA was measured with a standard Snellen chart at 6 meters and converted to logarithm of the minimum angle of resolution (logMAR) visual acuity for statistical analysis.

ForeseePHP was used for analysis of the PHP results. The patient sat approximately 50 cm away from a computer monitor with near-vision correction. After explaining and demonstrating the testing methods to the patients, PHP testing was performed in a dark room. PHP is used to assess the central 14° of the visual field with approximately 500 data points sampled 3 to 5 times each at a spatial resolution of 0.75°.[5] The stimulus is a series of dot-deviation signals (white dots on a black background for maximum contrast) flashed for 160 ms. These artificial distortions of different magnitudes act to both quantify the hyperacuity defects and as a reliability measure. The patient was asked to report any abnormalities in the dot-deviation signal by touching the screen at the location of the abnormality with a stylus. The patient's responses were recorded and analyzed by a pre-designed algorithm. A hyperacuity deviation map was marked as gray-scale or pink-scale according to the area and depth of metamorphopsia. Hyperacuity was indicated when the horizontal axis of the hyperacuity deviation map was identical to the fundus photograph, while the top and the bottom were reversed. When the results indicated low reliability, the testing process was explained to the subject again and a re-test was performed. To determine severity, we used the 'PHP test score' (a continuous global score between -30 and +600) and 'total volume of hyperacuity defect zones' (defect strength: arbitrary defect score units).

A Cirrus-HD OCT (Carl Zeiss Meditec, Dublin, CA) was obtained by a single experienced physician using macular cube (512 × 128) scans while monitoring central fixation. Patients were examined 30 minutes after administering 3 drops of intraocular mydriatics (Mydrin-P®, Santen, Osaka, Japan) applied with a 5-minute interval. The central foveal thickness (central 1-mm subfield thickness) was automatically measured using Cirrus analysis software (version 3.0).

Using this OCT device, we examined the status of the retinal microstructure. First, the status of the photoreceptor line was classified as intact or disrupted based on the integrity of the junction between the inner and outer segments of the photoreceptors [Fig. 1]. An intact photoreceptor line was defined as a continuous hyper-reflective line corresponding to the photoreceptor inner segment/outer segment junction. A photoreceptor line disruption was defined as a hypo-reflective disruption of the hyper-reflective photoreceptor inner segment/outer segment junction. Second, each eye was classified into one of two groups based on the intra-retinal pathology [e.g., intra-retinal cyst or hard exudates] on the OCT images.

Data were summed using Microsoft Excel. Data were compared using a Chi-square test, Mann-Whitney U, or Wilcoxon two-sample test. Statistical analysis was performed using PASW Statistics (ver. 18; SPSS Inc., Chicago, IL). A P value of less than 0.05 was considered statistically significant.

Results

Twenty-eight eyes of 28 patients were enrolled in the study. The eyes were categorized into two groups according to the hyperacuity defects of the PHP, as follows: Hyperacuity defect (17 patients, 17 eyes); and hyperacuity intact (11 patients, 11 eyes). The patient characteristics and OCT findings are shown in Table 1.

The patient characteristics (age, sex, and central foveal thickness) did not differ significantly between the two groups ($P > 0.05$). BCVA was significantly different between the two groups ($P = 0.014$). Presence of serous retinal detachment and PED was not different between the two groups ($P = 0.120$ and $P = 0.689$, respectively). The distribution of the state of the photoreceptor line differed between the two groups ($P = 0.0001$). In the hyperacuity defect group, all 17 eyes showed a disrupted

Table 1: Characteristics of eyes exhibiting hyperacuity defects and eyes exhibiting intact hyperacuity in preferential hyperacuity perimetry in patients with polypoidal choroidal vasculopathy

Variables	Hyperacuity intact group (*n*=11)	Hyperacuity defect group (*n*=17)	*P* value
Age (years)	68.1±6.6	72.3±8.2	0.416[a]
Sex	4:7	8:9	0.705[b]
Best-corrected visual acuity (logMAR)	0.46±0.39	0.82±0.37	0.014[a]
Central foveal thickness	300.5±136.6	322.4±99.9	0.485[c]
SRD (presence:absence)	8:3	6:11	0.120[b]
PED (presence:absence)	8:3	10:7	0.689[b]
Photoreceptor layer integrity (intact:defect)	10:1	0:17	0.0001[b]
Intraretinal pathology (absence:presence)	11:0	8:9	0.004[b]

logMAR: Logarithm of the minimum angle of resolution, SRD: Serous retinal detachment, PED: Pigment epithelial detachment, [a]Mann-Whitney U test, [b]Chi-square test, [c]Wilcoxon two-sample test

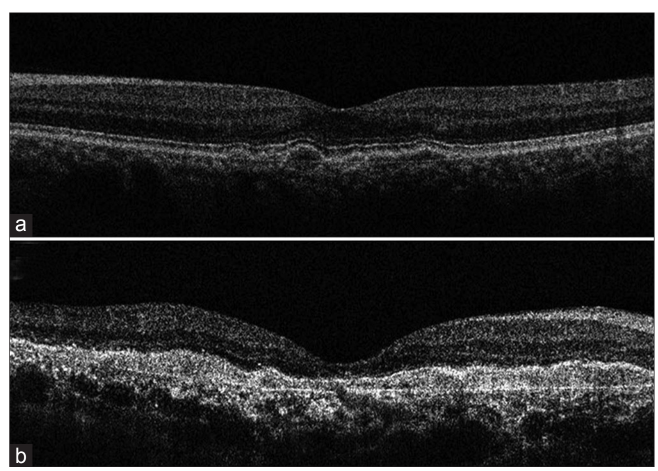

Figure 1: Optical coherence tomography image showing the classification of the junction between the inner segments and outer segments of the retinal photoreceptors (IS/OS). (a) Intact photoreceptor state. The IS/OS line was detected as a complete line. (b) Disrupted photoreceptor state. The IS/OS line could not be detected and the retinal pigment epithelium line was detected as an irregular broad line

and irregular photoreceptor line. In contrast, in the hyperacuity intact group, 10 of 11 eyes showed an intact photoreceptor line and the remaining 1 eye showed a disrupted photoreceptor line. Representative cases are shown in Fig. 2.

In the hyperacuity defect group, 9 eyes showed intra-retinal pathology and the remaining 8 eyes showed an intact neurosensory retina. In contrast, none of the 11 eyes in the hyperacuity intact group showed any intra-retinal pathology ($P = 0.004$).

Among the 17 eyes with a hyperacuity defect, the PHP test score and total volume of the hyperacuity defect zone were significantly larger in the 9 eyes with intra-retinal pathology, compared to the 8 eyes without intra-retinal pathology [Fig. 3, $P = 0.006$ and $P = 0.021$, respectively].

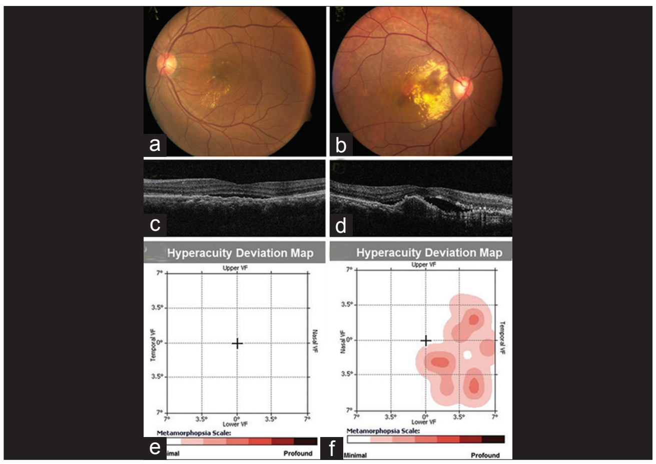

Figure 2: (a, b) Fundus photographs, (c, d) optical coherence tomography (OCT) scans, and (e, f) the results of preferential hyperacuity perimetry (PHP). (a, c, e) Fundus photograph shows a few hard exudates around the macula. OCT showed an intact photoreceptor line and serous retinal detachment. There was no hyperacuity defect on PHP. (b, d, f) Fundus photograph showed mild subretinal hemorrhage with massive hard exudates around the macula. OCT showed a disrupted photoreceptor line and serous retinal detachment. PHP showed multiple hyperacuity defects

Discussion

PHP is a psychophysical testing modality to assess the subjective symptoms of metamorphopsia. This technology is based on the concept of hyperacuity by projecting dot-deviation signals on a screen, and asking the patient to use a stylus to point to the location of the abnormality on the screen. Results of patients who recognize the deviation of the dotted line are considered normal, while those of patients who indicate a wrong area or fail to recognize the deviation at all are considered abnormal. The test is performed through an artificial distortion technique by displaying 100 lines within the range of 4200 μm × 4200 μm, which corresponds to the central 14° of the visual field, and allows for the measurement of 500 retinal data points in the central visual field, including the macular area, in a typical test. Hyperacuity defects are indicated on a gray-scale or pink-scale map in the PHP result report.

Alster *et al*. reported that PHP could detect recent-onset CNV resulting from AMD and could differentiate it from an intermediate stage of AMD with high sensitivity (82%) and specificity (88%).[5] At first, we analyzed 71 eyes of 71 patients (PCV 28 eyes, central serous chorioretinopathy (CSC) 10 eyes, epiretinal membrane 10 eyes, macular hole 6 eyes, diabetic retinopathy 6 eyes, normal 11 eyes, except age-related macular degeneration) who complained metamorphopsia. The sensitivity of PHP in PCV patients are relatively low compared to previous study of AMD (60.7%, unpublished data). In our study, 18 of the 28 eyes with PCV showed PED. Among 18 eyes, 8 eyes showed normal PHP finding. We guess there would be a correlation between PHP result and height of PED, and have plan to perform additional study on this.

The present study was conducted to investigate the association between hyperacuity defects measured with PHP and the retinal microstructural changes visible on OCT in patients with PCV. The findings demonstrated a clear association between hyperacuity defects and the status of the photoreceptor line on OCT. All patients of the hyperacuity group (17 eyes) showed a disrupted photoreceptor line on OCT, whereas only 1 patient revealed a photoreceptor defect in the

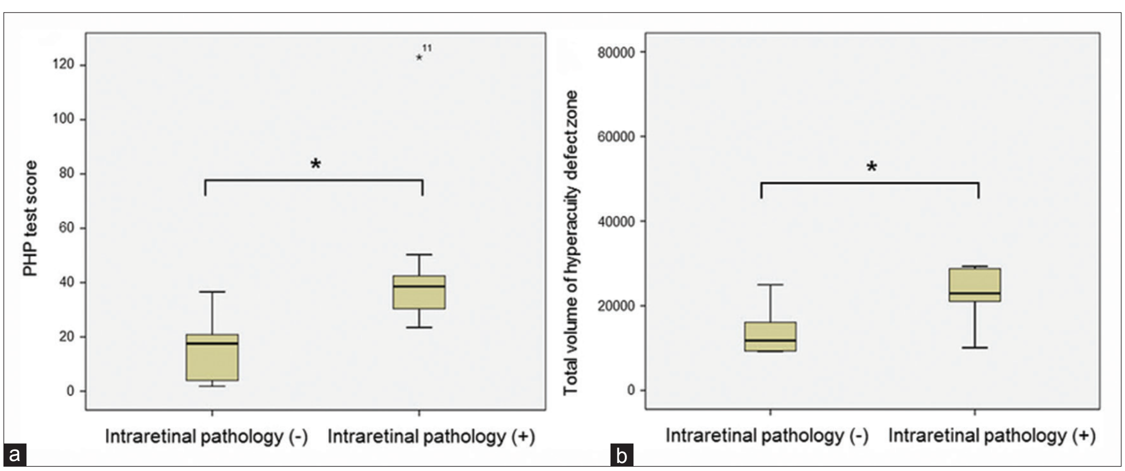

Figure 3: Graphs showing the preferential hyperacuity perimetry (PHP) test score and total volume of the hyperacuity defect zone according to intra-retinal pathology in the hyperacuity defect group. (a) PHP test score of the intra-retinal pathology (+) group was significantly higher than that of the intra-retinal pathology (–) group ($P = 0.006$). (b) Total volume of the hyperacuity defect zone in the intra-retinal pathology (+) group was significantly greater than that in the intra-retinal pathology (–) group ($P = 0.021$)

hyperacuity intact group. The integrity of the photoreceptor line is related to visual acuity in various diseases such as retinitis pigmentosa,[11-13] CSC,[14-17] acute zonal occult outer retinopathy,[18,19] branch retinal vein occlusion,[20-22] and macular hole treated with vitrectomy.[23] To our knowledge, this is the first study analyzing the relationship between hyperacuity defects and photoreceptor status using SD-OCT.

In this study, the presence of retinal PED was not different between the hyperacuity defect group (10 eyes) and the hyperacuity intact group (8 eyes). In other words, simple PED without an anatomic change in the outer retinal layer does not significantly affect hyperacuity defect, and the most important factor for hyperacuity defect is whether or not there is an anatomic change in the outer retinal layer. The present study, however, included only a small number of patients and, therefore, further studies must be performed to conclude that simple PED has no relation with hyperacuity defects.

We also analyzed the severity of metamorphopsia based on the intra-retinal pathology. Eyes with intra-retinal pathology had significantly higher PHP scores and a larger total hyperacuity defect zone volume. We speculate that this is due to the following: The simplest retinal circuit is a 3 neuron chain: Photoreceptor to bipolar cell to ganglion cell.[24] The inner nuclear layer contains the cell bodies of horizontal, bipolar, amacrine, and Muller cell bodies. Cells receive signals from photoreceptors from the outer retina to the inner retina, and the major synaptic layer is the inner plexiform layer.[25] Therefore, we suggest that hyperacuity defects are associated with intra-retinal pathology (e.g., intra-retinal cyst or hard exudates), resulting in insufficient synaptic junctions and photoreceptor disarrangement, and interfere with the one-to-one correspondence between the retinal image and the central nervous system, leading to worsening metamorphopsia.

The limitations of the present study are its retrospective nature and small sample size. In addition, the classification method of OCT images in this study was based on personal judgment, not specific or quantifiable amounts using a guide. Detection of the photoreceptor line may be influenced by the overlying pathologic retina or scar tissue.

In conclusion, a hyperacuity defect in PCV was associated with photoreceptor disarrangement on OCT. Furthermore, PCV lesions on the inner retina that invaded the photoreceptor layer were associated with a more severe hyperacuity defect. Large-scale studies are required to determine the relationship between visual acuity, hyperacuity, and retinal microstructure.

Acknowledgments

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