

# High-Pass Visual Acuity Loss and Macular Structure-Function Relationship in Patients With Primary Open-Angle Glaucoma

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**Received:** January 19, 2021

**Accepted:** March 18, 2021

**Published:** April 23, 2021

**Keywords:** visual acuity; vanishing optotype; central visual function; optical coherence tomography; retinal ganglion cells

**Citation:** Wen Y, Chen Z, Zuo C, Yang Y, Xu J, Kong Y, Cheng H, Yu M. High-pass visual acuity loss and macular structure-function relationship in patients with primary open-angle glaucoma. *Transl Vis Sci Technol.* 2021;10(4):26. <https://doi.org/10.1167/tvst.10.4.26>

**Purpose:** The Logarithm of the Minimum Angle of Resolution (logMAR) chart is the most common clinical test for assessing central visual function in glaucoma. However, based on the use of these charts, visual acuity (VA) often remains normal even when severe macular damage exists. Here, we aim to investigate the potential advantages of high-pass VA in detecting glaucoma compared with conventional VA.

**Methods:** Monocular best-corrected VA measurements were compared for a novel high-pass electronic VA chart (e-chart) and a conventional e-chart in 113 primary open-angle glaucoma (POAG) patients with normal logMAR VA and 65 age-similar healthy controls. One hundred thirty-nine POAG patients underwent spectral-domain optical coherence tomography (SD-OCT) for measurement of macular ganglion cell layer plus inner plexiform layer (GCL+IPL) thickness. Structure-function relationships between OCT measurements and the two VAs were compared. The enrolled eyes were divided into two groups for further analyses according to macular visual field (MVF) defects, specifically two or more adjacent abnormal points within the 12 central sites of 30-2 VF.

**Results:** The mean deviation (MD) of 30-2 VF test was  $-12.77 \pm 7.47$  dB for glaucoma group and  $-1.70 \pm 1.12$  dB for control group. The mean difference of the two VAs was slightly larger in glaucoma group (0.29 logMAR) than in control group (0.22 logMAR). The area under the receiver operating characteristic curve of the high-pass e-chart was larger than that of conventional e-chart (0.917 vs. 0.757,  $P < 0.001$ ). Significant correlations between high-pass VA and GCL+IPL thickness were found only in the MVF-damaged group. Compared with conventional VA, high-pass VA demonstrates stronger correlations with nasal-side macular GCL+IPL thickness (Fisher's Z-test, two-tailed,  $P_{2\text{mm in diameter}} = 0.033$  and  $P_{3\text{mm in diameter}} = 0.005$ ).

**Conclusions:** Compared with conventional VA, high-pass VA displays slightly higher sensitivity to visual loss in glaucoma and has a stronger correlation with the nasal-side macular GCL+IPL thickness.

**Translational Relevance:** The high-pass acuity test has the potential to be used as an ancillary tool to monitor glaucoma over time.

## Introduction

Glaucoma is the most common cause of irreversible blindness and visual impairment worldwide, and it is projected to affect 111.8 million people by 2040.<sup>1,2</sup>

Primary open-angle glaucoma has a global prevalence of approximately 3.1%, and it is the most common form of this disease.<sup>1</sup> The common features of glaucoma are pathologic loss of retinal ganglion cells (RGCs) and visual field (VF) defects.<sup>3,4</sup> It is traditionally regarded as peripheral vision damage that does

not involve the central vision until the final stage of the disease.<sup>5</sup> The basis of this assumption is black-on-white style visual acuity tests, such as the gold standard Early Treatment of Diabetes Retinopathy Study (ETDRS) logMAR VA test.<sup>6</sup> This relatively gross, subjective test evaluates the eye's resolving ability at a fixed high contrast.<sup>6</sup> However, resolution power is only a part of the complex visual perception, which is a sophisticated process concerning optical and neural factors. With normal documented VA, many late-stage glaucoma patients are thought to have entirely intact central vision. However, these patients frequently complain that their central vision is disturbed.<sup>7-9</sup>

Recently, mounting evidence suggests that glaucoma patients with normal VA present remarkable dysfunction in diversified central vision tasks.<sup>6,9,10</sup> For example, previous studies have confirmed that spatial contrast sensitivity (CS) declined in glaucoma patients with normal VA,<sup>11-13</sup> specifically at the high spatial frequency end.<sup>14,15</sup> Structural evidence also demonstrated significant thinning of the macular ganglion cell complex in glaucomatous eyes, which was correlated with reduction of sensitivity on macular VF.<sup>16-18</sup> However, the relationship between ETDRS logMAR VA and GCC thickness was noted only in the severe stage of the disease, with wide variability and weak correlation.<sup>19</sup> We realized that the most frequently used VA tests in clinical practice tended to underestimate damage in the central vision of glaucoma patients.<sup>11</sup> Therefore it is necessary to introduce a more comprehensive and efficient assessment for central visual function to detect glaucoma impairment.

Conventional optotypes and the gratings used in many CS tests involve very different mechanisms for assessing visual function. The former test is more sensitive to dioptric blur than the latter test.<sup>20</sup> This difference suggests that grating visibility is a good target for testing visual impairments limited by neural factors, but not optical factors. In 1978, Howland et al.<sup>21</sup> devised high-pass spatial frequency letters, somewhat like gratings, that are presented as the mean luminance of their black-and-white strokes averaged to the gray background. The special design of these optotypes makes the very low frequencies effectively absent and theoretically achieves a close apposition of detection and resolution thresholds under normal foveal viewing conditions. They are also called "vanishing optotypes," as these symbols would either be fully resolvable or not detectable. According to the renowned "recognition pyramid,"<sup>22</sup> detection is limited by optical filtering, whereas resolution is potentially determined by both optical quality and neural sampling. Although the exact perceptual mechanism remains unclear, the two thresholds may vary signif-

icantly in specific diseases, which results in different stimulus recognition outcomes in tasks when compared with normal cohorts.<sup>23</sup> Adopting gratings with the same mean luminance as their surroundings, many previous studies found that peripheral acuity has a difference between detection and resolution thresholds, which was not limited by optical filtering but by RGC sampling density.<sup>24</sup> It is then reasonable to assume that neural deficits may bring about a larger gap between detection and resolution thresholds in glaucomatous eyes with RGC damage, which will theoretically be reflected in a worse high-pass VA result.

Vanishing optotype VA tests have not yet been performed in glaucoma patients who present good results on ETDRS logMAR VA charts. Whether vanishing optotypes are able to detect the impact of glaucomatous macular damage on central pattern vision for these people is not known. If that were the case, whether it was related to structural damage (e.g., RGCs loss) in the macular region was also not known. The present study investigated how VA differed using vanishing optotypes and conventional black-on-white style letters in normal subjects and patients with glaucoma. We also examined the structure-function relationship in the macular region of glaucomatous eyes.

## Methods

The study protocol followed the Declaration of Helsinki and was approved by the ethics committee of the Zhongshan Ophthalmic Center. Written informed consent was obtained from all subjects before the experiment.

## Participants

A total of 239 participants were enrolled in this study: 174 patients with glaucoma (mean age  $48.45 \pm 14.79$  years) and 65 age-similar healthy controls (mean age  $47.26 \pm 2.18$  years). The participants were recruited from the Glaucoma Clinic and Optometry Department at Zhongshan Ophthalmic Center, Guangzhou, China.

Patients in the glaucoma group met the following inclusion criteria: (1) clinically diagnosed with primary open-angle glaucoma by specialists according to confirmed medical evidence<sup>25</sup>; (2) glaucomatous VF defects with values outside normal limits in the central 30-2 Glaucoma Hemifield Test program of Humphrey Field Analyzer; (3) best-corrected visual acuity (BCVA) better than or equal to 0.60 logMAR (ETDRS logMAR chart); and (4) no other ocular or

neurologic impairments. The inclusion criteria for the healthy controls were BCVA of no worse than 0.00 logMAR (ETDRS logMAR chart) and no ocular or significant systemic disease.

To control for the optical factors, we only included participants who had spherical equivalents between  $-6.0$  diopters (D) and  $+3.00$  D and cylinder correction within  $\pm 3$ D. In addition, we excluded individuals with severe cataracts (graded  $>N2$  by lens opacities classification system III, LOCS III).<sup>26</sup> Patients with severe dry eye and iatrogenic pupils were not included either. Moreover, to exclude any learning effect of the VF tests, the patients had taken at least two VF tests before the results were used in the current study.

## Visual Acuity Tests

### Apparatus

The VA test charts were generated by MATLAB (MathWorks, Inc., Natick, MA, USA) with Psychophysics Toolbox extensions for Windows 10, running on a laptop computer. Stimuli were presented on a liquid crystal display monitor (DELL, P2415Q, 23.8 inches, refresh rate: 60 Hz, resolution:  $3840 \times 2160$ ). Participants were seated 4 meters away from the front of the screen. A chair with a vertical back was used to ensure a correct and stable viewing distance. The room lights were turned off on the side of the screen, ensuring that the surrounding illuminance stabilized at 8 lux, whereas the lights on the side of the participants remained on, making the room illumination approximately 160 lux to avoid aberrations caused by dilated pupils.

### The Electronic Acuity Charts

Two different electronic charts (e-charts) were constructed: 1) the conventional e-chart, which followed the design of the current gold standard logMAR chart. We used the letter “E” of a  $5 \times 5$  black-on-white matrix as the optotype design. The contrast was defined as Weber Contrast. 2) The novel high-pass e-chart used the same layout except that it featured a high-pass optotype design. The high-pass “E” consisted of a lighter edge (luminance  $228 \text{ cd/m}^2$ ) and a darker core (luminance  $3 \text{ cd/m}^2$ ) with a constant ratio of 1:2:1 (edge: core: edge). The average luminance of the strokes was equal to the luminance of the gray background (luminance:  $112 \text{ cd/m}^2$ , see Fig. 1). The contrast was defined as the Michelson Contrast. The optotype sizes of both charts ranged from 58.18 mm to 2.92 mm, providing a test range from 1.0 logMAR to  $-0.3$  logMAR at a 4 meter distance. During the test, the rotating optotype “E” was presented randomly in four directions: up, down, left, and right. In each line,



**Figure 1.** Illustrations of the two optotypes: (A) High-pass designed letter “E” with average luminance of the strokes equaling to the luminance of the gray background. (B) Black-on-white style conventional letter.

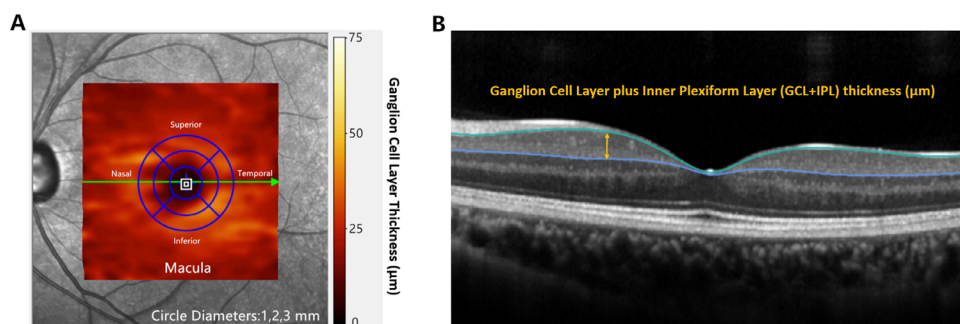
the space between optotypes was one letter “E” wide. Participants were instructed to identify the orientation of the “E” by pressing buttons on a keyboard. The visual chart went line by line on the center of the screen, with five optotypes per line. There was also a “backtrack” setting that provided a chance for the participant’s to change their mind before the subsequent optotype was read.

### Task Procedure

Proper refractive correction was used for each participant before the tests. For each test, participants were required to identify every optotype in each row using a forced choice procedure. Testing time was not restricted. Once they were unsure of an optotype, they were encouraged to guess. The tests automatically stopped when four or more errors occurred in a row. Then, the final VA score was calculated using the method described by Ferris et al.<sup>27</sup> In this study, VA was scored by the letter, and the results were converted to logMAR values. For each subject, the best-corrected monocular VA was measured at a 100% contrast setting. Participants were allowed to take a five-minute break between tests to reduce any effects of fatigue.

### Macular OCT Imaging

For the participants in the glaucoma group, macular retina thickness was measured using SD-OCT (Spectralis OCT BluePeak Heidelberg; Heidelberg Engineering, Inc., Heidelberg, Germany). Images were acquired using a high-resolution volume scan mode that generated dense raster scans by 49 B-scans consisting of 1024 A-scans covering a  $6 \times 6$  mm macular area centered on the fovea. The thickness of each layer was obtained from the automatic segmentation algorithm of the built-in software (Version 6.3.4). Each scan was carefully reviewed by two specialists to exclude poor



**Figure 2.** OCT imaging in this study: (A) Sectoral heat map of the GCL thickness. The average GCL thickness (in 1, 2, and 3 mm diameters) are shown for each of the nine sectors. The thickness of the inner plexiform layer was generated in the same manner. (B) The GCL+IPL thickness for evaluating structure-function relationships.

quality scans (quality signal strength score  $\leq 20$  dB) and incorrect segmentations. The macular areas were defined in nine ETDRS map sectors by the software: a circular 1 mm-diameter area, a 2 mm-diameter inner circle, and a 3 mm-diameter outer circle divided into four quadrants (see Fig. 2).

## Data Analysis

As our main purpose was to investigate the difference between high-pass VA and conventional VA in glaucoma patients with normal logMAR VA and healthy controls and to explore the potential structural basis of the functional results, we separately reported the statistical analysis comparing the two VAs and the relationships between sectoral ganglion cell layer plus inner plexiform layer (GCL+IPL) thickness (see Fig. 2) and VA results. Only one eye per participant was considered for analysis in each section.

First, distribution plots of differences between the two VAs were drawn, and normality was tested using the Shapiro-Wilk test. Then the Bland-Altman plots<sup>28</sup> were adopted to examine the test-retest reliability of the two e-charts and to compare the VA results in each group. Finally, receiver operating characteristic (ROC) curve analysis was performed to assess the discrimination performance of the two VA tests in glaucoma damage.

The relationships between sectoral GCL+IPL thickness and high-pass VA were evaluated using linear regression analyses. The high-pass VA was treated as the dependent variable, and thickness parameters were the independent variables in all regressions. Correlations between multiple sectoral GCL+IPL thickness and high-pass VA or conventional VA were evaluated using partial correlation analysis. Then Fisher's Z transformation was used for comparison of corre-

lations between GCL+IPL thickness and the VA results.

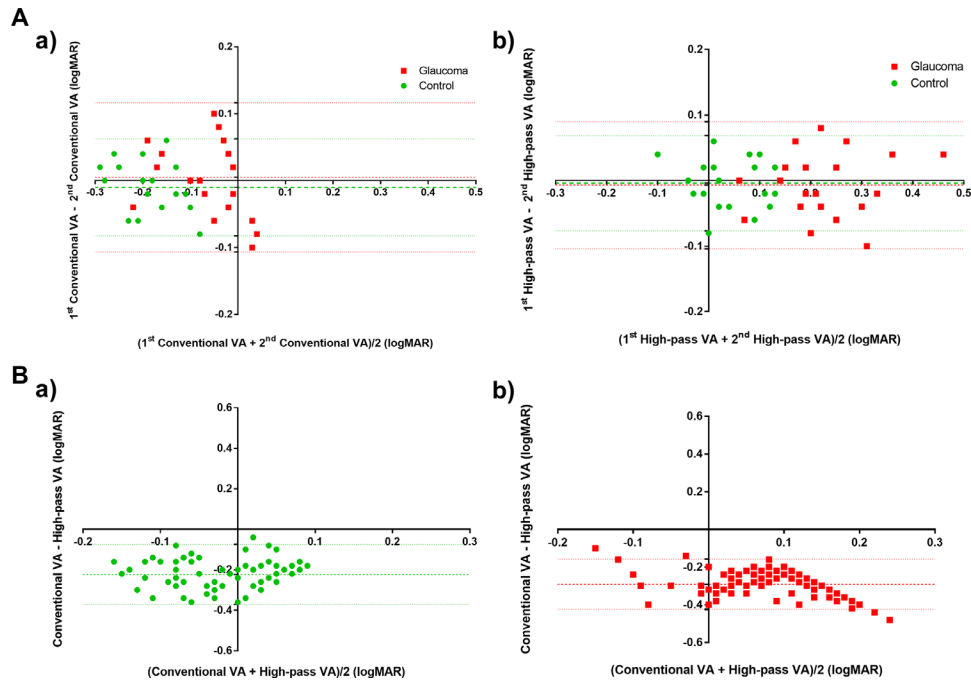
We also performed further analyses by dividing the enrolled eyes into two groups according to macular visual field (MVF) defects of central 30-2 VF results. Only VF results fulfilling the following criteria were included: fixation loss less than 20% and both false-positive rates and false-negative rates less than 15%. MVF defects were defined as two or more adjacent abnormal points within the 12 central sites ( $10^\circ$  of fixation) at  $P < 0.05$  or worse in total deviation (TD) values. Statistical analyses were performed using SPSS for Windows (version 20.0; SPSS, Inc., Chicago, IL, USA) and the GraphPad Prism statistical analysis package (version 6.01; GraphPad Software, Inc., La Jolla, California, USA).

## Results

### The Test-Retest Reliability of the Conventional e-Chart and the Novel High-Pass e-Chart

To examine the test-retest reliability of the two e-charts, 20 glaucoma patients with normal VA ( $\geq 0.00$  logMAR on the ETDRS logMAR chart) and 20 healthy controls underwent the tests on two different occasions. Normal distribution of the differences was verified. The results are illustrated on Bland-Altman plots for analysis in Figure 3A.

For the healthy controls, the mean differences between the first and second tests and the 95% limits of agreement were  $-0.010 \pm 0.037$  ( $-0.083$  to  $0.063$ ) for the conventional e-chart and  $-0.004 \pm 0.037$  ( $-0.077$  to  $0.069$ ) for the high-pass e-chart. In glaucomatous eyes, the numbers were  $-0.005 \pm 0.057$  ( $-0.107$  to



**Figure 3.** (A) Bland-Altman plots for test-retest reliability for (a) the conventional e-chart (first test versus second test) and (b) the high-pass e-chart (first test versus second test) with data for the healthy controls plotted in green (*dots*) and the glaucomatous eyes in red (*squares*). The *horizontal lines* represent the bias of the tests and 95% Limits of Agreements. (B) Bland-Altman plots display the differences between the two VAs in the (a) healthy controls and (b) the glaucoma group.

0.117) for the conventional e-chart and  $-0.007 \pm 0.050$  ( $-0.104$  to  $0.090$ ) for the high-pass e-chart. The variability of the two charts was similar in the healthy controls (two-tailed,  $P_{\text{conventional}} = 0.242$ ,  $P_{\text{high-pass}} = 0.635$ ) and glaucoma patients (two-tailed,  $P_{\text{conventional}} = 0.699$ ,  $P_{\text{high-pass}} = 0.535$ ).

### Visual Acuity Measured using Conventional e-Chart and High-Pass e-Chart in Glaucomatous Eyes With Normal Vision

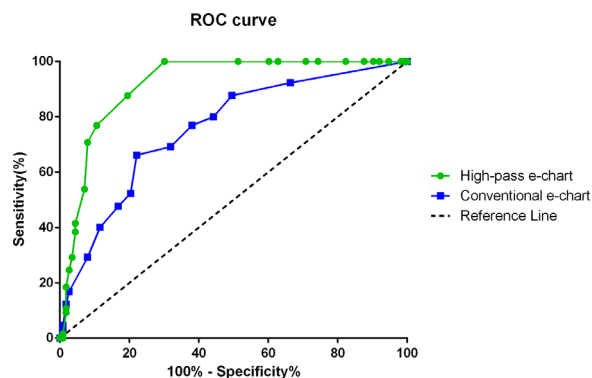
This section addressed whether there were any significant differences in high-pass VA between glaucoma patients with normal vision and healthy controls. Normal vision was defined as BCVA  $\geq 0.00$  logMAR (ETDRS logMAR chart). A total of 113 glaucomatous eyes (mean age  $47.61 \pm 13.78$  years) and 65 healthy eyes (mean age  $47.26 \pm 2.18$  years) met the above standard. The MD of 30-2 VF test was  $-12.77 \pm 7.47$  dB for the glaucoma group and  $-1.70 \pm 1.12$  dB for the control group.

The mean conventional VA was  $-0.063 \pm 0.07$  logMAR for glaucoma participants, and the value was  $-0.13 \pm 0.01$  logMAR in the control group. The data in both groups ranged from  $-0.28$  to

$0.00$  logMAR. The mean high-pass VA was  $0.23 \pm 0.09$  logMAR (range,  $-0.10$  to  $0.48$  logMAR) for the glaucoma participants and  $0.09 \pm 0.01$  logMAR (range,  $-0.08$  to  $0.18$  logMAR) for the healthy controls. The difference between the two VAs in the glaucoma group and control group was calculated. Regression analysis confirmed no statistical significance in the VA difference with age (glaucoma group:  $r^2 = 0.027$ ,  $P = 0.081$ ; control group:  $r^2 = 0.0016$ ,  $P = 0.753$ ).

Figure 3B (a) illustrates the comparison for the two charts in healthy controls, whereas Figure 3B (b) shows the data from the glaucoma group. The difference between the two VAs in glaucoma group was  $0.29$  logMAR (approximately three lines) at the  $0.00$  logMAR level, whereas in the healthy control group, the difference was approximately two lines ( $0.22$  logMAR) at the similar VA level. The comparison of the difference between the two VAs for the two groups was determined to be statistically significant (two-tailed  $P < 0.001$ ).

We also drew the ROC curves for the two VA tests (Fig. 4). The area under the ROC curve for the conventional e-chart and the high-pass e-chart was  $0.757$  (95%CI:  $0.687$ – $0.818$ ) and  $0.917$  (95%CI:  $0.867$ – $0.953$ ) respectively. Pairwise comparison of ROC curves



**Figure 4.** The ROC curves for the two acuity tests, conventional e-chart acuity test in blue (area under the ROC curve [AUC]: 0.757,  $P < 0.001$ ) and high-pass e-chart test in green (AUC: 0.917,  $P < 0.001$ ).

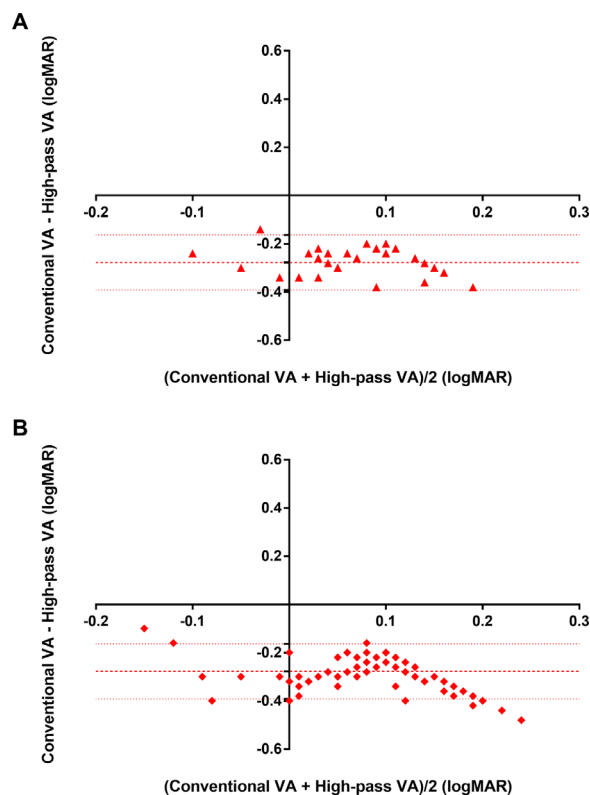
showed statistically significant difference with  $p$  value less than 0.001.

## Visual Acuity Results in Patients With Preserved and Damaged MVF

Here, we grouped the 113 glaucomatous eyes into two groups according to the MVF results (see Methods): the MVF-preserved group ( $N = 32$ ) and MVF-damaged group ( $N = 81$ ). There was no significant difference in conventional VA between the two groups ( $P = 0.374$ ). Comparison of data from high-pass VA found a marginally significant difference ( $P = 0.068$ ), specifically with  $0.21 \pm 0.08$  logMAR for the MVF-preserved group and  $0.24 \pm 0.10$  logMAR for the MVF-damaged group. Figure 5 shows the comparison of the two charts in the two groups. The MVF-preserved group and MVF-damaged group displayed similar figures on the difference between the two VAs ( $0.28$  logMAR vs.  $0.30$  logMAR; two-tailed  $P = 0.181$ ) at the  $0.00$  logMAR level. However, when compared with the control group, the difference between the two VAs was found to be significantly different, either in the MVF-preserved group (two-tailed  $P = 0.001$ ) or in the MVF-damaged group (two-tailed  $P < 0.001$ ).

## Relationship Between Macular GCL+IPL Thickness and High-Pass Visual Acuity

In this section, 139 glaucomatous eyes from 139 participants were analyzed. The scatter plots of GCL+IPL thickness parameters against high-pass VA ( $N = 139$ ) exhibited line-like patterns, especially plots formed by the superior and nasal side parameters (see Fig. 6). Regression analysis revealed that GCL+IPL thickness parameters were all significantly associated with high-pass VA ( $P < 0.001$ ); that is, the



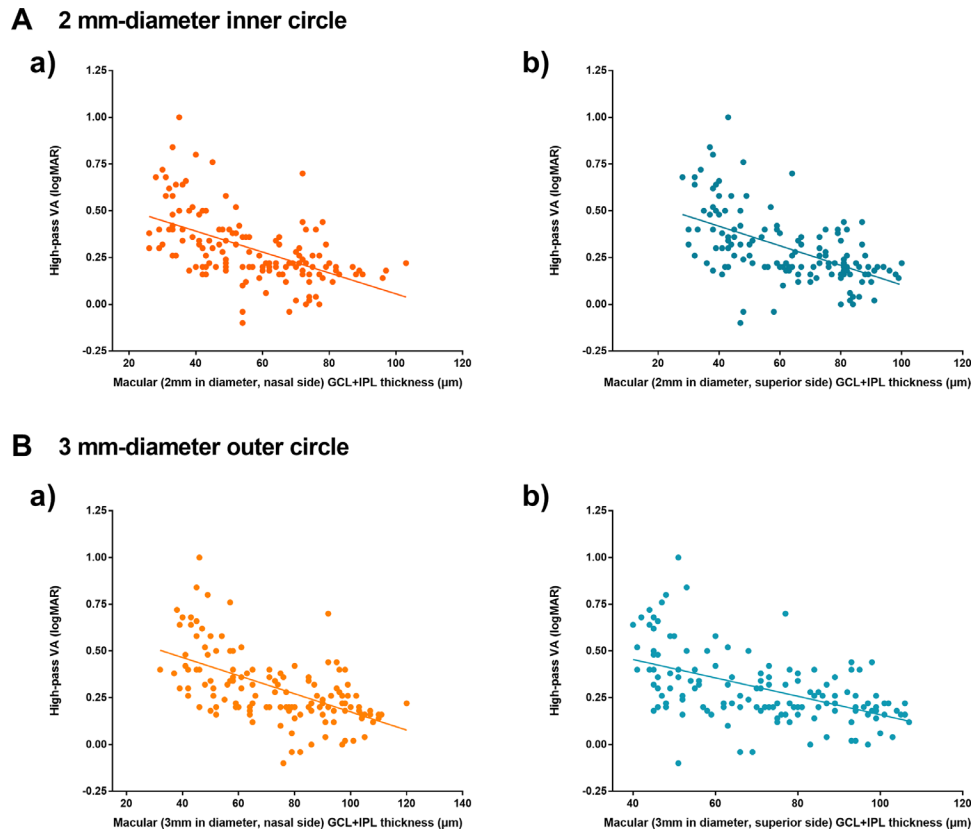
**Figure 5.** Bland-Altman plots display the differences between the two VAs in the (A) MVF-preserved group and the (B) MVF-damaged group, respectively.

thinner the GCL+IPL was, the worse the high-pass VA (see Table 1).

## Structure-Function Relationships in Patients With Preserved and Damaged MVF

For each enrolled eye, the means of the TD and pattern deviation (PD) values of the 12 innermost test points in the central 30-2 VF were calculated respectively. Table 2 summarizes the Pearson correlation analysis results between the TD or PD values and the two VA results. Fisher's Z-tests were conducted to compare the correlation coefficients separately, and no statistical significance was found (see Table 2).

Then, we performed further analyses of these 139 enrolled glaucoma eyes after dividing the eyes into two groups according to the MVF damage (see Methods): the MVF-preserved group ( $N = 32$ ) and MVF-damaged group ( $N = 107$ ). Table 3 summarizes the clinical characteristics of the involved participants. There was no significant difference in age, sex, or refractive power, but the TD values, PD values, and the two VAs were notably different between the two groups ( $P < 0.001$ ).



**Figure 6.** The scatterplots show the correlations between the sectoral GCL+IPL thickness (nasal side and superior side) and high-pass VA. A regression line of each diagram was generated mathematically and shows the structure-function relationships between the sectoral GCL+IPL thickness and high-pass VA. **(A)** The plots for OCT data from 2mm-diameter macular area versus high-pass VA. **(B)** The plots for OCT data from 3 mm-diameter macular area versus high-pass VA.

The correlations between macular GCL+IPL thickness and the two VAs were examined using partial correlation. The age of the participants and spherical equivalent of the eyes involved were considered as control variables. The strength of the correlations varied by sector, with stronger correlations gathering on the nasal side and the superior side (Table 4).

The figures were not significant for either high-pass VA or conventional VA in the MVF-preserved group. However, significant correlations were shown in all sectoral parameters in the MVF-damaged group. Among the structural parameters, the GCL+IPL thickness of the nasal side of the macular area (3 mm in diameter) showed the highest correlation ( $r = -0.548$ ;  $P < 0.001$ ) with high-pass VA in the MVF-damaged group, followed by the values of the superior ( $r = -0.531$ ;  $P < 0.001$ ) and nasal sides ( $r = -0.521$ ;  $P < 0.001$ ) GCL+IPL thickness in 2 mm-in-diameter scope. Fisher's Z-test confirmed that the high-pass VA correlated better with the nasal-side macular GCL+IPL thickness than the conven-

tional VA in glaucomatous eyes with damaged MVF ( $Z = 2.129, 2.807$ ; two-tailed  $P = 0.033, 0.005$ ).

## Discussion

Glaucoma is regarded as an irreversible disease characterized by a progressive loss of RGCs and VF damage.<sup>3,4</sup> Great focus has been placed on the degree of VF impairment and fundus changes<sup>29–31</sup> because it has long been believed that this disease has little impact on central vision until the late stage.<sup>5</sup> The ETDRS logMAR VA test is the most frequently used method for detecting central vision changes in clinical practice. However, it poorly reflects the true status of the visual system in glaucoma patients with good VA.<sup>19</sup>

As envisaged by Howland et al.,<sup>21</sup> high-pass filtered optotypes theoretically erased the very low frequencies, making the resolution and detection threshold almost identical in healthy people under foveal viewing.<sup>21</sup> Although this design has been discussed in several

**Table 1.** Univariate Regression Analysis for the Association Between GCL+IPL Thickness and High-Pass Visual Acuity (N = 139)

Sectoral GCL+IPL Thickness Parameters	Univariate Linear Regression		
	Regression Coefficient	R <sup>2</sup>	P Value
1 mm in diameter	−0.017	0.217	<0.001
2 mm in diameter			
Superior	−0.005	0.301	<0.001
Nasal	−0.006	0.290	<0.001
Inferior	−0.005	0.245	<0.001
Temporal	−0.006	0.285	<0.001
3 mm in diameter			
Superior	−0.005	0.268	<0.001
Nasal	−0.005	0.328	<0.001
Inferior	−0.004	0.185	<0.001
Temporal	−0.004	0.216	<0.001

**Table 2.** Correlations Between Visual Acuity Results and Macular Visual Field Damage (N = 139)

	Pearson Correlation Coefficient (r)		Fisher's Z-Value	P <sub>z</sub> Value (One-Tailed)
	Conventional VA	High-Pass VA		
The mean of TD values in macular visual field	−0.479*	−0.504*	0.850	0.198
The mean of PD values in macular visual field	−0.466*	−0.492*	0.877	0.190

The asterisk marked values are statistically significant at  $P < 0.01$  level (two-tailed).

**Table 3.** Characteristics of the Participants Grouped by MVF Damage (N = 139)

	MVF-Preserved Group (N = 32)	MVF-Damaged Group (N = 107)	P Value
Age, years	47.38 ± 13.45	48.68 ± 15.22	0.663
Gender, female/male, N	17/15	43/64	0.195
Spherical equivalent, diopters	−1.01 ± 2.10	−1.41 ± 3.24	0.405
TD values	−2.50 ± 2.38	−15.97 ± 8.53	<0.001
PD values	−1.67 ± 1.68	−14.07 ± 9.27	<0.001
Conventional VA, logMAR	−0.07 ± 0.10	0.06 ± 0.18	<0.001
High-pass VA, logMAR	0.20 ± 0.11	0.33 ± 0.20	<0.001

The data are shown in mean ± SD.

P value was obtained from independent sample t-test, except gender data was compared using the  $\chi^2$  test.

studies, actual VA tests using high-pass optotypes have not been performed in glaucoma patients. In the present study, we not only discussed whether VA chart using high-pass filtered optotypes is more sensitive in detecting glaucoma damage than conventional VA chart, but also explored the underlying structure-function relationship that may be responsible for this outcome.

Our results indicated that compared with healthy people, the difference between the two VAs was slightly larger among glaucoma patients with normal conventional VA (see Fig. 3B). Because test-retest reliabil-

ity was comparable for both charts in both groups (see Fig. 3B), the test-retest variability alone is unlikely to explain the larger difference in the glaucoma group. Optical factors, such as optical defocus, iatrogenic pupils, cataract, or dry eye, are known to affect the results. However, these were all relatively well controlled in our study, because we applied strict inclusion criteria. There were no significant differences in either optical aberrations or cataract severity between the glaucoma subjects and controls. In addition, the difference between the two VAs of the glaucoma group was also found to be larger than the bias caused by



**Table 4.** Correlations Between Visual Acuity Results and GCL+IPL Thickness (Partial Correlation Analysis)

Grouped by MVF Conditions	Sectoral GCL+IPL Thickness Parameters	Correlation Coefficient (r)		Fisher's Z-Value	P <sub>2</sub> Value (One-Tailed)
		Conventional VA	High-Pass VA		
MVF-preserved group (N = 32)					
	1 mm in diameter	-0.339	-0.352		
	2 mm in diameter				
	Superior	-0.193	-0.173		
	Nasal	-0.185	-0.241		
	Inferior	-0.220	-0.192		
	Temporal	-0.160	-0.118		
	3 mm in diameter				
	Superior	0.119	0.032		
	Nasal	-0.097	-0.176		
	Inferior	-0.029	0.022		
	Temporal	0.037	0.073		
MVF-damaged group (N = 107)					
	1 mm in diameter	-0.441*	-0.451*	0.292	0.385
	2 mm in diameter				
	Superior	-0.504*	-0.531*	0.825	0.205
	Nasal	-0.449*	-0.521*	<b>2.129</b>	0.017
	Inferior	-0.410*	-0.440*	0.865	0.194
	Temporal	-0.507*	-0.517*	0.305	0.380
	3 mm in diameter				
	Superior	-0.431*	-0.490*	1.726	0.042
	Nasal	-0.453*	-0.548*	<b>2.807</b>	0.003
	Inferior	-0.344*	-0.377*	0.922	0.178
	Temporal	-0.415*	-0.446*	0.896	0.185

The above results were calculated by partial correlation analysis adjusted by age and spherical equivalent.

The asterisk marked values are statistically significant at P < 0.01 level (two-tailed).

Bold value of 2.129 and 2.807 denotes statistically significant at the 0.05 level (two-tailed), with P<sub>2</sub> value of 0.033 and 0.005, respectively.

defocusing mentioned in a previous study (-0.26 vs. -0.05 logMAR).<sup>23</sup> We also plotted the ROC curves for the two tests to compare their ability to detect glaucoma damage (Fig. 4). The area under the curve for the high-pass e-chart was larger than that for the conventional e-chart (0.917 vs. 0.757, P < 0.001), which indicates that the high-pass VA may be a superior discriminating method for detecting glaucoma damage. We do not deny the effect of optical properties on high-pass VA results; however, our analysis suggests that these optical limitations alone were not enough to bring about larger differences in glaucoma patients. Neural limitations in glaucoma might be involved.

Shah et al.<sup>32</sup> confirmed that the difference in patients with age-related macular degeneration was approximately 4.5 lines at the 0.00 logMAR VA (ETDRS logMAR acuity chart) level, and the better the VA was, the larger the difference. Here, the glaucomatous eyes showed a much narrower gap between the two VAs. Obviously, we focused on different diseases. Dysfunctional photoreceptors in age-related macular degeneration may result in reduced retinal sampling, which brings about separation of detection and resolution limits.<sup>32</sup> In the case of glaucoma patients, retinal undersampling resulting from center-surround RGC

damage may explain the larger difference between the two VAs. Anderson et al.<sup>24</sup> pointed out that the resolution performance for high-pass optotypes was limited by the RGC sampling density in much of the same way as gratings. Recently, Liu et al.<sup>33</sup> confirmed that undersampling at the retinal level (loss of RGCs) resulted in elevated input noise in glaucomatous vision, which impaired foveal CS in glaucoma patients. In the current study, we found that glaucomatous eyes showed statistically significant but weak-to-moderate correlations between high-pass VA and the thinning of GCL+IPL thickness. When compared with conventional VA, high-pass VA showed stronger structure-function relationships only with nasal-side GCL+IPL thickness. This result could be related to the topography of RGCs. Previous studies have shown that peak RGC density was found in the fovea around the retina, and the site of peak density varies by person according to the probability distribution in the superior nasal retina (3/6), inferior nasal retina (1/6), or several sites in the nasal retina (2/6).<sup>34</sup>

Na et al.<sup>35</sup> showed that GCC thickness had a statistically significant structure-function association with macular VF. Shin et al.<sup>36</sup> further reported that macular sectoral GCL+IPL thicknesses were

significantly associated with sectoral central VF sensitivity. Kim et al.<sup>19</sup> demonstrated significant correlation between ETDRS logMAR VA and overall GCC thickness, which proved to be more significant in advanced stage. Here, we used high-pass VA as a functional outcome and made a comparison with the conventional black-on-white style VA. In addition, we conducted further analyses according to the central field damage in the 30-2 VF results to examine the possible link between high-pass VA and the central VF. VA is a more straightforward component of central visual perception. Theoretically, high-pass optotype may better serve as a stimulus to detect visual dysfunction for it could not only be used for testing the resolving power of the eye but also form a more targeted range of spatial frequencies than conventional optotype. However, the results of the current study showed that, compared with conventional black-on-white VA chart, there is no distinct advantage for high-pass VA test on detecting RGCs damage in glaucoma, because the structure-function relationship between high-pass VA and macular GCL+IPL thickness is only slightly stronger. Results showed in Table 4 point out that the correlations between high-pass VA and most of the OCT parameters were not statistically significantly higher than the correlations between these structural parameters and conventional VA (Fisher's Z-test,  $P > 0.05$ ). The high-pass VA only showed statistically stronger correlations with nasal-side GCL+IPL thickness (Fisher's Z-test,  $P < 0.05$ ). Therefore our data did not support the assumption that the high-pass VA precedes conventional VA in detection of RGCs damage in glaucomatous eyes. Significant structure-function relationship could only be found in the MVF-damaged eyes, whereas in MVF-preserved group the structure-function correlations were not statistically noted. This hints that high-pass VA loss may be much greater in central vision-impaired patients. However, the difference of the two VAs was found to be statistically significant compared with the control group in both the MVF-preserved and MVF-damaged groups (two-tailed  $P < 0.01$ ). This may result from the limitations of the central 30-2 VF, which may not reflect the defects of visual function required for the central high-pass resolution tasks. VF tests (24-2 or 30-2) with light detection tasks are more sensitive to peripheral visual deficits while underestimating central VF damage.<sup>10</sup> Therefore confirmed glaucoma patients may still exhibit some degree of high-pass VA loss even in the MVF-preserved group.

There are certain limitations in our study. First, the glaucoma severity range was circumscribed to some degree. Since the VA thresholds obtained using

the high-pass letters are generally larger than the thresholds obtained using conventional letters, we only included patients with ETDRS logMAR VA better than 0.60 logMAR. Thus the population here does not well represent the full range of glaucomatous damage. This bias may also weaken the relationship between the structure measures and the functional results. Second, the participants enrolled were relatively young on average, and therefore the findings may not be directly applicable to the typical older glaucoma patients, in whom cataract, myopic degeneration, and macular pathologies are common. Moreover, we did not analyze the exact central VF data using 10-2 VF tests or macular threshold programs. Although we grouped the glaucoma patients according to the central sites of the 30-2 program, which is the most comprehensive routine setting of the VF test, it may weaken the structure-function relationships in this classification. Similarly, the CS function results may also be better references. Further study is needed to replenish the research to explore the relationship between high-pass VA and central visual function (10-2 VF tests or CS tests).

In conclusion, compared with the conventional VA e-chart, the high-pass VA e-chart displayed slightly higher sensitivity to visual loss in glaucoma. The structure-function relationships between macular GCL+IPL thickness and high-pass VA were noted merely in glaucoma patients with damaged MVF. The high-pass VA only showed statistically stronger correlations with nasal-side parameters of the parafoveal region. Although the high-pass acuity chart generally appears to be unable to act as a tool for detecting macular damage in glaucoma, its peculiar properties may offer a uniquely simple way to devise an ancillary test to monitor glaucoma over time.

## Acknowledgments

Supported by the Space Medical Experiment Project of China Manned Space Program (HYZHXM01015), the Natural Science Foundation Team Project of Guangdong Province Grant 2015A030312016 (MY), and the National Natural Science Foundation for Young Scientists 81600761 (ZC).

Disclosure: **Y. Wen**, None; **Z. Chen**, None; **C. Zuo**, None; **Y. Yang**, None; **J. Xu**, None; **Y. Kong**, None; **H. Cheng**, None; **M. Yu**, None

\* YW and ZC contributed equally to the work.

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