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Original Article

Morphologic characteristics of optic disc in normal population with physiologic large cup in Chinese Han people

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Abstract: Background: The early diagnosis of glaucoma is a global problem. Physiologic large cup (PLC) with an abnormally high cup/disc ratio may be confused with changes of the optic disc in early glaucoma. However, fewer reports are available regarding PLC in normal population. Heidelberg Retina Tomograph (HRT) can provide quantitative topographic parameters of the optic discs and be used widely. Consequently, we desire to find the rule of morphologic changes of PLC in Chinese Han people using HRT for differentiating it from glaucoma. Methods: One hundred (100) subjects with PLCs and 74 subjects with normal cups (NCs) were examined by HRT. The topographic parameters were analyzed and the characteristics of the inferior, superior, nasal, and temporal quadrants of PLCs were examined. Parameters obtained from HRT were compared between two groups. The effect of age, refractive error, and disc area on each parameter was analyzed by the multiple linear regression model. This was a prospective study and the mean length of follow-up of the subjects was 28 months. Results: Compared to NC group, PLC group had larger disc ($P < 0.0001$) but smaller mean retinal nerve fiber layer thickness (mRNFLt) ($P<0.0001$). The nasal quadrant of disc area was larger than the inferior quadrant. Mean cup depth and maximum cup depth were unaffected by refractive error ($P = 0.0539$, 0.2228, respectively), age ($P = 0.1981$, 0.8207, respectively) or disc area ($P = 0.1927$, 0.3718, respectively). There was no significant change in disc area or cup shape measure ($P = 0.847$, 0.051, respectively). Conclusions: Optic disc structural parameters in PLC presented a similar pattern to NC, while PLC's disc area was larger but mRNFL thickness was smaller than the NC's. There were some changes in the topographic parameters of the optic discs of PLC overtime, but no glaucomatous damage was detected during our follow up.

Keywords: Physiologic large cup, optic disc, Heidelberg Retina Tomograph, follow up, morphologic change

Introduction

Cupping of the optic disc is a typical feature of glaucomatous optic nerve damage. Its extension has been estimated as the ratio of the cup to disk diameter. The major pathological processes of glaucoma are loss of ganglion cell axons, resulting in the gradual erosion along the rim and enlargement of the disc cup. But about 40% to 50% of function loss in optic nerve fibers has been presented prior to remarkable glaucomatous visual field defects [1]. Morphological changes in both the optic disc and nerve fiber layer provide strong evidence for early diagnosis of glaucoma. Morphologic parameters of the optic nerve and their associated alteration play an important role in diagnosis of glaucoma and are of interest to many researchers. One of the challenges for early diagnosis of glaucoma is the physiologic large cup (PLC), with an abnormally high cup/disc ratio but no pathologic findings and visual function are not compromised with large disc cup [2], which may be confused with changes of the optic discs in early glaucoma. Differentiation of glaucoma from PLC is essential to timely diagnosis and treatment. Previous studies indicated that refractive error, age and disc area

Tabel 1. Comparison of optic nerve head parameters between physiologic large cup and control

HRT Parameters	Control mean (std)	PLC mean (std)	Difference	*P* value
Total Number	74	100		
DA	2.34 (0.46)	2.72 (0.64)	0.38	< 0.0001
CA	0.48 (0.28)	1.19 (0.54)	0.71	< 0.0001
CDR	0.20 (0.10)	0.43 (0.14)	0.23	< 0.0001
RA	1.86 (0.38)	1.53 (0.45)	-0.33	< 0.0001
CV	0.10 (0.10)	0.32 (0.29)	0.22	< 0.0001
RV	0.50 (0.19)	0.33 (0.16)	-0.17	< 0.0001
MeCD	0.18 (0.08)	0.28 (0.13)	0.1	< 0.0001
MxCD	0.57 (0.21)	0.64 (0.25)	0.07	0.044
CSM	-0.25 (0.06)	-0.09 (0.08)	0.16	< 0.0001
HVC	0.41 (0.12)	0.35 (0.15)	-0.06	0.003
mRNFLt	0.27 (0.08)	0.22 (0.09)	-0.05	< 0.0001
RNFLcsa	1.47 (0.48)	1.25 (0.51)	-0.22	0.0016

HRT (Heidelberg Retina Tomograph), Physiologic large cup (PLC), Normal cup (NC), disc area (DA), cup area (CA), cup/disc area ratio (CDR), rim area (RA), cup volume (CV), rim volume (RV), mean cup depth (MeCD), maximum cup depth (MxCD), cup shape measure (CSM), height variation contour (HVC), mean retinal nerve fiber layer thickness (mRNFLt), retinal nerve fiber layer cross-section area (RNFLcsa).

affected the normal optic nerve morphology [3-6]. However, fewer reports are available regarding factors associated with PLC in normal population.

Previous morphologic studies on the optic disc were based on the qualitative assessment using either ophthalmoscope or fundus photography with poor criteria and reliability. Since computer image processing technology continues to evolve, several devices and software have been applied to quantitative evaluation of the fundus in the diagnosis of glaucoma. Heidelberg Retina Tomograph (HRT) provides 3D fundus image, which has better repeatability in fundus measurement [7, 8]. Using HRT, we studied feature of PLC in order to provide a tool to aid clinical diagnosis.

The purpose of our study is to evaluate and compare the topographic parameters of the optic discs between PLCs and normal cups (NCs) and to identify possible associated factors that contribute to the morphologic change of PLCs, which may be useful in diagnosis and differential diagnosis.

Patients and methods

Patients

This study protocol was approved by the Institutional Review Board (IRB) and all study procedures adhered to the principles outlined in the Declaration of Helsinki for research involving human subjects. All participants gave written informed consent before their participation. One hundred subjects with PLCs and 74 subjects with NCs were selected in the department of ophthalmology at Eye and ENT Hospital of Fudan University in Shanghai, China. One eye from each subject was selected for this prospective study.

Inclusion criteria of PLC: vertical cup/disc ratio (C/D) ≥ 0.5, no retinal nerve fiber layer defects, intraocular pressure (IOP) ≤ 21 mmHg (1 mmHg = 0.133 kPa), normal visual field, no family history of glaucoma.

Inclusion criteria of NC: vertical C/D < 0.5 (C/D difference between right and left eye < 0.2), IOP ≤ 21 mmHg, normal visual field, no optic nerve or retinal diseases, no family history of glaucoma.

Exclusion criteria: IOP higher than 21 mmHg at the time of testing, history of elevated IOP, poor-quality photographs, unreliable results or generalized depression on visual field testing, or the presence of other significant ocular diseases.

All subjects underwent a complete ophthalmic evaluation, including medical history, visual acuity, corrected visual acuity, anterior segment slit-lamp biomicroscopy and the optic nerve head photography (Canon CR A 45VAF). IOP was measured by Goldmann applanation tonometry and perimetry visual field was examined with automated static perimetry (Octopus 101-Perimeter) using dynamic strategy, mean sensitivity (MS) and mean defect (MD) were recorded. Axial length was measured by Sonomed 4000 A-scan.

All tested eyes had a best corrected visual acuity of 20/40 or better. Refractive error was between +3.00 and -6.00 diopters. All subjects

Tabel 2. Comparison of optic nerve head parameters of physiologic large cup among four quadrants

HRT Parameters	Quadrant inferior mean (SD)	Quadrant nasal mean (SD)	Quadrant temporal mean (SD)	Quadrant superior mean (SD)	*P* value
Total Number	100	100	100	100	
DA	0.70 (0.16)	0.68 (0.17)	0.68 (0.18)	0.70 (0.16)	0.4364
CA	0.25(0.12)	0.24 (0.16)	0.43 (0.18)	0.30 (0.14)	< 0.0001
CDR	0.35 (0.14)	0.34 (0.20)	0.62 (0.15)	0.42 (0.16)	< 0.0001
RA	0.45 (0.13)	0.44 (0.16)	0.25 (0.10)	0.40 (0.13)	< 0.0001
CV	0.06 (0.06)	0.06 (0.07)	0.11 (0.10)	0.09 (0.08)	< 0.0001
RV	0.11 (0.06)	0.10 (0.06)	0.02 (0.02)	0.10 (0.06)	< 0.0001
MeCD	0.26 (0.12)	0.26 (0.15)	0.29 (0.14)	0.33 (0.16)	< 0.0001
MxCD	0.58 (0.24)	0.58 (0.25)	0.56 (0.23)	0.65 (0.27)	0.0009
CSM	-0.07 (0.11)	-0.08 (0.13)	-0.01 (0.10)	-0.03 (0.13)	< 0.0001
HVC	0.23 (0.12)	0.13 (0.08)	0.14 (0.08)	0.20 (0.11)	< 0.0001
mRNFLt	0.26 (0.11)	0.24 (0.14)	0.08 (0.07)	0.29 (0.13)	< 0.0001
RNFLcsa	0.38 (0.17)	0.34 (0.19)	0.11 (0.04)	0.42 (0.18)	< 0.0001

HRT(Heidelberg Retina Tomograph), disc area (DA), cup area (CA), cup/disc area ratio (CDR), rim area (RA), cup volume (CV), rim volume (RV), mean cup depth (MeCD), maximum cup depth (MxCD), cup shape measure (CSM), height variation contour (HVC), mean retinal nerve fiber layer thickness (mRNFLt), retinal nerve fiber layer cross-section area (RNFLcsa).

Tabel 3. Pairwise comparison of optic nerve head parameters of physiologic large cup among four quadrants

HRT Parameters/*P* value	Inferior VS nasal	Inferior VS temporal	Inferior VS Superior	Nasal VS temporal	Nasal VS Superior	Temporal VS superior
Total Number	100	100	100	100	100	100
DA	0.6175	0.6569	1	0.9999	0.6398	0.6788
CA	0.9457	< 0.0001	0.0045	< 0.0001	0.0006	< 0.0001
CDR	0.9533	< 0.0001	0.0001	< 0.0001	< 0.0001	< 0.0001
RA	0.8122	< 0.0001	0.0006	< 0.0001	0.0144	< 0.0001
CV	1	< 0.0001	0.002	< 0.0001	0.0017	0.2124
RV	0.9367	< 0.0001	0.7755	< 0.0001	0.9828	< 0.0001
MeCD	0.9997	0.2131	0	0.2532	< 0.0001	0.0384
MxCD	1	0.8923	0.0138	0.8873	0.0143	0.0012
CSM	0.8383	< 0.0001	0.0003	< 0.0001	< 0.0001	0.4565
HVC	< 0.0001	< 0.0001	0.027	0.89	< 0.0001	< 0.0001
mRNFLt	0.3544	< 0.0001	0.0262	< 0.0001	0.0001	< 0.0001
RNFLcsa	0.0616	< 0.0001	0.0216	< 0.0001	< 0.0001	< 0.0001

HRT (Heidelberg Retina Tomograph), disc area (DA), cup area (CA), cup/disc area ratio (CDR), rim area (RA), cup volume (CV), rim volume (RV), mean cup depth (MeCD), maximum cup depth (MxCD), cup shape measure (CSM), height variation contour (HVC), mean retinal nerve fiber layer thickness (mRNFLt), and retinal nerve fiber layer cross-section area (RNFLcsa).

were Chinese Han people and were followed up at least one year.

In PLC group, 54 male and 46 female were enrolled, the mean age was 31.44 ± 17.17 years and refractive error was -1.75 ± 2.32 diopters. In NC group, 37 male and 37 female were enrolled and the mean age was 34.86 ± 19.28. There were no significant differences in age, gender, and refractive error between the two groups (P > 0.05).

Heidelberg retina tomograph (HRT)

In all subjects, the optic nerve head was scanned and analyzed with HRT (software version 2.01; Heidelberg Engineering GmbH, Heidelberg, Germany). This device has been

Tabel 4. HRT parameters stratified by age, refractive error, and DA

HRT Parameters	Age		Refractive Error		DA	
	Beta coefficient (95% CI)	*P* value	Beta coefficient (95% CI)	*P* value	Beta coefficient (95% CI)	*P* value
CA	-0.0043 (-0.0074, -0.0012)	0.0069	0.0382 (0.0161, 0.0604)	0.0009	0.5820 (0.5005, 0.6634)	< .0001
CDR	-0.0013 (-0.0024, -0.0002)	0.0203	0.0144 (0.0066, 0.0222)	0.0004	0.0535 (0.0248, 0.0822)	0.0003
RA	0.0043 (0.0012, 0.0074)	0.007	-0.0382 (-0.0604, -0.0161)	0.0009	0.4181 (0.3366, 0.4995)	< .0001
CV	-0.0026 (-0.0047, -0.0004)	0.0213	0.0293 (0.0138, 0.0449)	0.0003	0.1733 (0.1162, 0.2304)	< .0001
RV	0.0018 (0.0005, 0.0031)	0.0081	-0.0200 (-0.0293, -0.0106)	< .0001	0.0495 (0.0151, 0.0838)	0.0052
MeCD	-0.0007 (-0.0018, 0.0004)	0.1981	0.0076 (-0.0001, 0.0154)	0.0539	0.0189 (-0.0095, 0.0473)	0.1927
MxCD	-0.0003 (-0.0024, 0.0019)	0.8207	0.0097 (-0.0058, 0.0252)	0.2228	0.0260 (-0.0310, 0.0830)	0.3718
CSM	-0.0009 (-0.0016, -0.0003)	0.0057	0.0065 (0.0017, 0.0112)	0.0082	0.0158 (-0.0016, 0.0333)	0.0773
HVC	0.0009 (-0.0003, 0.0022)	0.1411	-0.0131 (-0.0221, -0.0041)	0.0047	-0.0229 (-0.0560, 0.0101)	0.1756
mRNFLt	0.0004 (-0.0003, 0.0012)	0.2819	-0.0112 (-0.0166, -0.0059)	< .0001	-0.0309 (-0.0505, -0.0113)	0.0023
RNFLcsa	0.0028 (-0.0014, 0.0070)	0.1915	-0.0661 (-0.0963, -0.0359)	< .0001	0.0396 (-0.0715, 0.1508)	0.4854

HRT (Heidelberg Retina Tomograph), disc area (DA), cup area (CA), cup/disc area ratio (CDR), rim area (RA), cup volume (CV), rim volume (RV), mean cup depth (MeCD), maximum cup depth (MxCD), cup shape measure (CSM), height variation contour (HVC), mean retinal nerve fiber layer thickness (mRNFLt), retinal nerve fiber layer cross-section area (RNFLcsa).

Tabel 5. The effect of axial length on the parameters of the optic nerve head of physiologic large cup

HRT parameters	Regression Equation	*P* value
DA (mm^2)		0.537
CA (mm^2)	y = -0.625x+25.22	0.002
CDR	y = -3.41x+26.26	0.000
RA (mm^2)	y = 0.93x+23.29	0.001
CV (mm^2)	y = -0.93x+25.06	0.008
RV (mm^2)	y = 2.63x+23.88	0.000
MeCD (mm)		0.219
MexCD (mm)		0.721
CSM	y = -4.51x+0.16	0.002
HVC (mm)		0.085
mRNFt (mm)	y = 4.23x+23.83	0.000
RNFLcsa (mm^2)	y = 0.71x+23.84	0.001

HRT (Heidelberg Retina Tomograph), disc area (DA), cup area (CA), cup/disc area ratio (CDR), rim area (RA), cup volume (CV), rim volume (RV), mean cup depth (MeCD), maximum cup depth (MxCD), cup shape measure (CSM), height variation contour (HVC), mean retinal nerve fiber layer thickness (mRNFLt), retinal nerve fiber layer cross-section area (RNFLcsa).

shown to provide reproducible results. An imagine field of 15 degrees×15 degrees, scanning depth was from 0.5 mm to 4.0 mm. Diopter adjustment range was within ± 12.0D. For each eye, three series topographies were obtained and then converted to be one averaged image. To demonstrate the structure of the optic discs, the margin of a disc was traced by the same operator through a standard reference plane. Parameters associated with the characteristics of optic disc were disc area (DA), cup area (CA), cup/disc area ratio (CDR), rim area (RA), cup volume (CV), rim volume (RV), mean cup depth (MeCD), maximum cup depth (MxCD), cup shape measure (CSM), height variation contour (HVC), mean retinal nerve fiber layer thickness (mRNFLt), and retinal nerve fiber layer cross-section area (RNFLcsa). The optic nerve head was divided into four quadrants: the temporal side of the horizontal level was defined as 0°, clockwise rotated below is negative, temporal (316° to 45°), superior (46° to 135°), nasal (136° to 225°) and inferior (226° to 315°). The characteristics of the inferior, superior, nasal and temporal quadrants of PLCs were examined.

We continued to follow up 100 PLC subjects for at least 24 months with the interval of every three months. Topographic parameters using HRT, IOP, visual fields, refractive error and axial lengths were evaluated at the end of follow up.

Statistical analysis

Continuous variables, DA, CV, CDR, RA, CV, RV, MeCD, MxCD, CSM, HVC, mRNFLt and RNFLcsa, were summarized as mean ± standard deviation and 95% confidential interval. PLC and NC groups were compared using student's t-test. Then ANOVA with Tukey test was performed to compare these measurements among four quadrants. We then compared the changes in morphology during follow-up using paired t-test. The association between multiple predictors (age, refractive error, DA, axial length, MD, MS) and each topographic parameter was accessed using linear regression (PROC GLM). All analysis was conducted using SAS (Cary, NC, version 9.2). *P* values less than 0.05 were considered statistically significant.

Tabel 6. The effect of mean defect (MD) on the parameters of the optic nerve head of physiologic large cup

HRT parameters	Regression Equation	*P* value
DA (mm^2)		0.543
CA (mm^2)		0.140
CDR	y = 5.746X-0.03244	0.004
RA (mm^2)	y = -1.645X+5.039	0.005
CV (mm^3)	y = 1.057X+1.993	0.043
RV (mm^3)	ŷ = -5.194X+4.248	0.002
MeCD (mm)		0.154
MxCD (mm)		0.567
CSM	y = 8.456X+3.250	0.017
HVC (mm)		0.570
mRNFLt (mm)	y = -7.044X+4.143	0.010
RNFLcsa (mm^2)	y = -1.419X+4.398	0.004

HRT (Heidelberg Retina Tomograph), disc area (DA), cup area (CA), cup/disc area ratio (CDR), rim area (RA), cup volume (CV), rim volume (RV), mean cup depth (MeCD), maximum cup depth (MxCD), cup shape measure (CSM), height variation contour (HVC), mean retinal nerve fiber layer thickness (mRNFLt), retinal nerve fiber layer cross-section area (RNFLcsa).

Tabel 7. The effect of mean sensitivity (MS) on the parameters of the optic nerve head of physiologic large cup

HRT Parameters	Regression Equation	*P* value
DA (mm^2)		
CA (mm^2)		0.435
CDR	ŷ = -5.168X+28.745	0.015
RA (mm^2)	ŷ = 1.78X+23.742	0.004
CV (mm^3)		0.119
RV (mm^3)	ŷ = 5.475X+24.643	0.002
MeCD (mm)		0.275
MxCD (mm)		0.817
CSM	ŷ = -8.326X+25.739	0.027
HVC (mm)		0.521
mRNFLt (mm)	ŷ = 7.854X+24.661	0.007
RNFLcsa (mm^2)	ŷ = 1.63X+24.318	0.002

HRT (Heidelberg Retina Tomograph), disc area (DA), cup area (CA), cup/disc area ratio (CDR), rim area (RA), cup volume (CV), rim volume (RV), mean cup depth (MeCD), maximum cup depth (MxCD), cup shape measure (CSM), height variation contour (HVC), mean retinal nerve fiber layer thickness (mRNFLt), retinal nerve fiber layer cross-section area (RNFLcsa).

Results

The mean age in the NC group was 34.86 ± 19.28 years, compared with 31.44 ± 17.17 years in PLC group. There were no significant differences in age, gender, and refractive error among the two groups (P > 0.05). Comparison of optic nerve head parameters between PLC and NC (**Table 1**) showed that DA, CA, CDR, CV, MeCD, MxCD and CSM of PLC were significantly larger than those of NC (P < 0.05). RA, RV, HVC, mRNFLt and RNFLcsa of PLC were significantly smaller than those of NC (P < 0.05).

Characteristics of the inferior, superior, nasal, and temporal quadrants of PLC

There was no statistically significant difference among four quadrants of DA (P > 0.05). The temporal quadrant of CA, CDR and CV was the largest, intermediate in superior and inferior, nasal was the smallest (P < 0.05), there was no significant difference between inferior and nasal (P > 0.05). Inferior and nasal of RA were much larger than superior and temporal, temporal was the smallest (P < 0.05), there was no significant difference between inferior and nasal (P > 0.05). The temporal quadrant of RV was much smaller than other three quadrants (P < 0.05), there was no significant difference among inferior, superior and nasal (P > 0.05). The superior quadrant of MeCD and MxCD was the largest (P < 0.05), there was no significant difference among other three quadrants (P > 0.05). The temporal and superior quadrants of CSM were larger than nasal and inferior (P < 0.05), there was no significant difference between temporal and superior, neither was nasal or inferior (P > 0.05). Inferior > superior > temporal > nasal in HVC. The superior quadrant of mRNFLt and RNFLcsa was larger than inferior and nasal, temporal was the smallest (P < 0.05), there was no significant difference between inferior and nasal (P > 0.05, **Tables 2** and **3**).

The effects of age, refractive error, and DA on the topographic parameters of the optic nerve head (ONH) of PLC

RA and RV were positively correlated with age (P < 0.05). CA, CDR, CV and CSM were negatively correlated with age (P < 0.05). There was no significant correlation among MeCD, MxCD, mRNFLt, RNFLcsa and age (P > 0.05). Large DA was corresponding to be large CA, CV, CDR, RA, and RV (P < 0.05) but small mRNFLt (P < 0.05). RA, RV, HVC, mRNFLt, RNFLcsa were positively correlated with the diopter of myopia (P < 0.05).

Tabel 8. Following up of optic nerve head parametersof physiologic large cup

HRT parameters	First examination	Last examination	*P* value
DA	2.799 (1.515,4.083)	2.797 (1.519,4.075)	0.847
CA	1.232 (0.136,2.328)	1.283 (0.183,2.383)	0.017
CDR	0.429 (0.168,0.690)	0.450 (0.187,0.713)	0.003
RA	1.567 (0.716,2.418)	1.514 (0.632,2.396)	0.018
CV	0.333 (-0.218,0.884)	0.388 (-0.145,0.921)	< 0.001
RV	0.330 (0.026,0.634)	0.384 (0.002,0.766)	< 0.001
MeCD	0.287 (0.044,0.530)	0.336 (0.113,0.559)	< 0.001
MxCD	0.652 (0.150,1.154)	0.742 (0.283,1.201)	< 0.001
CSM	-0.098 (-0.257,0.061)	-0.068 (-0.444,0.308)	0.051
HVC	0.347 (0.067,0.627)	0.397 (0.072,0.722)	0.002
mRNFLt	0.218 (0.046,0.390)	0.249 (0.073,0.425)	< 0.001
RNFLcsa	1.272 (0.276,2.268)	1.440 (0.380,2.500)	< 0.001

HRT (Heidelberg Retina Tomograph), disc area (DA), cup area (CA), cup/disc area ratio (CDR), rim area (RA), cup volume (CV), rim volume (RV), mean cup depth (MeCD), maximum cup depth (MxCD), cup shape measure (CSM), height variation contour (HVC), mean retinal nerve fiber layer thickness (mRNFLt), and retinal nerve fiber layer cross-section area (RNFLcsa).

Tabel 9. Following up of visual field, axial length and refractive error of physiologic large cup

	First examination	Last examination	*P* value
Intraocular pressure (mmHg)	17.5 (11.8,23.2)	16.9 (11.0,22.8)	0.002
MS	26.2 (19.5,32.9)	27.4 (21.9,32.9)	0.003
MD	2.8 (-3.5,9.1)	1.8 (-3.1,6.7)	0.006
Axial length (mm)	24.9 (22.4,27.5)	25.1 (22.4,27.8)	0.007
Refractive error (D)	1.57 (-4.47,7.61)	2.56 (-1.89,7.01)	< 0.001

Mean sensitivity (MS) , mean defect (MD).

CA, CDR, CV and CSM were negatively correlated with the diopter of myopia ($P < 0.05$, **Table 4**).

The effect of axial length on the parameters of the ONH of PLC

RA, RV, mRNFLt, and RNFLcsa were positively correlated with axial length. CA, CV, CDR and CSM were negatively correlated with axial length ($P < 0.05$, **Table 5**).

The effect of MD and MS on the parameters of the ONH of PLC

RA, RV, mRNFLt and RNFLcsa were positively correlated with MS ($P < 0.05$), CDR and CSM were negatively correlated with MS ($P < 0.05$). CDR, CV and CSM were positively correlated with MD ($P < 0.05$). RA, RV, RNFLcsa, mRNFLt were negatively correlated with MD ($P < 0.05$, **Tables 6** and **7**).

Study of the follow-up of eyes with PLC

We continued to follow up 100 PLC subjects (Vertical C/D ≥ 0.5, no retinal nerve fiber layer defects, IOP ≤ 21 mmHg, normal visual field, no family history of glaucoma and Chinese Han people) with the interval of every 3 months. 26 out of 100 subjects were excluded due to incomplete data. The mean length of follow-up of the remaining 74 subjects was 28 months (from 24 months to 32 months).

There were significant increases in CA, CDR, CV, RV, MeCD, MxCD, HVC, mRNFLt and RNFLcsa ($P < 0.05$), significant decrease in RA ($P < 0.05$), but no significant change in DA or CSM. In the long follow up, we also found that decreased IOP, increased MS, decreased MD, increased axial length with the increasing myopic diopters ($P < 0.05$, **Tables 8** and **9**).

Discussion

From 1990 to 2010, the prevalence of blindness and moderate and severe vision impairment (MSVI) caused by glaucoma increased 1.5% and 0.68% respectively in east Asia [9]. So we need to pay more attention about the diagnosis of glaucoma. As PLC is a confusable physiologic performance for early glaucoma, it is necessary to study characteristics of optic nerve head of PLCs comprehensively. Several authors and our study team [4, 10-14] have reported that normal eyes with greater optic disc were accompanied with greater DA, CA, CDR, RA, CV and less thickness of mRNFLt. In our present study, we found DA of PLC group was significantly larger than that of NC group. So the previous finding could help analyze the different parameters of disc cup and retinal nerve fiber layer between the two groups. DA directly affected other parameters of optic disc.

Large cup subject with large disc may not necessarily be a sign of glaucoma. On the contrary, small cup with small disc may come up with a pathologic disc.

Loss of nerve fibers is a main cause of narrow RA in glaucoma patients [6, 10, 15-18]. RA is an important indicator for pathologic changes and used to evaluate the outcome of clinical treatment. Aiarksinen et al. [19] compared RA among normal subjects, suspicious glaucoma and glaucoma, demonstrated remarkable statistical difference. In his measurement, lower 95% confidence interval was 1.09 mm^2. Min KH et al. [20] evaluated RA among normal subjects, PLCs and early glaucoma with HRT. They found the rim area value of PLC eyes tended to be less than that of normal eyes in this study, although the difference was not significant. Possible reasons for this result that they listed are about individual differences mostly. In 2013, Onmez F E et al. [21] evaluated and compared ONH parameters and RNFL thickness between macrodiscs and normal-sized healthy discs, demonstrated RA and RNFL thickness (inferior, superior, and mean) were found to be similar in both groups, while DA, CA, vertical C/D ratio, horizontal C/D ratio and CDR of marcodiscs were remarkably higher than that of normal discs ($P < 0.0001$). In our measurement, average RA of PLC was 1.53 ± 0.45 mm^2. Although the RA value was lower than normal subjects, risk of glaucoma may still be higher than that of a normal cup eye, the RA value may still be within the physiologic range, higher than the lower range of normal value (1.09 mm^2). Interestingly, normal RA varies with different location: the highest RA and RV value is located in inferior portion, followed by superior portion, and then nasal and temporal side [4]. However, nasal of RA is higher than the superior side in PLC, which could be one of the characteristics of PLC.

Previous studies demonstrated that large DA contained more amounts of optic nerve fibers but fewer fibers in per unit [10, 22]. Moreno-Montañés J et al. [23] evaluated the RNFL thickness with HRT-III among normal eyes, hypertensive eyes and glaucoma eyes, demonstrated that there was significant difference among the three groups. In their results, the median global RNFL thickness value was 0.25 mm (IR, 18 to 30) in normal eyes, 0.22 mm (IR, 0.16 to 0.27) in ocular hypertensive eyes, and 0.16 mm (IR, 0.11 to 0.22) in glaucomatous eyes ($P = 0.001$). Our data showed that DA of PLC was significantly larger than NC, while mRNFLt and RNFLcsa of PLC were remarkably lower. These findings were in compliance with the reduction of the fiber number per unit in normal eye. Normal optic nerve fibers present a regular and unique distribution. Thickness of optic nerve fibers varies in a different sub-area, with the maximum located superior and inferior sides of a disc, whereas, nasal and temporal sides have only half of the maximal thickness. In our study, we found that mRNFLt and RNFLcsa of PLC varied over four quadrants: the superior was maximal, the inferior and nasal were intermediate, and the temporal was minimal. Meanwhile, all PLCs presented a twin-peak shape, which matches the features of a NC.

In 2010, Songfeng Li et al. [24] evaluated and compared ONH and RNFL between normal, early glaucoma and advanced glaucoma eyes. The highest area under curve (AUCs) were vertical C/D (0.782) for ONH parameters and mRNFLt (0.816) for RNFL thickness between normal and early glaucomatous eyes, which confirmed these two parameters were the best for discriminating normal from early glaucomatous eyes. In 2013, Renato Lisboa et al. [25] also demonstrated that only average RNFL thickness and vertical C/D showed higher AUCs than other parameters for detecting preperimetric glaucomatous damage in a cohort of glaucoma suspects. Our study showed significant difference in DA, CA, CDR, RA, CV and RNFL thickness between two groups and further studies should evaluate whether a combination of these parameters can improve the performance of this technology to identify PLC from normal and early glaucoma eyes.

It's worth mentioning that we have stratified each parameter by age, refractive error, and disc area and then applied a multiple linear regression model, which provides additional results and more appropriate interpretation compared Mardin et al. [26]. Yamazaki et al. [10] reported that RV, mRNFLt and RNFLcsa were positively correlated with the diopter of myopia in normal eyes. Our data supported that PLC had similar features. Additionally, CA, CDR, CV, and CSM are negatively correlated with the diopter of myopia in PLC, while Yamazaki et al. failed to find statistical correlation [10]. Tsai et al. [27] identified no correlation between refractive error and MeCD by HRT in 180 normal subjects (43 African-American, 45 Asian, 48 Hispanic and 44 white subjects). Our data is in compliance with Tsai's report. Other reports showed that the refractive error did not influence any disc parameters in normal eyes [6, 28].

We found that RA, RV, mRNFLt and RNFLcsa were positively correlated with axial length. CA, CV, CDR and CSM were negatively correlated with axial length, which were consistent with our finding that RA, RV, mRNFLt and RNFLcsa were positively correlated with the diopter of myopia. CA, CV, CDR and CSM were negatively correlated with the diopter of myopia. They indicated axial length and refractive error had the same effect on the topographic parameters of the optic disc of PLC.

Varma et al. [6] reported that there was no age-related difference in any of the disc measurements, or CDR was increased with aging though their correlation is minimal [29]. Our data showed mRNFLt in PLC had no statistical correlation with age. CA, CDR, CV and CSM were negatively correlated with age, while RA and RV were positively correlated with age. We demonstrated that most of the optic disc parameters in PLC were closed to NC. A few exceptions: DA of PLC was significantly larger while mRNFLt less than NC. Nasal quadrant was larger than superior quadrant in RA. CA and CDR were negatively correlated with either the diopter of myopia or age; RA was positively correlated with age. There was no linear relationship between MeCD, MxCD and refractive error, age or DA, so they could be two markers for evaluation of structural parameters of PLC.

We continued to follow up 100 PLC subjects for at least 24 months with the interval of every 3 months. 26 out of 100 subjects were excluded due to incomplete data. The mean length of follow-up of the remaining 74 subjects was 28 months (from 24 months to 32 months). We found significant increases in CA, CV, CDR, MxCD and MeCD, meanwhile decreases in RA. These changes were consistent with the results done by many other authors [29, 30]. Previous studies demonstrated that the amounts of optic nerve fibers reduced with increase of age, decreasing optic nerve fibers caused increased C/D ratio and decreased RA, but without glaucoma-like damage [28, 30-33]. Additionally, our results showed that RV, mRNFLt, RNFLcsa were increased in PLC. The inconsistency between our results and the results of the most other investigators could be related with shorter follow up time and small sample size. However, at least, our results confirmed that there was no loss of nerve fiber in PLC.

Increased MS, decreased MD and reduced IOP do not support that PLC evolve to glaucoma during our follow up. We should exclude some other factors affecting the reliability of results during the follow up. For example, some of PLC subjects in our study population were adolescent and poorly cooperative in the first eye exam, which could affect the results of visual field and IOP. The follow up visit, they became more cooperative and familiar with the instrument, which could lead to elevation of threshold of visual fields. We found myopia was 0.99D deeper along with axial length 0.194 mm longer in PLC, indicating strong association between deepening of myopia and increasing of axial length. Myopic eyes have longer axial eye length and thinner ocular wall than emmetropic eyes [34]. Additionally, thinner ocular wall would cause underestimating IOP. This may explain the decrease of IOP.

Optical coherence tomography (OCT) is a high-resolution, cross-sectional imaging technique whose measurement of the RNFL thickness is better than that of HRT [3]. However until now HRT is still being frequently used and studied [35-40]. Schuman et al. noted that cup-to-disk area ratio and rim volume were the HRT parameters with the highest diagnostic precision by comparing OCT with HRT I [4]. Klamann MK et al. found that the anterior chamber depth (ACD) could affect measurement of the optic disc size with the OCT while that of HRT 3 turned out to be independent of the ACD [5]. Sevda Aydin Kurna et al. used HRT to evaluate optic nerve head differences among the patients with Alzheimer's disease (AD), glaucoma and control [2]. Chang ST et al. correlated optic nerve diffusion tensor imaging (DTI) parameters with the rim area obtained with HRT in glaucoma patients and controls [6]. Barleon L etal used HRT to screen for major ophthalmological diseases in a large working population [40].

Future study is needed to detect the characteristic of PLC using OCT.

Conclusion

Optic disc structural parameters in PLC presented a similar pattern to normal subject, while PLC has its characters. There were some changes in the topographic parameters of the optic discs of PLCs overtime, but no glaucomaous damage was detected during our follow up.

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Disclosure of conflict of interest

None.

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