Alterations of Macular Structure in Non-Glaucomatous Subjects With Obstructive Pulmonary Function

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Purpose. The purpose of this study was to identify possible associations between obstructive pulmonary function and macular structure parameters on optical coherence tomography (OCT) and angiography in subjects without glaucomatous optic neuropathy.

Methods. A total of 70 patients were prospectively enrolled from June to December 2021 as a part of All About Life Yongin-Pulmonary/Psychiatry, Rehabilitation, Eye (AALY PRE) cohort in Yongin Severance Hospital. Patients underwent intraocular pressure (IOP), visual acuity measurements, cirrus OCT, OCT angiography, and pulmonary function testing (PFT) on the same day. Subjects with glaucomatous optic nerve damage were excluded. Those whose first second of forced expiration (FEV_1) to forced vital capacity (FVC) ratio was below 70% were diagnosed with obstructive pulmonary function. Vessel densities (VDs) of retinal superficial vascular plexus were compared.

Results. Patients with obstructive function ($n = 30$) were significantly older than those with normal pulmonary function ($n = 40$, $P < 0.001$). After adjusting for age, IOP, and average ganglion cell-inner plexiform layer (GCIPL) thickness, macular VD was significantly decreased in all sectors except for the nasal sector in subjects with obstructive pulmonary function in comparison to those with normal function ($P = 0.006$). Multivariate regression analysis demonstrated that macular VD was linearly associated with FEV_1/FVC ($\beta = 0.102$, $P = 0.031$). In subjects with obstructive function, the severity of pulmonary obstruction, FEV_1, was linearly associated with GCIPLT ($\beta = 0.302$, $P = 0.017$).

Conclusions. Obstructive pulmonary function is associated with reduced macular VD in subjects without glaucoma. Among subjects with obstructive pulmonary function, the severity of pulmonary obstruction is associated with GCIPL thickness in the macular region. Further studies are needed on the relationship between pulmonary function and macular disease.

Keywords: chronic obstructive pulmonary disease (COPD), ganglion cell-inner plexiform layer (GCIPL), macular vessel density, open-angle glaucoma, optical coherence tomography (OCG), optical coherence tomography angiography

Recent advances in optical coherence tomography (OCT) angiography have enabled noninvasive visualization of perfused blood vessels as well as quantitative analysis of vascular density and blood flow to optic nerve head (ONH) and retina, using motion contrast and scattering effects of moving red blood cells.[1] The retinal microvasculature is a complex system that is affected by both ocular and systemic diseases.[2,3] Therefore, understanding the status of microvasculature may not only help diagnose systemic disease, but also helps examine the association between systemic disease and ocular disease.[4,5]

Obstructive pulmonary disease, including chronic obstructive pulmonary disease (COPD), is one of the leading causes of mortality worldwide.[6] It is a disease with indolent evolution and often irreversible systemic repercussions.[7] Cardiovascular disease, renal failure, stroke, musculoskeletal dysfunction, and autoimmune disorders are just a few of the numerous conditions which have been associated with this pulmonary disease,[8] yet there have been relatively few investigations in the context of ocular disease. Although studies have been conducted in the past to quantify peripapillary retinal vessel density (VD) and retinal nerve fiber layer (RNFL) thickness in COPD in an attempt to identify its association with optic neuropathies, such as glaucoma,[9–11] they were primarily concerned with ONH and yielded somewhat inconsistent results. In this study, we attempt to conduct a cross-sectional comparative analysis on the difference in structural parameters of the macula between patients with COPD and healthy controls as the macula is known to be especially vulnerable to systemic disease.[12] The aim of this study was to identify damages in macular structure, including VD and ganglion cell-inner

plexiform layer (GCIPL) thickness, in non-glaucomatous subjects with obstructive pulmonary disease in comparison to those without pulmonary disease and examine a potential association of pulmonary disease with optic neuropathies.

Methods

Study Population

Patients in the All About Life Yongin-Pulmonology & Psychiatry, Rehabilitation & Eye - (AALY-PRE), an ongoing, prospective, longitudinal cohort study at Yongin Severance Hospital, Yonsei University College of Medicine, were enrolled in this cohort study. The cohort was developed in order to assess characteristics associated disease prevalence, diagnosis, and treatment of residents in Yongin, Gyeongido, Republic of Korea. Patients enrolled in the AALY-PRE cohort undergo spirometry, impulse oscillometry, heart rate variability, body mass index, hand grip strength test, and ophthalmologic examinations in a single day. The data for the present study are those collected at the time of cohort enrollment. The study protocol was approved by the Institutional Review Board of Yongin Severance Hospital (approval number 9-2021-0014), and the study was conducted in adherence to the tenets of the Declaration of Helsinki. All patients provided written informed consent at the time of enrollment.

Inclusion criteria for the present study were (1) age at the time of enrollment of 40 years or older; (2) best-corrected visual acuity greater than 20/16, and (3) refractive errors within 6 diopters of sphere and 3 diopters of cylinder. Exclusion criteria were (1) diagnosis of open-angle or angle-closure glaucoma; (2) history of any retinal or optic nerve disease affecting OCT measurements (including but not limited to ischemic optic neuropathy, multiple sclerosis, myelin-oligodendrocyte glycoprotein antibody-associated disease and neuromyelitis optica spectrum disorder, uveitis, and age-related macular degeneration); (3) intraocular pressure (IOP) exceeding 21 mm Hg; (4) history of ocular trauma or intraocular surgery other than simple cataract extraction; (5) clinical evidence of intracranial lesion, neurologic disorder, rheumatologic disease, or systemic vasculitis; and (6) history of systemic medication use known to induce optic neuropathy (e.g. ethambutol, digoxin, and vigabatrin). Based on the aforementioned criteria, one eye of each patient was included in this study. In cases where both eyes met the inclusion criteria, the eye with the lower average RNFL thickness was considered as the study eye.

Ophthalmologic Examinations

All subjects underwent complete ophthalmologic assessments on a single day, during which pulmonary function test, OCT and OCT angiography were all conducted. A medical history was obtained. Visual acuity and refraction error were measured. IOP was obtained with a Goldmann applanation tonometer (GAT; Haag-Streit model BQ-900; Haag-Streit, Inc., Bern, Switzerland). Slit-lamp examinations, gonioscopy, and dilated fundus examinations with a 90 D lens were conducted by a single investigator (author S.Y.L.). Patients also underwent color disc stereophotography. Two experienced graders (authors J.S.L. and B.B.) assessed optic disc stereographs and OCT to exclude subjects with manifest glaucoma (n = 9). Glaucoma was diagnosed when glaucomatous optic disc changes (such as localized or diffused neuroretinal rim thinning, a difference of cup-to-disc ratio greater than 0.2 between 2 eyes) were noted on stereo-disc photographs, and RNFL defect was identified on cirrus OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA). Any discrepancy between the two graders was resolved by a third adjudicator (author S.Y.L.)

Pulmonary Function Test

Spirometry (Vmax 22; Sensor-Medics, Yorba Linda, CA, USA) was conducted by trained technicians, following guidelines outlined by the American Thoracic Society/European Respiratory Society for standardizing pulmonary function tests at the time of cohort enrollment.[13] Spirometry test produced forced expiratory volume in 1 second (FEV_1; maximum volume exhaled during the first second of expiration as a measurement of large airway obstruction), forced expiratory flow 25% to 75% (FEF 25–75%; mean forced expiratory flow in the middle half of forced vital capacity as a measurement of middle to small airway obstruction), peak expiratory flow (PEF; maximum flow obtained as a measurement of large airway function), and forced vital capacity (FVC; the volume of air forcefully exhaled after maximal inhalation). An "acceptable spirometry curve" was defined as that which shows the start of the test and expiration $\geq$6 seconds, shows greatest differences between the 2 measurements of FEV_1 and FVC <150 mL. A test that produced two acceptable spirometry curves was considered valid and included for analysis. Subjects were categorized as having "obstructive" pulmonary function if the ratio of FEV_1 to FVC (FEV_1/FVC) was below 70% according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[14] The severity of airflow limitation was determined according to the same criteria, using FEV_1. GOLD criteria state that in individuals with FEV1/FVC below 70%, decreasing FEV_1 indicates more severe obstruction (GOLD1 FEV_1 80 or above, GOLD2 50–79, GOLD3 30–49, and GOLD4 FEV_1 below 30). Subjects were considered to have normal pulmonary function if FEV_1/FVC $\geq$70% and FVC $\geq$80% predicted. Patients identified to have COPD following the spirometry test were directed to consult with pulmonologists for prescriptions of appropriate inhalers.

OCT and OCT Angiography

Peripapillary RNFL and macular GCIPL thickness were measured with Cirrus OCT (Carl Zeiss Meditec, Inc., Dublin, CA, USA) using the 200 × 200 optic disc cube and 512 × 128 macular cube protocols of Cirrus OCT version 6.0 software, respectively. OCT angiography (AngioPlex; Carl Zeiss Meditec) was performed and 6 × 6 mm^2 of peripapillary and macular areas were collected. Its algorithm is described in detail elsewhere.[15] Briefly, en face microvascular images are generated by taking 350 A-scans 5 µm apart along the horizontal dimension of a B-scan for 350 B-scans. The internal limiting membrane was set as the inner surface of the superficial retinal layer and the outer border of the inner plexiform layer as the outer surface. VD of superficial vascular plexus of retina was calculated by adding the total length (mm) of perfused vasculature per mm^2 of a 6 mm-diameter circle by the AngioPlex software. All OCT and OCT angiography scans were evaluated for image quality by a single investigator (author J.S.L.) and only those scans with a signal strength greater than 6 and without any artifacts were selected for analysis.

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Statistical Analysis

All statistical analyses were performed with version 23 of SPSS (SPSS Inc., Chicago, IL, USA). Wilk-Shapiro test was conducted to determine the distribution of data. Normally distributed continuous data were presented as mean ± standard deviation (SD), and categorical data were presented as a number (percentage). Comparisons between the obstructive and normal pulmonary function groups were made with Student's *t*-test for continuous variables and Chi-square test for categorical variables. Retinal superficial VD were compared between the two groups using analysis of covariance (ANCOVA) in order to adjust for age, sex, and either baseline RNFL or GCIPL thickness. Univariate linear regression analyses were performed separately for each variable. To build a multivariate model, a stepwise selection method was adopted with the entry P value of < 0.1 and a stay P value of < 0.05. Age and sex were additionally adjusted in multivariate models. A P value < 0.05 was considered statistically significant.

Table 1. Baseline Characteristics of Subjects According to Pulmonary Function Types

	Obstructive ($n = 30$)	Normal ($n = 40$)	*P* Value
Age, y	75.9 ± 3.7	72.0 ± 4.7	<0.001
Females, *n* (%)	9 (30.0)	33 (82.5)	<0.001
Pseudophakia, *n* (%)	11 (36.7)	11 (27.5)	0.288
IOP, mm Hg	12.8 ± 2.1	13.4 ± 2.5	0.370
SE, D	0.1 ± 1.4	0.6 ± 1.9	0.182
BMI, kg/m^2	25.0 ± 2.7	24.1 ± 3.2	0.257
Systemic conditions, *n* (%)			
Hypertension	10 (33.3)	18 (45.0)	0.230
DM	6 (20.0)	8 (20.0)	0.621
Dyslipidemia	5 (16.7)	13 (32.5)	0.073
Smoking, *n* (%)			0.014
Current smoker	4 (13.3)	2 (5.0)	
Exsmoker	8 (26.7)	3 (7.5)	
Never smoker	18 (60.0)	35 (87.5)	
PFT, %			
FEV_1	75.3 ± 17.7	98.7 ± 10.3	<0.001
FVC	80.6 ± 15.2	93.6 ± 10.8	<0.001
FEV_1/FVC	62.3 ± 7.9	76.6 ± 4.0	<0.001
FEF 25-75%	41.5 ± 15.3	86.0 ± 25.1	<0.001
PEF	86.3 ± 23.4	99.9 ± 22.7	0.011
RNFLT, um			
Average	89.7 ± 17.6	90.1 ± 12.0	0.916
Superior	104.2 ± 25.9	108.2 ± 22.2	0.484
Inferior	110.7 ± 20.4	117.1 ± 21.6	0.217
Nasal	74.3 ± 26.1	66.9 ± 9.0	0.100
Temporal	69.5 ± 16.2	68.4 ± 12.5	0.736
GCIPL thickness, um			
Average	74.2 ± 18.6	77.3 ± 12.5	0.414
Minimum	65.5 ± 21.5	69.6 ± 18.6	0.403
Superior	71.0 ± 20.6	75.9 ± 14.3	0.246
Superotemporal	73.1 ± 18.8	77.0 ± 14.2	0.329
Inferotemporal	75.5 ± 18.6	78.5 ± 17.5	0.484
Inferior	72.0 ± 20.0	75.7 ± 16.2	0.392
Inferonasal	75.4 ± 20.0	78.7 ± 11.2	0.392
Superonasal	78.0 ± 20.0	78.0 ± 13.3	0.998

P value < 0.05 was considered statistically significant.

IOP, intraocular pressure; SE, spherical equivalent; BMI, body mass index; DM, diabetes mellitus; CVA, cerebrovascular accident; PFT, pulmonary function test; FEV_1, forced expiratory volume; FVC, full vital capacity; FEF, forced expiratory flow; PEF, peak expiratory flow; RNFLT, retinal nerve fiber layer thickness; GCIPL thickness, ganglion cell-inner plexiform layer thickness.

Results

Baseline Characteristics

Baseline characteristics of subjects included in the study are presented in Table 1. The obstructive group ($n = 30$) consisted of less women (30.0%) than the normal group ($n = 40$, 82.5% women, $P < 0.001$). The subjects with obstructive function (75.9 ± 3.7 years) were significantly older than those with normal function (72.0 ± 4.7 years, $P < 0.001$). Of the COPD group, current smokers comprised of 3 men and 1 woman, and exsmokers of 8 men, and never-smokers of 10 men and 8 women (Supplementary Table S1). Of the normal group, 1 man and 1 woman were current smokers, 3 women exsmokers, and 6 men and 29 women never-smokers. Baseline IOP and visual acuity were comparable between the 2 groups, and no significant difference was found in the proportions of subjects diagnosed with hypertension or type 2 diabetes mellitus (DM). A detailed list of comorbidities and medications at the time of enrollment is provided as Supplementary Table S2. The RNFL and GCIPL thicknesses were comparable in all sectors between the two groups at baseline.

Table 2. Comparison of Superficial Vessel Densities Between Subjects With Obstructive and Normal Pulmonary Function Types

	Obstructive ($n = 30$)	Normal ($n = 40$)	*P* Value
Disc signal strength	8.6 ± 1.2	9.0 ± 2.2	0.282
Peripapillary VD, mm/mm^2*			
Inner			
Average	15.0 ± 4.4	17.1 ± 1.5	0.064
Superior	15.5 ± 4.6	17.3 ± 1.6	0.199
Inferior	15.6 ± 4.6	17.7 ± 1.2	0.031
Nasal	15.1 ± 4.9	17.1 ± 2.2	0.135
Temporal	13.7 ± 4.6	16.1 ± 2.4	0.148
Outer			
Average	16.2 ± 4.2	17.9 ± 1.0	0.172
Superior	16.3 ± 4.7	18.0 ± 1.6	0.164
Inferior	16.4 ± 4.3	18.3 ± 1.4	0.104
Nasal	14.8 ± 4.1	16.4 ± 2.4	0.377
Temporal	17.2 ± 4.8	18.8 ± 1.1	0.412
Full	15.6 ± 4.0	17.3 ± 1.0	0.094
Macula signal strength	8.6 ± 1.2	8.9 ± 1.3	0.260
Macular VD, mm/mm^2,†			
Inner			
Average	13.3 ± 4.9	16.5 ± 1.8	0.006
Superior	13.8 ± 5.2	16.9 ± 1.9	0.014
Inferior	13.5 ± 5.0	16.5 ± 2.0	0.016
Nasal	13.4 ± 5.2	16.2 ± 2.8	0.059
Temporal	12.5 ± 5.3	16.6 ± 1.9	0.004
Outer			
Average	14.2 ± 4.7	17.2 ± 1.7	0.007
Superior	14.2 ± 4.8	17.4 ± 1.9	0.008
Inferior	14.2 ± 4.7	17.3 ± 2.2	0.006
Nasal	16.2 ± 5.5	18.4 ± 1.9	0.131
Temporal	12.0 ± 4.9	15.9 ± 2.3	0.017
Full	13.7 ± 4.6	16.8 ± 1.7	0.006

* P value from ANCOVA, adjusting for age, IOP and average RNFL thickness.

† P value from ANCOVA, adjusting for age, IOP, and average GCIPL thickness.

VD, vessel density; IOP, intraocular pressure; RNFL thickness, retinal nerve fiber layer thickness; GCIPL thickness, ganglion cell-inner plexiform layer thickness.

Decreased Macular VD in Subjects With Obstructive Pulmonary Function

Retinal superficial VDs of the macular region were compared between the subjects with COPD and the normal pulmonary function groups (Table 2). After adjusting for age, IOP, and average GCIPL thickness, the obstructive group showed significantly reduced macular retinal VD in all sectors in comparison to the normal group according to ANCOVA analysis, except for the nasal sector. In comparison, after adjusting for age, IOP, and average RNFL thickness, no difference was found in the peripapillary retinal VD between the two groups except for the inner inferior quadrant (15.6 ± 4.6 mm/mm^2 obstructive vs. 17.7 ± 1.2 mm/mm^2 normal, $P = 0.031$).

Associations Among Macular Superficial VD, GCIPL, and Pulmonary Function

Linear regression analyses were performed to identify variables showing significant associations with macular VD (Table 3). A univariate linear regression analysis found that age, spherical equivalent, average GCIPL thickness, and FEV_1/FVC were significantly associated with macular VD. Of note, macular VD did not show significant associations with any of the underlying disease identified (Supplementary Table S3). Subsequent multivariate analysis that adjusted for age, spherical equivalent, sex, and average GCIPL thickness demonstrated that the measure of pulmonary obstruction, FEV_1/FVC, has a positive linear correlation with macular VD ($\beta = 0.102$, 95% confidence interval [CI] = 0.009–0.194, $P = 0.031$). The positive linear correlation between FEV_1/FVC and macular VD remained significant even after smoking history was adjusted ($\beta = 0.247$, 95% CI = 0.001–0.185, $P = 0.048$). Then, subjects with obstructive function were further analyzed with linear regression analyses to examine whether the severity of pulmonary obstruction was associated with GCIPL thickness, as shown in Table 4. FEV_1 was considered an indicator of pulmonary obstruction severity, where more severe obstruction is indicated by lower FEV_1 values. A univariate analysis identified age, spherical equivalent, and FEV_1 to be associated with GCIPL thickness.

Table 3. Linear Regression Analysis to Identify Association With Macular Superficial Vessel Density

	Univariate			Multivariate*			Multivariate†		
	β	95% CI	*P* Value	β	95% CI	*P* Value	β	95% CI	*P* Value
Age, y	−0.209	−0.370 to −0.047	0.012	−0.046	−0.221 to −0.129	0.599	−0.047	−0.214 to 0.141	0.686
Female	1.189	−0.0318 to −2.697	0.120	0.037	−1.598 to 1.671	0.965	0.013	−1.542 to −1.713	0.917
SE	0.430	0.035 to 0.824	0.033	0.264	−0.118 to −0.646	0.173	0.149	−0.110 to −0.662	0.158
IOP	−0.177	−0.440 to −0.086	0.183						
BMI	−0.170	−0.405 to −0.066	0.157						
Smoking history	−0.940	−2.112 to −0.241	0.117				−0.076	−0.771 to −1.605	0.487
Hypertension	−0.044	−1.534 to −1.446	0.953						
DM	−0.375	−2.214 to −1.464	0.686						
Dyslipidemia	0.024	−1.411 to −1.749	0.832						
Average RNFL thickness	0.023	−0.029 to −0.076	0.379						
Average GCIPL thickness	0.076	0.027 to 0.125	0.003	0.062	0.013 to 0.111	0.014	0.264	0.013 to 0.112	0.014
FEV_1/FVC	0.123	0.046 to 0.201	0.002	**0.102**	**0.009 to 0.194**	**0.031**	**0.247**	**0.001 to 0.185**	**0.048**

P values < 0.05 were considered statistically significant.

* Multivariate analysis adjusted for age, sex, and variables with $P < 0.1$ in univariate analysis.

† Multivariate analysis adjusted for age, sex, smoking history, and variables with $P < 0.1$ in univariate analysis.

CI, confidence interval; SE, spherical equivalent; IOP, intraocular pressure; BMI, body mass index; DM, diabetes mellitus; RNFL thickness, retinal nerve fiber layer thickness; GCIPL thickness, ganglion cell-inner plexiform layer thickness; FEV_1, forced expiratory volume; FVC, full vital capacity.

Table 4. Linear Regression Analysis to Identify Association With GCIPL thickness in Subjects With Obstructive Pulmonary Function

	Univariate			Multivariate*			Multivariate†		
	β	95% CI	*P* Value	β	95% CI	*P* Value	β	95% CI	*P* Value
Age, y	−2.389	−3.666 to −1.111	<0.001	−2.137	−3.353 to −0.921	0.001	−2.137	−3.388 to −0.886	0.001
Female	2.002	−8.267 to −12.271	0.698	3.171	−5.707 to −12.049	0.478	3.533	−6.126 to −15.192	0.398
SE	5.094	1.833 to 8.355	0.003	4.221	1.188 to 7.254	0.007	3.366	1.247 to 7.486	0.007
IOP	1.646	−0.818 to −4.109	0.186						
BMI	−0.617	−2.429 to −1.195	0.499						
Smoking history	−0.093	−9.618 to −4.417	0.462				−0.976	−7.944 to −5.991	0.780
Hypertension	−7.436	−17.390 to 2.518	0.140						
DM	2.946	−8.548 to 14.441	0.610						
Dyslipidemia	6.080	−15.792 to 27.952	0.574						
Average RNFLT	−0.029	−0.347 to −0.290	0.859						
FEV_1	0.276	−0.007 to −0.560	0.056	**0.302**	**0.056 to 0.547**	**0.017**	**0.314**	**0.061 to 0.566**	**0.016**

P values < 0.05 were considered statistically significant.

* Multivariate analysis adjusted for age, sex, and variables with $P < 0.1$ in univariate analysis.

† Multivariate analysis adjusted for age, sex, smoking history, and variables with $P < 0.1$ in univariate analysis.

GCIPL thickness, ganglion cell-inner plexiform layer thickness; COPD, chronic pulmonary obstructive disease; CI, confidence interval; SE, spherical equivalent; IOP, intraocular pressure; BMI, body mass index; DM, diabetes mellitus; RNFL thickness, retinal nerve fiber layer thickness; FEV_1, forced expiratory volume.

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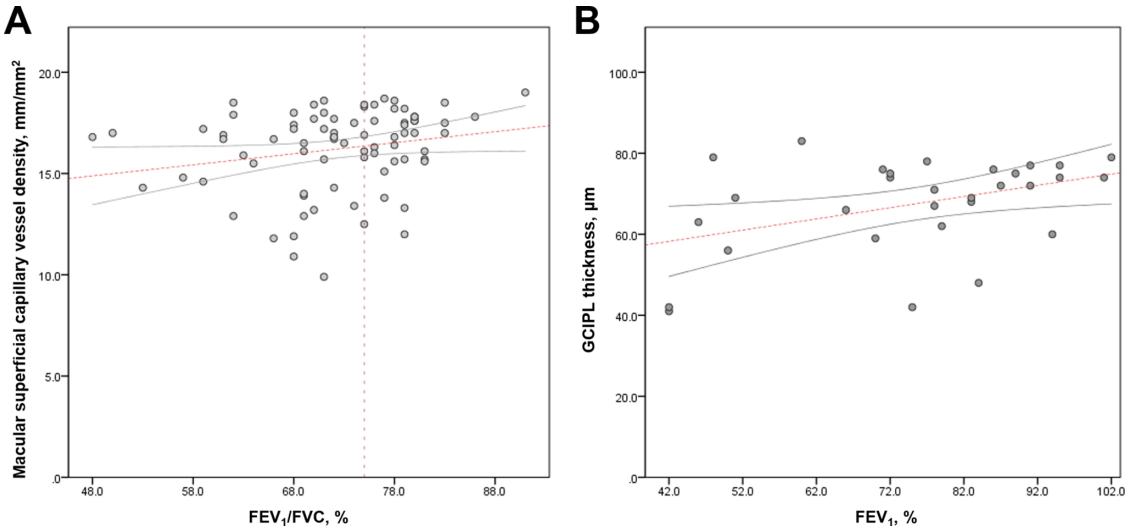

Figure. Scatterplots of macular structure and pulmonary function. (**A**) Superficial vessel density of the macula was linearly associated with FEV1/FVC in a positive manner, indicating subjects with pulmonary obstruction tended to have decreased vessel density in the macula. The red dotted line indicates FEV1/FVC 75%, below which is considered pulmonary obstruction. (**B**) The GCIPL thickness of the macula of those subjects with pulmonary obstruction (i.e. FEV1/FVC <75%) was plotted against FEV1, which indicates the severity of obstruction in COPD. Subjects with more severe pulmonary obstruction tended to show thinner GCIPL.

Following multivariate analysis that adjusted for age, sex and spherical equivalent, FEV_1 was found to have a positive linear relationship with GCIPL thickness in subjects with obstructive pulmonary function ($\beta = 0.302$, 95% CI = 0.056–0.547, $P = 0.017$ before correction for smoking history; $\beta = 0.314$, 95% CI = 0.061-0.566, $P = 0.016$ after correction for smoking history), indicating that more severe pulmonary obstruction was associated with thinner GCIPL thickness in subjects with COPD (see the Fig.).

Discussion

The present study evaluated OCT and OCT angiography measurements of the macula in non-glaucomatous subjects with obstructive pulmonary function. In comparison to those with normal pulmonary function, macular superficial VD were significantly decreased in subjects with obstructive pulmonary function. According to our analysis, macular VD showed a statistically significant positive correlation with FEV_1/FVC ratio. Furthermore, the severity of obstruction, FEV_1, was found to have a positive linear correlation with macular GCIPL thickness in subjects with obstructive pulmonary function.

Relatively few studies have investigated the relationship between obstructive pulmonary disease and optic neuropathies in the past, and underlying etiological mechanisms remain unclear. Generally, however, these studies show in common that nerve fiber layers and peripapillary vasculature are damaged in patients with obstructive pulmonary disease.[9–11] For instance, both Ugurulu et al. and Gok et al. demonstrated thinner peripapillary RNFL in inferior and nasal quadrants in those with COPD.[10,11] Kocamis et al. demonstrated decreased subfoveal choroidal thickness in subjects with COPD.[16] Ozcimen et al. further revealed that peripapillary choroidal tissues in the inferonasal and inferotemporal quadrants were thinner in patients with COPD.[17] In their study, they postulated that the difference was likely due to increased vascular resistance and resultant decrease in blood flow to ONH in COPD. Their hypothesis was in part supported by Alkan et al., who reported that the mean peripapillary retinal VDs were significantly lower in patients with COPD in comparison to healthy controls.[9] The authors proposed that decreases in retinal VD are the reason for RNFL thinning observed in patients with COPD. Through this present study, we sought to evaluate whether previously reported associations between optic nerve structures and pulmonary functions hold true in light of our most recent findings that women with COPD are at increased risks for open-angle glaucoma in comparison to women without the disease,[18] by evaluating structural parameters in non-glaucomatous subjects with obstructive pulmonary function.

According to our analysis, subjects with obstructive pulmonary function demonstrated generally reduced vessel densities in comparison to those with normal pulmonary function. Such alterations in retinal vascular vessels demonstrated in our study may be a result of systemic pathophysiologic changes in the form of vascular structure loss and vasoconstriction in obstructive pulmonary disease.[9] The literature describes chronic hypoxemia, systemic inflammation, endothelial dysfunction, and increased sympathetic activity in COPD to be the underlying mechanisms.[8] More specifically, chronic hypoxemia and resultant oxidative stress and systemic inflammation produce endothelial dysfunction in COPD such that the critical balance is altered among vasoregulators, including nitric oxide (NO) and endothelin-1 (ET-1),[19,20] which also happen to be the most important determinants of ocular blood flow and retinal arterial tone.[21,22] Increased serum ET-1 and decreased NO levels have been reported in patients with COPD, especially during nocturnal oxyhemoglobin desaturation.[23] The results of previous color Doppler ultrasonography studies also support this notion, as vascular resistance was found to be increased in the central retinal artery and posterior ciliary artery in patients with COPD.[24,25] Our findings additionally support the hypothesis laid out by previous studies that the altered pulmonary milieu may be associated with systemic vascular changes that can also be found in ocular structures.

Our findings, however, are distinguished from those of previous studies in that macular structure was chiefly analyzed. Our primary focus was based on emerging evidence which suggests that the site of early structural damage holds pathoetiologic importance in optic neuropathies.[26,27] In glaucoma, for example, when microvascular damage and vascular hypoperfusion are mainly implicated at an IOP comparable to that of the normal population, earliest structural damage is said to take place predominantly in the macular GCIPL over the peripapillary RNFL.[28] A previous study also demonstrated that systemic inflammation in COPD is strongly associated with pathological arterial stiffness,[29,30] which we recently identified to be an important risk factor in predominantly macular GCIPL damage in early glaucoma.[15] So if, as previous studies argue, the relationship between obstructive pulmonary disease and optic neuropathies is explained by vascular dysfunction, we suspected that earliest alterations were more likely to be present in the macula. Consistent with this hypothesis, the difference in retinal VD between obstructive and normal pulmonary function types was statistically significant only in the macular area in our study subjects.

The structural alterations in the macula instead of the peripapillary area in non-glaucomatous subjects in our study partly contrast findings of previous studies, and they may be interpreted in the following contexts. First, if vascular dysfunction plays a role in nerve fiber layer damage as we suspect, and if cardiovascular disease predominantly damages the macula first as studies on glaucoma suggest,[28] then initial damages in this region might not have been detected by previous studies,[9–11] which have put relatively less emphasis on the macular structure. Different extents to which vascular dysfunction affected nerve fiber layer may have been the reason for the discrepancies in the locations of VD loss and RNFL thinning among them. In addition, most of previous studies excluded subjects with cardiovascular disease,[9,10] with which obstructive pulmonary disease is closely associated.[7] By excluding these subjects with systemic complications, effects of vascular dysfunction were likely not represented. Second, the differences in the proportions of ever smokers may have influenced the outcome. The majority of the obstructive group in our study were never smokers, and a growing number of studies are identifying differences in smoker and non-smoker COPD.[31] For instance, nonsmoker COPD is associated with lower oxygen saturation levels and more frequent acute exacerbation rates.[32,33] More severe oxidative stress is thought to occur during acute exacerbations in nonsmoker COPD compared to smoker COPD.[34] Furthermore, acute exacerbations in general are thought to be followed by a period during which subjects are particularly vulnerable to cardiovascular events.[35] We acknowledge that there exists a possibility that obstructive pulmonary disease is associated with optic neuropathies through cardiac disease, with which it shares common risk factors and pathophysiological processes.[7,36] Therefore, longitudinal studies are necessary to test our hypothesis that impaired ocular hemodynamics and vasoregulator imbalance cause direct anoxic neuronal damage in obstructive pulmonary disease.

In obstructive pulmonary disease, systemic inflammation, once established, is thought to persist and progress with time regardless of whether causative factors such as smoking and other environmental pathogens are eliminated or not.[37] Systemic inflammation in turn aggravates airway obstruction, systemic oxidative stress, and vascular dysregulation. Fittingly, multiple meta-analyses show that the severity of endothelial dysfunction in obstructive pulmonary disease is positively correlated with the degree of airway obstruction, as reflected in reduced FEV_1.[38–40] This surrogate marker of obstructive pulmonary disease severity has also been found to negatively correlate with cardiovascular risks, including heart failure, in epidemiological studies.[41,42] In the present study, in subjects with obstructive pulmonary disease, FEV_1 showed a significant positive relationship with GCIPL thickness of the macula, after controlling for confounders such as age, sex, refraction error, and baseline GCIPL thickness. In the past, a study by Alim et al. indicated a possible difference in GCIPL thickness depending on the presence of pulmonary obstruction as their simple, unadjusted comparison between patients with COPD and healthy controls revealed a statistically significant difference.[43] Similarly, Gok et al. illustrated an inverse relationship, albeit statistically nonsignificant, between RNFL thickness and COPD severity.[10] In their study, GCIPL thickness was significantly reduced in subjects with COPD compared to healthy controls, and the difference was more marked when subjects with severe COPD were compared to healthy controls. In another study, Alkan et al. described a significant positive relationship between FEV_1 and peripapillary retinal VD.[9] Similarly, Kurtul et al. demonstrated a simple (albeit unadjusted) positive linear correlation of subfoveal vessel density with both FEV_1 and FEV_1/FVC.[44] These correlations, including the one demonstrated in the present study, suggest that obstructive pulmonary disease may induce nerve damage and cause optic neuropathies through systemic inflammation and associated vascular dysfunction.

Although we believe that the study presents findings that help establish obstructive pulmonary disease as a possible risk factor for optic neuropathies like glaucoma, we acknowledge that there are several limitations to the study. First, the study is limited by its small sample size. The numbers of smokers were also small in each group, preventing a reliable analysis on the association between smoking and macular VD. Second, our analysis because of its cross-sectional nature cannot ascertain any causal relationship between optic nerve structure alteration and obstructive pulmonary disease. Third, the study population is racially homogenous, consisting only of Koreans, and the cohort consists of patients who reside in a single city, so the results may not be generalizable. Fourth, medical history was obtained through a questionnaire and prior therapeutic interventions (including medications) were not completely identified (see Supplementary Table S2). Furthermore, the current study design did not include assessments for endocrine or nutritional status. Hence, the role of medication, nutritional status, and other medical conditions on the association between pulmonary obstruction and superficial vascular density of the macula and its GCIPL thickness needs to be further assessed in the future. However, we believe that the exclusion criteria prevented inclusion of any cases that might have significantly affected the results.

In conclusion, non-glaucomatous subjects with obstructive pulmonary function demonstrated significantly reduced retinal superficial VD in the macula in comparison to subjects with normal pulmonary function. The degree of airway obstruction was correlated with superficial VD of macula, such that VD was reduced in subjects with more severe airway obstruction. Among subjects with obstructive pulmonary function, the severity of airway obstruction was correlated with GCIPL thickness of the macula. Further

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studies are necessary to identify the mechanism through which pulmonary disease is associated with optic neuropathies.

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