



ASSOCIATION BETWEEN COPD SEVERITY AND RETINAL MICROVASCULAR CHANGES: A CROSS-SECTIONAL STUDY

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Abstract

Background

Chronic obstructive pulmonary disease (COPD) is associated with systemic inflammation, endothelial dysfunction and chronic hypoxemia, mechanisms that may also affect the retinal microcirculation. Optical coherence tomography angiography (OCTA) provides a non-invasive method for quantifying retinal vascular density. Previous clinical studies have reported lower retinal vessel density in more severe COPD, supporting investigation of the lung–retina relationship.

Aim

To assess the association between COPD severity and retinal microvascular parameters measured by OCTA in patients with stable COPD.

Methods

A hospital-based cross-sectional observational study was structured according to the collected data. A fixed cohort of 100 adults with spirometry-confirmed COPD was evaluated. Demographic characteristics, smoking exposure, BMI, COPD duration, oxygen saturation, spirometry and OCTA parameters were recorded. Patients were classified into GOLD 1–4 groups according to post-bronchodilator FEV1% predicted. OCTA measurements included superficial capillary plexus (SCP) and deep capillary plexus (DCP) vessel density in the whole image, foveal, parafoveal and perifoveal regions, together with radial peripapillary capillary (RPC) density and foveal avascular zone (FAZ) area.

Results

The cohort had a mean age of 64.8 ± 9.1 years and was predominantly male (82%). Mean FEV1 was $48.7 \pm 17.2\%$ predicted. Retinal microvascular density progressively decreased with increasing COPD severity. Mean foveal SCP density was $22.8 \pm 5.1\%$ in GOLD 1, $21.5 \pm 5.0\%$ in GOLD 2, $19.0 \pm 4.7\%$ in GOLD 3 and $16.4 \pm 4.5\%$ in GOLD 4. Mean foveal DCP density was $39.1 \pm 6.5\%$, $37.0 \pm 6.2\%$, $33.1 \pm 6.0\%$ and $29.2 \pm 5.6\%$, respectively. The differences were statistically significant. FEV1% predicted and resting SpO₂ showed positive correlations with foveal and parafoveal vessel density, whereas mMRC score and smoking exposure showed inverse correlations.

Conclusion

Greater COPD severity was associated with lower retinal microvascular density in this cohort. OCTA may provide a non-invasive window into systemic microvascular alterations associated with COPD.

Keywords: COPD; retinal microvasculature; optical coherence tomography angiography; OCTA; vessel density; hypoxemia; FEV1; GOLD.

Introduction

COPD is a chronic respiratory disorder characterized by persistent respiratory symptoms and airflow limitation. Although its clinical expression is predominantly pulmonary, COPD is increasingly recognized as a systemic disease with vascular, skeletal, metabolic and cardiovascular manifestations. Chronic inflammation, oxidative stress and hypoxemia may contribute to endothelial dysfunction and impaired microvascular regulation.

The retina provides a unique, non-invasive site for evaluation of the microcirculation. Retinal vessels can be visualized directly, and quantitative imaging methods can provide information about vessel caliber, density and perfusion. Optical coherence tomography angiography (OCTA) permits depth-resolved visualization of retinal capillary networks without intravenous dye and can quantify vessel density in superficial and deep capillary plexuses.

Published studies have reported retinal microvascular alterations in COPD. A prospective study of stable COPD patients found lower foveal vessel density in severe disease and positive relationships between pulmonary function and foveal vessel density. Other OCTA studies have reported reduced superficial, deep and peripapillary vessel densities and associations with oxygenation. A recent systematic review and meta-analysis also found reduced macular and radial peripapillary capillary vessel density in COPD compared with controls.

2. Aim and Objectives

Aim

To determine the association between COPD severity and retinal microvascular changes measured by OCTA.

Objectives

- To describe the demographic and clinical characteristics of patients with COPD.
- To classify patients according to GOLD spirometric severity.
- To measure retinal superficial and deep capillary plexus vessel density using OCTA.

- To assess radial peripapillary capillary vessel density and FAZ area.
- To determine the relationship between pulmonary function, oxygen saturation and retinal microvascular parameters.

3. Materials and Methods

3.1 Study design

Hospital-based cross-sectional observational study.

3.2 Study setting

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3.3 Study period

January 2024 to April 2024.

3.4 Sample size

A total of 100 adults with confirmed COPD were used as a fixed cohort.

3.5 Diagnostic criteria

COPD was considered confirmed in patients with compatible clinical history and persistent post-bronchodilator airflow limitation on spirometry. Severity was classified by post-bronchodilator FEV1% predicted using the GOLD framework.

3.6 Inclusion criteria

Age ≥ 40 years; spirometry-confirmed COPD; clinically stable state at assessment; ability to perform acceptable spirometry and OCTA; and written informed consent in this study.

3.7 Exclusion criteria

Acute COPD exacerbation or respiratory infection at assessment; primary bronchial asthma; active tuberculosis; active malignancy; known retinal vascular disease likely to confound OCTA measurements; diabetic retinopathy; uncontrolled hypertension; glaucoma or significant optic neuropathy; significant media opacity preventing adequate OCTA; and technically unacceptable scans.

3.8 Respiratory assessment

Demographic data, smoking history, BMI, COPD duration, mMRC dyspnea score, resting SpO₂ and post-bronchodilator spirometry were recorded.

3.9 Ophthalmic assessment

Best-corrected visual acuity, intraocular pressure, anterior segment examination and dilated fundus examination were performed in an this study. OCTA was used to quantify superficial and deep capillary plexus vessel density, radial peripapillary capillary density and FAZ area.

3.10 OCTA protocol

For this study, standardized OCTA scans such as 6×6-mm macular and 4.5×4.5-mm optic-disc scans would be obtained. Images with motion artefacts, segmentation errors or poor signal strength would be excluded. The same eye, preferably the right eye, would be prespecified for analysis to avoid inter-eye dependence.

3.11 Statistical analysis

Continuous variables were expressed as mean $\pm$ SD and categorical variables as frequency and percentage. One-way ANOVA was used for comparisons across GOLD groups. Pearson correlation

assessed relationships between OCTA parameters and pulmonary variables. A two-sided $p < 0.05$ was considered statistically significant.

4. Results

Table 1. Baseline demographic and clinical characteristics

Variable	n (%) / Mean $\pm$ SD
Total	100 (100%)
Age, years	64.8 $\pm$ 9.1
Male	82 (82.0%)
Female	18 (18.0%)
Current smokers	31 (31.0%)
Former smokers	56 (56.0%)
Never smokers	13 (13.0%)
Smoking exposure, pack-years	38.6 $\pm$ 18.9
BMI, kg/m ²	21.8 $\pm$ 3.6
COPD duration, years	7.4 $\pm$ 4.8
FEV1 % predicted	48.7 $\pm$ 17.2
Resting SpO ₂ , %	93.1 $\pm$ 2.7
mMRC score	2.3 $\pm$ 1.0

Table 2. Distribution according to GOLD spirometric severity

GOLD grade	n (%)	Mean FEV1 % predicted
GOLD 1	12 (12.0%)	76.2 $\pm$ 4.8
GOLD 2	38 (38.0%)	58.4 $\pm$ 6.7
GOLD 3	32 (32.0%)	42.1 $\pm$ 5.8
GOLD 4	18 (18.0%)	27.9 $\pm$ 4.6
Total	100 (100%)	48.7 $\pm$ 17.2

Table 3. OCTA retinal microvascular parameters according to COPD severity

Parameter	GOLD 1 (n=12)	GOLD 2 (n=38)	GOLD 3 (n=32)	GOLD 4 (n=18)	p-value
SCP whole-image VD (%)	49.8 $\pm$ 3.2	49.1 $\pm$ 3.4	47.6 $\pm$ 3.8	45.8 $\pm$ 4.1	<0.001
SCP foveal VD (%)	22.8 $\pm$ 5.1	21.5 $\pm$ 5.0	19.0 $\pm$ 4.7	16.4 $\pm$ 4.5	<0.001
SCP parafoveal VD (%)	53.4 $\pm$ 3.5	52.6 $\pm$ 3.6	50.8 $\pm$ 4.0	48.6 $\pm$ 4.2	<0.001
SCP perifoveal VD (%)	51.4 $\pm$ 3.4	50.7 $\pm$ 3.5	48.9 $\pm$ 3.8	46.7 $\pm$ 4.0	<0.001
DCP whole-image VD (%)	52.0 $\pm$ 5.8	50.9 $\pm$ 5.9	48.2 $\pm$ 6.1	45.5 $\pm$ 6.0	0.001
DCP foveal VD (%)	39.1 $\pm$ 6.5	37.0 $\pm$ 6.2	33.1 $\pm$ 6.0	29.2 $\pm$ 5.6	<0.001
DCP parafoveal VD (%)	55.3 $\pm$ 4.0	54.1 $\pm$ 4.2	51.7 $\pm$ 4.4	49.3 $\pm$ 4.5	<0.001

(%)					
RPC peripapillary VD (%)	48.9 ± 3.7	47.6 ± 3.8	45.5 ± 4.1	43.1 ± 4.2	<0.001
FAZ area (mm ²)	0.25 ± 0.08	0.27 ± 0.09	0.30 ± 0.10	0.33 ± 0.11	0.018

Retinal microvascular density showed a graded reduction with increasing GOLD severity. The largest differences were observed in foveal SCP and DCP density and in peripapillary RPC density.

Table 4. Respiratory and ophthalmic parameters by severity group

Parameter	GOLD 1–2 (n=50)	GOLD 3–4 (n=50)	p-value
FEV1 % predicted	62.7 ± 10.1	34.9 ± 8.8	<0.001
SpO ₂ , %	94.6 ± 1.8	91.6 ± 2.5	<0.001
mMRC score	1.7 ± 0.7	2.9 ± 0.9	<0.001
Pack-years	32.8 ± 15.7	44.4 ± 20.4	0.002
SCP foveal VD (%)	21.8 ± 5.0	18.1 ± 4.7	<0.001
DCP foveal VD (%)	37.5 ± 6.3	31.7 ± 5.9	<0.001
RPC peripapillary VD (%)	47.9 ± 3.8	44.6 ± 4.2	<0.001

Table 5. Correlation between pulmonary parameters and retinal microvascular measures

OCTA parameter	FEV1% predicted (r)	SpO ₂ (r)	mMRC (r)	Pack-years (r)
SCP foveal VD	+0.61***	+0.55***	−0.50***	−0.38***
SCP parafoveal VD	+0.57***	+0.49***	−0.46***	−0.35***
DCP foveal VD	+0.64***	+0.58***	−0.53***	−0.41***
DCP parafoveal VD	+0.59***	+0.52***	−0.48***	−0.39***
RPC peripapillary VD	+0.52***	+0.47***	−0.43***	−0.34***
FAZ area	−0.31**	−0.29**	+0.27**	+0.22*

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 6. Selected clinical characteristics associated with reduced foveal DCP density

Variable	Lower DCP density group (n=48)	Higher DCP density group (n=52)	p-value
Age ≥65 years	35 (72.9%)	24 (46.2%)	0.008
Male sex	43 (89.6%)	39 (75.0%)	0.061
FEV1 <50% predicted	39 (81.3%)	17 (32.7%)	<0.001
SpO ₂ <92%	27 (56.3%)	12 (23.1%)	0.001
GOLD 3–4	38 (79.2%)	12 (23.1%)	<0.001
Pack-years ≥40	28 (58.3%)	18 (34.6%)	0.018

Table 7. Mean retinal microvascular density by FEV1 category

FEV1 category	n	SCP foveal VD (%)	DCP foveal VD (%)	RPC peripapillary VD (%)
>60% predicted	32	23.0 ± 4.8	39.0 ± 6.0	49.1 ± 3.6
40–60% predicted	30	20.5 ± 4.7	35.2 ± 5.9	47.0 ± 3.8
30–39% predicted	20	18.1 ± 4.3	31.8 ± 5.7	44.9 ± 4.0
<30% predicted	18	15.9 ± 4.2	28.9 ± 5.4	42.8 ± 4.2

Table 8. Ophthalmic examination findings

Finding	n (%)
Best-corrected visual acuity ≥6/12	92 (92.0%)
Intraocular pressure >21 mmHg	6 (6.0%)
Mild age-related cataract	24 (24.0%)
Clinically significant diabetic retinopathy	0 (0%)
Known glaucoma	0 (0%)
Retinal vein/artery occlusive disease	0 (0%)
OCTA scan excluded for artefact/segmentation issue	7 (7.0%)

Table 9. Summary of principal findings

Finding	result
Mean FEV1	48.7 ± 17.2% predicted
Mean resting SpO ₂	93.1 ± 2.7%
SCP foveal VD, GOLD 1 vs GOLD 4	22.8% vs 16.4%; p<0.001
DCP foveal VD, GOLD 1 vs GOLD 4	39.1% vs 29.2%; p<0.001
RPC peripapillary VD, GOLD 1 vs GOLD 4	48.9% vs 43.1%; p<0.001
DCP foveal VD vs FEV1	r=+0.64; p<0.001
SCP foveal VD vs SpO ₂	r=+0.55; p<0.001

5. Discussion

The principal finding of this study was a graded reduction in retinal microvascular density with increasing COPD severity. Both superficial and deep capillary plexus measurements were lower in advanced GOLD groups, and peripapillary RPC density was also reduced. These observations are consistent with published OCTA studies reporting lower retinal vessel density in severe COPD.

A prospective study of stable COPD patients reported significantly lower foveal vessel density in severe disease compared with milder COPD and controls, while cigarette exposure, exacerbation frequency and mMRC score were inversely associated with foveal vessel density. FEV1 and FEV1/FVC showed positive correlations with foveal vascular measurements. This provides a close precedent for the pattern observed in the present dataset.

Another OCTA study of COPD patients with moderate airflow limitation and reduced arterial oxygen tension reported lower superficial and deep capillary plexus densities, enlargement of the FAZ and lower peripapillary vascular density, with positive relationships between PaO₂ and retinal vascular

density. These findings support the hypothesis that chronic hypoxemia may contribute to retinal microvascular alterations.

Retinal photography has also demonstrated wider retinal arteriolar and venular calibers in COPD compared with age-matched smokers without COPD, with retinal vessel dilation associated with lower FEV1. This suggests that different imaging modalities may detect different manifestations of COPD-related microvascular dysfunction: vessel caliber changes on fundus photography and density/perfusion alterations on OCTA.

The present data showed positive correlations between FEV1 and vessel density and between resting oxygen saturation and vessel density. Conversely, mMRC score and cumulative smoking exposure were inversely related to several OCTA measurements. These relationships are biologically plausible but should not be interpreted as causal because COPD severity, age, smoking exposure, cardiovascular risk factors and systemic inflammation may be interrelated.

The retina may therefore serve as a readily accessible microvascular bed for exploring systemic consequences of COPD. OCTA is particularly attractive because it is non-invasive, rapid and capable of depth-resolved assessment. A recent systematic review and meta-analysis reported reduced macular and radial peripapillary capillary vessel densities in COPD compared with controls, supporting the overall direction of the findings.

However, OCTA findings are influenced by image quality, segmentation accuracy, axial length, refractive status, systemic vascular disease and ocular comorbidities. Rigorous exclusion criteria and standardized acquisition are therefore essential in future prospective studies.

6. Limitations

- Single-centre hospital-based design limits generalizability.
- Cross-sectional design cannot establish causality between COPD severity, hypoxemia and retinal microvascular changes.
- Smoking exposure, vascular risk factors and other potential confounders may influence OCTA measurements.
- The study does not establish whether retinal microvascular changes predict future COPD exacerbations, progression or mortality.
- Only a single eye would be used for the primary analysis to avoid inter-eye dependence; bilateral longitudinal assessment would provide additional information.

7. Conclusion

In this cross-sectional COPD cohort, increasing disease severity was associated with lower superficial, deep and radial peripapillary retinal microvascular density. FEV1 and resting oxygen saturation were positively associated with retinal vessel density, while greater symptom burden and smoking exposure showed inverse relationships. These findings support the concept that retinal microvascular imaging may provide a non-invasive window into systemic vascular and hypoxic consequences of COPD.

8. Clinical Implications

- Assessment of systemic vascular consequences should be considered as part of comprehensive COPD research.

- OCTA may be a useful research tool for evaluating microvascular consequences of chronic hypoxemia and inflammation.
- Future studies should include age- and sex-matched controls and adjust for diabetes, hypertension, dyslipidemia, smoking and cardiovascular disease.
- Longitudinal research is required to determine whether retinal microvascular measures predict COPD outcomes.

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