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ORIGINAL ARTICLE

Retinal vascular changes in patients with chronic obstructive pulmonary disease

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Summary

Introduction: Chronic obstructive pulmonary disease (COPD) is a progressive and inflammatory disease of the airways that often leads to cardiovascular and microvascular changes. This study aimed to analyze retinal microcirculation in patients with COPD using optical coherence tomography angiography (OCTA)

Materials and methods: Cross-sectional study. A total of 44 subjects were analyzed, including 28 with COPD and 16 healthy controls. Inclusion criteria were subjects older than 18 years with a confirmed COPD diagnosis based on spirometric parameters.

Results: Statistically significant differences were observed between the groups for the following parameters: deep capillary plexus macular ($p = 0.009$), parafoveal ($p = 0.026$), and perifoveal ($p = 0.034$). A significant negative correlation was observed between the ratio of residual volume to total lung capacity (RV/TLC) and the vessel density in the macular and perifoveal superficial capillary plexus regions ($p<0.05$). The choriocapillaris flow also demonstrates a significant inverse relationship with the RV/TLC ratio. Regarding the deeper retinal layers, our analysis revealed a significant negative correlation between outer retina Flow and forced vital capacity (FVC).

Conclusion: Monitoring changes in OCTA parameters, particularly in relation to lung volume parameters such as RV/TLC and FVC, suggests that OCTA may provide valuable insights into systemic vascular progression and the overall severity of the disease in COPD patients.

Keywords: optical coherence tomography angiography, chronic obstructive pulmonary disease, vessel density, biomarkers

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory disease of the airways that, in addition to respiratory disorders, often leads to systemic consequences, including cardiovascular and microvascular changes (1). Due to chronic hypoxemia, oxidative stress, and endothelial dysfunction, patients with COPD are susceptible to microcirculatory damage, including in the retinal vascular system (2). Optical coherence tomography angiography (OCTA) is a non-invasive diagnostic tool that quantifies retinal perfusion characteristics, including vascular density across different retinal layers and the size of the foveal avascular zone (FAZ) (3). Although OCTA is widely used to assess patients with diabetes, glaucoma, and various retinal dystrophies (4-6), studies involving patients with COPD are limited, and the available results are often contradictory (7-9). According to the available literature, only a few studies have evaluated OCTA in COPD patients, and their results indicate a significant reduction in vascular density, particularly in the deep macular layers, the radial peripapillary plexus, and the optic disc area, correlating with disease stage and degree of hypoxemia (8-10). To date, the relationship between lung hyperinflation parameters and OCTA-derived vascular indices has remained largely unexplored.

This study aimed to analyze retinal microcirculation in patients with COPD using OCTA and compare it to a control group. Special attention was given to analyzing vascular density and flow parameters in superficial and deep capillary plexuses and to examining potential biomarkers of vascular changes in COPD patients.

MATERIALS AND METHODS

The cross-sectional study. A total of 44 subjects were analyzed, including 28 with COPD and 16 healthy controls matched by gender and age. Inclusion criteria were subjects older than 18 years with a confirmed COPD diagnosis based on spirometric parameters. Patients with systemic diseases such as uncontrolled hypertension or diabetes, and ocular conditions, including media opacities, glaucoma, or other retinal pathologies that could interfere with OCTA image quality or microvascular findings, were excluded from the study. The control group consisted of participants with no history of systemic or ocular diseases. The study was approved by the Ethics Committee of the University Clinical Center of Serbia, University of Belgrade (number 95/79, date March 31, 2026), and informed consent was obtained from all participants.

All subjects, both patients and controls, underwent ophthalmological examination, including determination of best-corrected visual acuity, measurement of intraocular pressure using applanation tonometry (Goldmann method), biomicroscopy of the anterior eye segment, and indirect ophthalmoscopy of the ocular fundus using a 90D lens under pharmacologic dilation. OCTA imaging was then performed using the Optovue device (Fremont, CA, USA). The following parameters were analyzed: central macular thickness (CMT) within 1 mm of the central retina, expressed in micrometers (μm), foveal avascular zone (FAZ) in mm^2; vascular density (VD) expressed in percentage (%) in the macular, foveal, parafoveal, and perifoveal regions in both superficial and deep capillary plexuses (SCP – superficial capillary plexus; DCP – deep capillary plexus), and flow area in the outer retina (OR) and choriocapillaris (CC), expressed in mm^2. All OCTA images were centered on 6×6 mm2 cross-sections. We reviewed an image quality. Scans were considered "poor" if the signal strength index was less than 50 or if excess motion, poor clarity, media opacity, or other artifacts were present. If multiple scans were obtained, the highest-quality scan was included in the analysis. Optovue devices provide the Quality Index (QI), a 1–10 scale that assesses data quality for signal strength, motion artifacts, and defocus. Images with a QI of 7 or higher were used in the study. The forced expiratory volume in 1 second (FEV1%), forced vital capacity (FVC%), residual volume (RV) and the ratio of residual volume to total lung capacity (RV/TLC), expressed as a percentage, residual Volume Index (%) were measured in all patients with COPD, as well as the FEV1/FVC ratio (%). We monitored smoking status, as well as the type of therapy (dual/triple). Dual therapy included a long-acting B2 agonist and a long-acting muscarinic receptor antagonist, while triple therapy included inhaled corticosteroids. We also monitored comorbidities such as hypertension, cardiomyopathy, angina pectoris, allergic rhinitis, lung cancer, and pulmonary tuberculosis.

In this study, we prioritized FEV1, FVC, TLC, and the RV/TLC ratio as the primary pulmonary function markers. FEV1 and FVC provide standardized measures of airway obstruction and disease severity, which are essential for correlating systemic airflow limitation with retinal microvascular changes. Because COPD is characterized by structural lung remodeling, we also included TLC and the RV/TLC ratio. These parameters are critical markers of lung hyperinflation and air trapping, which contribute significantly to chronic systemic hypoxia and increased cardiovascular strain. By comparing these markers with OCTA parameters (such as vessel density and FAZ area), we aim to demonstrate how the severity of pulmonary hyperinflation mirrors the degree of retinal vascular impairment.

Statistic

The normality of data distribution was assessed using the Shapiro-Wilk test and by visual inspection of histograms and Q-Q plots. Continuous variables with normal distributions are presented as mean±standard deviation (SD), and differences between the two groups (COPD vs. controls)

were analyzed using an Independent-Samples t-test. For variables that deviated from a normal distribution, data are expressed as median and range (minimum-maximum). In these cases, the Mann-Whitney U test was used to compare group differences. Categorical variables were compared using the Chi-square test. Correlation analysis was performed using Pearson's correlation coefficient (r) for pairs of normally distributed variables and Spearman's rank correlation coefficient (ρ) for pairs where at least one variable deviated from a normal distribution. All statistical analyses were performed using SPSS for Windows, version 20.0 (SPSS, Chicago, Illinois, USA). A p-value of less than 0.05 was considered statistically significant.

RESULTS

The study included 44 participants: 28 (63.7%) in the COPD group and 16 (36.3%) in the control group. The average age of patients was 64.54 ± 6.98 years (range, 47–75 years), and in the control group, 60.75 ± 7.76 years (range, 50-74 years). In the COPD group, 20 women (71.43%) and 8 men (28.57%) were included, while in the control group, 13 women (81.25%) and 3 men (18.75%) were included. No statistically significant difference was found between participants in terms of age and gender (p = 0.104, p = 0.469, respectively). The average duration of COPD was 7.16 ± 3.59 years. Fundus examination was normal with no signs of retinal disease, and all patients had normal visual acuity and intraocular pressure in the normal range. The laboratory characteristics of COPD patients are summarized in **Table 1**.

In comparing OCTA parameters, statistically significant differences were observed between the groups for the following parameters: DCP macular (p = 0.009), DCP parafoveal (p = 0.026), and DCP perifoveal region (p = 0.034). These results indicate a significant decrease in vascular density in the deep capillary plexus in patients with COPD compared with the control group **(Table 2)**. No statistically significant differences were found in

Table 1. The laboratory characteristics of patients with COPD

Investigated trait	Mean[a]/Median[b]	Standard deviation (SD)[a]/Range (minimum-maximum)[b]
FVC (%)[a]	107.96	26.47
FVC (l)[a]	302.82	91.14
FEV 1 (%)[a]	77.37	27.62
FEV 1 (l)[a]	190.25	63.80
FEV1/FVC (%)[a]	58.37	14.81
DLCO (%)[a]	56.96	13.79
KCO[a]	61.30	15.95
SaO2[b]	96.00	89.00-99.00
PEF (l)[a]	490.71	177.66
PEF (%)[a]	78.21	21.34
FEF 50 (l)[a]	134.28	86.35
FEF 50 (%)[a]	36.46	22.83
FEF 75 (l)[a]	43.32	35.96
FEF 75 (%)[a]	29.18	16.04
RV (l)[a]	195.68	65.42
RV (%)[a]	100.00	21.40
ERV (l)[a]	84.53	51.34
ERV (%)[b]	100.00	36.00-274.00
VCin (l)[a]	323.21	75.70
VCin (%)[a]	104.18	20.05
TLC (l)[b]	512	49.00-777.00
RV/TLC (%)[b]	104.00	72.00-120.00
Smoking		
Yes	17 (63.0%)	
No	1 (3.7%)	
Ex smoker	9 (33.3%)	
Treatment type; n(%)		
Double	15 (55.6%)	
Triple	14 (44.4%)	

FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume in the first second; DLCO: Diffusing Capacity of Lung of Carbon Monoxide; KCO: Carbon Monoxide Transfer Coefficient; SaO2: Arterial Oxygen Saturation; PEF: Peak Expiratory Flow; FEF50: Forced Expiratory Flow at 50% of FVC; FEF75: Forced Expiratory Flow at 75% of FVC; RV: Residual Volume; ERV: Expiratory Reserve Volume; VCin: Inspiratory Vital Capacity; TLC: Total Lung Capacity; RT/TLC: ratio of Residual Volume and Total Lung Capacity

Note: [a] Data presented as mean±standard deviation for normally distributed variables; [b] Data presented as median and range (minimum-maximum) for variables with non-normal distribution

Table 2. Comparison between groups as regards the optical coherence tomography angiography outcomes

Group / OCTA parameters	COPD	Control	P-value
Superficial Macula density (%)[a]	46.21±3.04	48.15±4.36	0.096[c]
Superficial foveal density (%)[a]	19.10±5.91	19.31±6.69	0.915[c]
Superficial parafoveal density (%)[b]	47.85 (37.60-53.20)	50.15 (35.80-55.20)	0.140[d]
Superficial perifoveal density (%)[a]	46.89±3.04	47.85±4.70	0.424[c]
Deep Macula density (%)[a]	42.43±3.60	46.74±4.30	**0.009**[**c]
Deep foveal density (%)[a]	35.67±6.16	34.46±9.66	0.206[c]
Deep parafoveal density (%)[a]	48.67±4.28	51.51±3.32	**0.029**[*c]
Deep perifoveal density (%)[a]	42.39±5.23	46.28±4.35	**0.017**[*c]
Flow rate OR[b]	0.801 (0.160-1.696)	0.702 (0.239-1.896)	0.393[d]
Flow rate CC[b]	2.051 (1.859-2.520)	2.062 (0.398-2.272)	0.766[d]
FAZ area (mm^2)[a]	0.27±0.10	0.23±0.06	0.315[c]

COPD: chronic obstructive pulmonary disease; OCTA: optical coherence tomography angiography; OR: outer retina; CC: choriocapillaris; FAZ: foveal avascular zone; *Significant at the 0.05 level (2-tailed); ** Significant at the 0.01 level (2-tailed). Note: Data presented as mean±standard deviation for normally distributed variables; [b] Data presented as median and range (minimum-maximum) for variables with non-normal distribution; [c] Independent t-test; [d] Mann-Whitney U test

other OCTA parameters, including FAZ, SCP, OR, or CC Flow.

A significant negative correlation was observed between the RV/TLC ratio and vessel density in the SCP, particularly in the macular and perifoveal regions ($p<0.05$). On the other hand, there is a significant positive correlation between RV/TLC and DCP. Furthermore, the OR Flow also demonstrates a significant inverse relationship with the RV/TLC ratio. Regarding the deeper retinal layers, our analysis revealed a significant positive correlation between CC Flow and FVC. The correlation between the lung function indices and all OCTA parameters is shown in **Table 3**.

DISCUSSION

Our study shows that patients with chronic obstructive pulmonary disease (COPD) exhibit significant changes in the retinal microcirculation, which can be objectively assessed using optical coherence tomography angiography. In our study, we observed a decrease in vessel density in the deep capillary layers, including the macular, parafoveal, and perifoveal regions, in patients with COPD compared with healthy controls. No statistically significant differences were observed in the parameters of the FAZ, vascular density of the superficial capillary plexus, flow area of the outer retina, or choriocapillaris. Songur et al. reported results that contradict ours, noting reduced vascular density of the SCP and a significant increase in the FAZ parameter (1). On the other hand, Alkan et al. found that parafoveal vascular density of the DCP decreased in patients with COPD.

In contrast, they did not observe statistically significant changes in vascular density in the SCP, findings similar to ours (2). These differences in the results obtained for the vascular density parameters of the superficial and deep capillary plexuses highlight the importance of the anatomical and physiological characteristics of the blood vessels within each plexus. The reasons for these changes can be primarily attributed to the anatomical localization and structure of these two plexuses. The SCP is located in the ganglion cell layer, while the DCP is located in the inner nuclear layer. Vertically placed blood vessels connect these two plexuses (11). Venous collecting channels that create an area similar to a basin, where oxygen saturation can be lower than in the outer retina, form the DCP. The SCP is directly connected to retinal arterioles and may have a higher perfusion pressure. Anatomical differences in vascular distribution may explain why the DCP is more susceptible to ischemic changes than the SCP (12).

In our study, a statistically significant negative correlation was observed between vascular density in the macular and perifoveal SCP and the RV/TLC ratio (expressed as a percentage). In contrast, no such correlation was observed with FEV1 or FVC. These results suggest that patients with more pronounced pulmonary hyperinflation and air trapping have lower retinal microcirculation density. This finding supports the hypothesis that the severity of obstructive lung disease and accompanying chronic hypoxia led to a progressive decrease in retinal perfusion, which can be monitored non-invasively using OCTA technology. This negative correlation further supports the hypothesis that COPD is not just a localized lung disease, but also a systemic vascular condition. High RV/TLC reflects advanced small airway dysfunction and increased intrathoracic pressure, which can impair systemic venous return and exacerbate chronic hypoxia, leading to the observed decline in SCP vessel density. The reduction in SCP density in the macular, parafoveal, and perifoveal regions could serve as an early warning biomarker of systemic microvascular

Table 3. The correlation between the lung function indices and all OCTA parameters

	FEV1	FVC	RV/TLC (%)	TLC	FEF50%
Superficial Macula density CC	r=0.083,p=0.694	r=0.171,p=0.413	**ρ=-0.456*,p=0.019**	ρ=0.193,p=0.346	r=0.159,p=0.437
Superficial foveal density CC Sig.	r=-0.023,p=0.914	r=0.075,p=0.721	ρ=-0.212,p=0.298	ρ=0.067,p=0.744	r=0.126,p=0.538
Superficial parafoveal density CC Sig.	ρ=-0.145 p=0.480	ρ=0.116 p=0.572	ρ=-0.158,p=0.440	ρ=0.133,p=0.519	ρ=-0.080,p=0.697
Superficial perifoveal density CC Sig.	r=0.111,p=0.598	r=0.108,p=0.608	**ρ=-0.468*,p=0.016**	ρ=0.098,p=0.633	r=0.195,p=0.340
Deep Macula density CC Sig.	r=0.000,p=0.998	r=0.258,p=0.213	**ρ=0.502**,p=0.005**	ρ=0.288,p=0.123	r=-0.322,p=0.109
Deep foveal density CC Sig.	r=-0.135,p=0.521	r=0.038,p=0.857	ρ=0.257,p=0.171	ρ=-0.260,p=0.166	r=-0.103,p=0.618
Deep parafoveal density CC Sig.	r=-0.041,p=0.847	r=0.220,p=0.290	ρ=0.330,p=0.075	**ρ=0.364*,p=0.048**	**r=-0.396,p=0.045***
Deep perifoveal density CC Sig.	r=0.221,p=0.289	r=0.260,p=0.290	**ρ=0.490**,p=0.006**	**ρ=0.420*,p=0.021**	r=-0.220,p=0.279
Flow rate CC CC Sig.	r=0.282,p=0.171	r=0.559,p=0.004	ρ=-0.257,p=0.170	**ρ=-0.372*,p=0.043**	r=-0.046,p=0.822
Flow rate OR CC Sig.	r=0.221,p=0.289	r=0.260,p=0.209	**ρ=-0.402*,p=0.042**	ρ=-0.015,p=0.942	r=-0.033,p=0.872
FAZ area CC Sig.	r=-0.108,p=0.606	r=0.006,p=0.977	ρ=0.059,p=0.773	ρ=0.086 ,p=0.675	r=-0.167,p=0.414

FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; RT/TLC: ratio of Residual Volume and Total Lung Capacity; TLC: Total Lung Capacity; FEF50%: Forced Expiratory Flow at 50%; CC – Choriocapillaris; OR – Outer retina; FAZ: foveal avascular zone; CC, correlation coefficient; Sig, significant; *Significant at the 0.05 level (two-tailed). **Significant at the 0.01 level (two-tailed).
Note: r - Pearson correlation coefficient (used for pairs of normally distributed variables); ρ - Spearman's rank correlation coefficient (used for pairs where at least one variable derives from a normal distribution)

damage driven by disease progression. Interestingly, our study found a negative correlation between FEF50% and DCP in the parafoveal region. While one might expect a reduction in VD with worsening lung function, this inverse relationship could reflect a compensatory vasodilatatory response in DCP to chronic mild hypoxia associated with small airway obstruction. This is supported by the following results: a positive correlation in DCP density with hyperinflation parameters (TLV and RV/TLC), which may indicate a compensatory vasodilatory response of the remaining vessels to worsening pulmonary function.

A significant positive correlation was observed between CC flow and FVC. Higher FVC (better lung function) correlates with better flow in the choriocapillaris. This confirms that good lung function is directly related to better circulation in the deepest layers of the eye. In addition, our results showed that, in addition to SCP, the OR flow significantly negatively correlates with RV/TLC. Since the outer retina is physiologically avascular, but the most metabolically active part of the eye, this result may represent a compensatory hemodynamic shift or altered oxygen diffusion patterns in response to the severe systemic hypoxia associated with reduced lung function. This suggests that the metabolic demand of the photoreceptors triggers a vascular response in the adjacent layers that is captured as increased flow when pulmonary function is significantly compromised.

The pathogenesis of COPD is based on the action of inflammatory cytokines, tissue hypoxia, activation of the cascade in the process of oxidative stress and reduction of anti-oxidative capacities, and smoking stands out as a

significant risk factor (13). In earlier studies, Ozcimen et al. found that hypoxia in patients with COPD affects choroidal thickness, and thinning can occur due to increased vascular resistance and reduced flow (14). Numerous factors influence the regulation of retinal and choroidal blood vessel flow. The autonomic nervous system and hormones regulate blood flow through the choroidal circulation, while blood flow through the retinal blood vessels is auto-regulated. The retina maintains a constant blood flow through the retinal blood vessels despite variations in perfusion pressure, blood gases, and intraocular pressure (15).

Recent studies using OCTA have consistently reported a significant reduction in vessel density within the superficial and deep capillary plexuses in COPD patients compared to healthy controls (16, 17). For instance, Kornfield et al. demonstrated that FEV1 levels positively correlate with macular vessel density, suggesting that airflow obstruction mirrors retinal microvascular loss (15). However, while most literature focuses on FEV1 and FVC, our study uniquely identifies the RV/TLC ratio as a more sensitive marker for retinal and OR impairment, highlighting the impact of lung hyperinflation on ocular perfusion.

Our study shows that chronic obstructive pulmonary disease significantly affects retinal microcirculation, reflecting the systemic nature of the disease. While a general reduction in DCP density was observed in COPD patients compared with healthy controls, the correlation analysis revealed that distinct pulmonary impairments drive distinct vascular changes. The most significant finding is the strong negative correlation between the RV/TLC ratio and both SCP and OR flow, suggesting that lung hyperinflation and air trapping, rather than simple airflow obstruction (FEV1), are the primary drivers of microvascular rarefaction in the retina. Increased intrathoracic pressure and chronic systemic hypoxia, associated with high RV/TLC, appear to impair perfusion of this sensitive vascular bed, particularly at lower lung volumes. Furthermore, the positive correlation between CC Flow and FVC indicates that better lung function is associated with better circulation in the deepest layer of the eye.

CONCLUSION

In conclusion, our preliminary findings highlight the potential of OCTA parameters to serve as auxiliary, non-invasive indicators of systemic microvascular damage in COPD. Monitoring changes in the SCP and CC Flow, particularly in relation to lung volume parameters such as RV/TLC, may provide valuable insights into systemic vascular progression and the overall severity of the disease in COPD patients. Given the study's pilot nature, further research on a larger scale is warranted to validate the clinical utility of these findings.

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Conflicts of Interest: The authors declare no conflict of interest to report.

Author contributions: Conceptualization, Writing, Reviewing, Editing, Project Administration, J.V, Investigation, Resources, M.L.L; Methodology, T.K; J.P; Data Curation, K.S; Original Draft Writing, A.P; Formal Analysis, M.S, Software, Validation, S.P; Supervision, Project Administration, I.K.

Ethical approval: This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University Clinical Center of Serbia in Belgrade, record number 95/79, March 31, 2026.

Informed consent: Informed consent was obtained from all patients participating in the study after receiving a full explanation of the study.

Data availability statement: The datasets used and/or analyzed during the current study are available without restriction from the corresponding author. All relevant data are within the paper.

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RETINALNE VASKULARNE PROMENE KOD PACIJENATA SA HRONIČNOM OPSTRUKTIVNOM BOLEŠĆU PLUĆA

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Sažetak

Uvod: Hronična opstruktivna bolest pluća (HOBP) je progresivna i inflamatorna bolest disajnih puteva koja često dovodi do kardiovaskularnih i mikrovaskularnih promena. Cilj ove studije bio je da se analizira mikrocirkulacija mrežnjače kod pacijenata sa HOBP korišćenjem optičke koherentne tomografske angiografije (OCTA).

Materijali i metode: Studija preseka. Analizirano je ukupno 44 ispitanika, uključujući 28 sa HOBP i 16 zdravih kontrola. Kriterijumi za uključivanje bili su ispitanici stariji od 18 godina sa potvrđenom dijagnozom HOBP na osnovu spirometrijskih parametara.

Rezultati: Statistički značajne razlike su primećene između grupa za sledeće parametre: duboki kapilarni pleksus makule (p = 0,009), parafovealni (p = 0,026) i perifovealni region (p = 0,034). Značajna negativna korelacija je primećena između odnosa rezidualne zapremine i ukupnog kapaciteta pluća (RV/TLC) i gustine krvnih sudova u makularnom i perifovealnom površinskom kapilarnom pleksusu (p<0,05). Protok horiokapilarisa takođe je pokazao značajnu inverznu vezu sa odnosom RV/TLC. Što se tiče dubljih slojeva mrežnjače, naša analiza je otkrila značajnu negativnu korelaciju između protoka spoljašnje mrežnjače i forsiranog vitalnog kapaciteta (FVC).

Zaključak: Praćenje promena OCTA parametara, posebno u vezi sa parametrima plućnog volumena, kao što su RV/TLC i FVC, zaključujemo da OCTA može pružiti vredne uvide u sistemsku vaskularnu progresiju i ukupnu težinu bolesti kod pacijenata sa HOBP.

Ključne reči: optička koherentna tomografija angiografija, hronična obstruktivna bolest pluća, gustina krvnih sudova, biomarkeri

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