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Is it useful to do OCTA in coronary artery disease patients to improve SYNTAX-based cardiac revascularization decision?

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ABSTRACT

Background: To investigate retinal and optic disk microcirculation using optical coherence tomography angiography (OCTA) in order to predict related outcomes based on the SYNergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) score (SS) system in coronary artery disease patients.

Methods: 104 patients were grouped based on coronary angiography results: 32 chronic coronary syndrome (CCS) patients, 35 acute coronary syndrome (ACS) patients, and 37 healthy controls. The SS system determined atherosclerosis degree and lesion-related mortality risk, followed by scoring as SYNTAX I score (SS-I) and SYNTAX II score (SS-II). Patients were further subdivided into SS-I, SS-II percutaneous coronary intervention (PCI), and SS-II coronary artery by-pass grafting (CABG) groups. Following a thorough ophthalmological examination, an OCTA Angio Retina mode (6 × 6 mm) automatically quantified retinal and optic disk microcirculation.

Results: The mean ages did not differ significantly among groups ($p = 0.940$). The outer retinal select area varied significantly among groups, with the highest values found in ACS patients ($p = 0.040$). Despite non-significant differences between SS-I patients and healthy controls, the former had lower capillary plexus vessel densities in all regions and in foveal vessel density 300 μm around foveal avascular zone (FD-300) ($p>0.05$). Vessel densities were lowest in SS-II PCI≥28.5 patients, particularly in whole ($p = 0.034$) and parafoveal ($p = 0.009$) superficial capillary plexus, and in FD-300 ($p = 0.019$). Vessel densities were lowest in SS-II CABG ($p = 0.020$), and perifoveal ($p = 0.017$) deep capillary plexus, and in FD-300 ($p = 0.003$). The outer retina flow area increased the most in SS-II CABG≥25.1 patients ($p = 0.020$).

Conclusions: Using OCTA, a non-invasive imaging technique, to assess retinal and optic disk microcirculation appears to have the potential to yield significant clinical results in the early diagnosis or prognosis of cardiovascular diseases.

1. Introduction

Coronary artery disease (CAD) is the most prevalent cardiovascular disease [1]. This disease is characterized by decreased heart muscle blood circulation caused by atherosclerotic plaque formation in cardiac arteries, as well as vasospasm [2]. It is a leading cause of mortality globally [3], with symptoms ranging from stable angina to unstable angina, myocardial infarction, and sudden cardiac death [4]. In developed countries, CAD-related mortality rate has decreased to some extent; however, this disease still accounts for one-third of deaths in people over the age of 35 [5,6].

In addition to renal and cerebral vascular pathologies, there has been

Abbreviations: CAD, Coronary artery disease; OCTA, Optical coherence tomography angiography; VD, Vessel density; SCP, Superficial capillary plexus; DCP, Deep capillary plexus; FAZ, Foveal avascular zone; SYNTAX, SYNergy between PCI with TAXUS and cardiac surgery; TAXUS, Paclitaxel-eluting stent (PES; TAXUS® express2tm[TAXUS express2], Boston scientific, Natick, Ma); SS, Syntax score; CCS, Chronic coronary syndrome; ACS, Acute coronary syndrome; LogMAR, Logarithm of the minimum angle of resolution; PERIM, Foveal avascular zone perimeter; FD-300, Foveal vessel densities 300 μm around foveal avascular zone; PCI, Primary percutaneous coronary intervention; CABG, Coronary artery by-pass grafting; SPSS, Statistical package for the social sciences program.

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evidence of a link between CAD and ocular vasculopathy [7–9]. A human retina is composed of ten layers that are supplied with blood by two major vascular sources: retinal arteries and choriocapillaris. The former nourishes the retinal inner five layers, while the latter nourishes the retinal outer five layers. An ophthalmic artery, which is an internal carotid artery branch, forms both retinal arteries and choriocapillaris. Given that fundus microvasculature is roughly the same size as coronary microvasculature, we hypothesize that assessing the retinal microvascular morphology will provide clinicians with insight into the processes that occur in subclinical coronary stenosis [10].

Traditional techniques for clinically evaluating retinal and optic disk microvascular system include ophthalmoscopy, funduscopy, fundus photography, as well as fundus fluorescein angiography. Despite the risks associated with intravenous fluorescein administration, fundus fluorescein angiography has been regarded as the "gold standard" for assessing retinal microvasculature and capillary beds for over 50 years [11]. Optical coherence tomography angiography (OCTA) is a novel non-invasive imaging technique that has recently been used in ophthalmology clinics. This diagnostic tool facilitates direct assessment of the retinal vessel densities (VDs), as well as capillary flow and optic disk microcirculation [12,13]. Unlike fundus fluorescein angiography, OCTA can also provide information about the retinal superficial capillary plexus (SCP) and deep capillary plexus (DCP) separately. Besides, it can reveal details about the foveal avascular zone (FAZ), capillary non-perfusion zones, and microstructural VDs [14,15].

The current study aimed to evaluate the retinal and optic disk microvascular morphology using OCTA in CAD patients undergoing coronary angiography in order to predict related outcomes based on the SYNergy between PCI with TAXUS (paclitaxel-eluting stent) and Cardiac Surgery (SYNTAX) score (SS) system. We anticipate that by using OCTA, clinicians will be able to predict and potentially prevent CAD-related risks and mortality earlier.

2. Materials and methods

2.1. Study design

This interdisciplinary single-centered cross-sectional study was carried out between February and July 2022 in accordance with the Helsinki Declaration, with researchers from XX University's Ophthalmology department, Retina unit, and Cardiology department participating. The XX University Clinical Research Ethics Committee granted approval for the study, with approval date and number 2022/234.

2.2. Participants

A total of 104 patients who had coronary angiography performed by two senior cardiologists (IED&OFY) were studied. These patients were divided into three groups based on coronary angiography results, with 32 having chronic coronary syndrome (CCS), 35 having acute coronary syndrome (ACS), and 37 having no pathology (healthy controls).

Patients with macular edema-causing pathologies such as uveitis, diabetic retinopathy, age-related macular degeneration, and choroidal neovascularization were excluded from the study, as was significant corneal or lens opacity that could impede OCTA acquisition. Also excluded were those with the following conditions: (a) a history of ocular anterior or posterior surgery and/or trauma, (b) a recent use of eye lubricants or contact lenses, (c) an intraocular pressure $\geq$21 mmHg, (d) a high refractive error ($>\pm$1.5 Diopter), (e) an axial length $>$26.5 mm, (f) inability to cooperate with OCTA procedure, (g) a declaration of inability to participate due to CAD severity, (h) a history of any malignancy or Behçet's disease, and (i) a regular alcohol consumption

2.3. Ophthalmic assessment

After gathering information such as age and gender, two senior ophthalmologists (IEA&HHG) performed a comprehensive ophthalmological examination. This included determining best-corrected visual acuity in Logarithm of the Minimum Angle of Resolution (logMAR), and performing anterior and posterior segment slit-lamp biomicroscopy before and after artificial mydriasis with tropicamide 1% and phenylephrine 10%.

2.4. Optical coherence tomography angiography

All OCTA procedures in patients undergoing coronary angiography were carried out 3–7 days later by the same trained technician using the same OCTA device (AngioVue Avanti RTVue-XR, OptoVue, Fremont, CA) before hospital discharge between 10:00 AM and 12:00 AM to avoid the effects of diurnal variation. The axial length and refractive errors were corrected, and the image polarization was adjusted using the 'Auto Adjust' mode during the procedure. Angio Retina mode (6 $\times$ 6 mm) was used for OCTA under standard conditions. Ocular movement artifacts were reduced and eliminated using an integrated eye-tracking mode and motion correction technology, respectively. All OCTA scans were scrutinized to ensure correct segmentation and maximum image quality (signal strength index $\geq$60; scan quality index $\geq$8). Despite repeated OCTA scanning due to poor angiograms, those with a low-quality index ($<$8) or a low signal strength index ($<$60), segmentation errors, and artifacts or opacities caused by blinking or motion that interfered with retinal image viewing were disqualified.

The RTVue-XR version 2017.1.0.155 software from AngioVue Analytics (Optovue, Inc., Fremont, California, USA) automatically measured VDs (%) in the in the SCP and DCP. Furthermore, the software automatically measured other parameters such as (a) FAZ parameters like FAZ area (mm^2), FAZ perimeter (PERIM) (mm), and foveal VDs 300 μm around FAZ (FD-300) (%), (b) outer retinal and choriocapillary flow areas of a 3-mm diameter circle (mm^2), as well as (c) optic disk retinal nerve fiber layer thickness (μm) and VDs (%), using their respective functional modes (Fig. 1A–G).

2.5. Coronary syndromes

Based on the European Society of Cardiology guide on CCS, published in 2019, the following clinical scenarios are the most common in patients with suspected or established CCS: (a) suspected CAD patients with "stable" anginal symptoms and/or dyspnea, (b) patients with newly diagnosed heart failure or left ventricular dysfunction, and CAD history, (c) asymptomatic and symptomatic patients with symptoms that have stabilized a year after initial diagnosis or revascularization, (d) asymptomatic or symptomatic patients $>$1 year after initial diagnosis or revascularization, (e) patients with angina and suspected vasospastic or microvascular disease, and (f) asymptomatic CAD patients identified during screening [16].

The European Society of Cardiology 2020 guideline defines ACS as a condition in which patients have acute chest pain and persistent ST-segment elevation ($>$20 min). This is known as an ST-segment elevation ACS, and it generally indicates an acute total or subtotal coronary occlusion. The vast majority of patients will eventually develop the ST-segment elevation myocardial infarction. In these patients, the mainstay of treatment is immediate reperfusion via primary percutaneous coronary intervention (PCI) or, if available, fibrinolytic therapy. In addition, non-ST-segment elevation ACS patients could have electrocardiography changes that include: (a) transient ST-segment elevation, (b) persistent or transient ST-segment depression, and (c) T-wave inversion, flat T waves, or pseudo-normalization of T waves. Alternatively, the electrocardiography may be normal [17].

2.6. The SYNTAX score-based cardiologic assessment

The SS system [18] was used in the current study to determine the degree of atherosclerosis associated with CAD and lesion-related

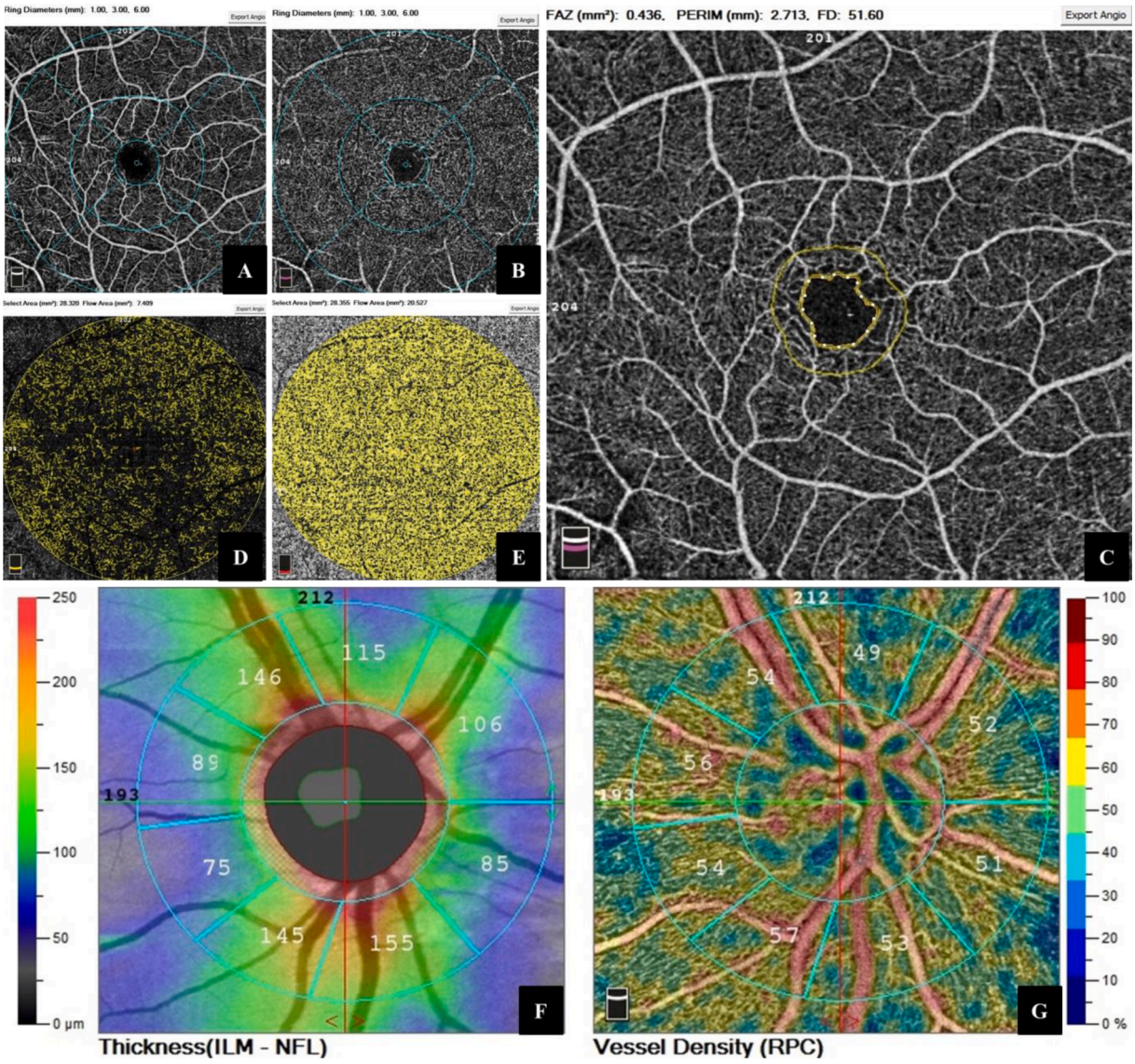

Fig. 1. Optical coherence tomography angiograms demonstrating automatic quantification of vessel densities in the whole, foveal, parafoveal, and perifoveal superficial capillary plexus (A) and deep capillary plexus (B), as well as foveal avascular zone parameters (D), including foveal avascular zone area, foveal avascular zone perimeter, and foveal vessel density 300 μm around foveal avascular zone (FD-300). Capillary flow areas in the outer retina (D) and choriocapillary (E) were also measured, as were optic disk retinal nerve fiber layer thickness (F) and vessel densities (G). Only optical coherence tomography angiograms with a signal strength index ≥60 (scan quality index ≥8) were considered eligible for analysis after all parameters were automatically quantified using their respective functional modes.

mortality risk, followed by SS calculation in atherosclerosis patients.

2.6.1. The SYNTAX I score (SS-I)

This system was developed for the SYNTAX trial which aimed to determine the best treatment strategy in patients with three vessel disease or significant lesions in the left main coronary artery. It is based on the evaluation criteria, which include: (a) the American Heart Association coronary vessel segment classification system planned for the 'Arterial Revascularization Therapies Study'; (b) the American Heart Association stenosis classification system; (c) The Computed Tomography-adapted Leaman Score; (d) the full congestion classification system; (e) the Duke and Institut Cardiovasculaire Paris Sud criteria classification systems for bifurcation lesions; and (f) the expert opinions [19–21]. The SS-I is an independent predictor of major adverse cardiac and cerebrovascular events in patients treated with PCI rather than coronary artery by-pass grafting (CABG). Main aspect of the SS-I is that it is lesion-based, with a separate SS calculated for each lesion.

In the current study, the SS-I was calculated online using the SS Calculator version 2.1. (www.syntaxscore.com). Scoring included any coronary vessel thicker than 1.5 mm in diameter and any lesion causing >50% stenosis. Actually, the SS-1 contains 12 basic questions, with the first three questions addressing dominance, the total number of lesions, and the vessel segment in which lesions are located. The score obtained from each lesion separately is then used to calculate the total SS-I. Furthermore, once the algorithm has been completed, the characteristics and score of each lesion are reported. A total score of 0–22, 23–32, and ≥33 indicates a patient's low, medium, and high SS-I, respectively [18].

2.6.2. The SYNTAX II score (SS-II)

In the current study, the SS-II was generated online using SS Calculator version 2.1 (*www.syntaxscore.com*). Aside from the SS-I, the SS-II includes two anatomical variables (anatomical SS and unprotected left main coronary artery) and six clinical variables (age, creatinine

clearance, left ventricular ejection fraction, gender, chronic obstructive pulmonary disease and peripheral arterial disease) [22]. All patients were evaluated for the presence of left ventricular ejection fraction and peripheral arterial disease. A chronic obstructive pulmonary disease diagnostic evaluation was performed, and patients who were on medications were presumed to have chronic obstructive pulmonary disease. Following the SS-II calculation, two separate scores for PCI and CABG were obtained. The SS-II PCI denoted the effect of stenting for atherosclerosis on mortality, while the SS-II CABG denoted the effect of by-pass for atherosclerosis on mortality.

Patients were further subdivided into SS-I, SS-II PCI, and SS-II CABG groups, and OCTA data was compared. Following that, it was determined whether mortality calculation parameters such as SS-I, SS-II PCI, and SS-II CABG, which are based on data obtained via coronary angiography, an invasive procedure, were compatible with data obtained via a non-invasive OCTA device.

2.7. Statistical analysis

The Statistical Package for the Social Sciences program (SPSS Inc., version 26.0, Chicago, IL, USA).) was used to conduct the statistical analysis. The data descriptive statistics included arithmetic mean and standard deviation for continuous variables, frequency and percentage for categorical variables. The Shapiro-Wilk test was used to determine conformity to the normal distribution when comparing mean values among groups. When comparing group means of variables with three or more categories, the ANOVA test was used in parametric conditions and the Kruskal-Wallis test was used in non-parametric conditions. The Dunn post-hoc test was used to determine which group or groups were responsible for the difference. A statistical significance level was set at $p<0.05$.

3. Results

The mean ages were 62.00±8.00, 61.00±10.00, and 60.00±7.00 years in CCS and ACS patients, as well as healthy controls, respectively ($p = 0.940$). The female-to-male ratio was 32:9 in CCS patients, 35:8 in ACS patients, and 37:12 in healthy controls ($p = 0.854$). All patients had 0.00±0.00 logMAR uncorrected or best-corrected visual acuity.

3.1. CAD status-based OCTA parameter analysis

Although CCS and ACS patients had lower whole, foveal, parafoveal, and perifoveal SCP and DCP than healthy controls, the difference was not statistically significant ($p>0.05$ for all). The FAZ area ($p = 0.787$) and PERIM ($p = 0.758$) of CCS and ACS patients were statistically non-significantly higher than healthy controls. Meanwhile, CCS and ACS patients had lower FD-300 than healthy controls, a condition that was close to statistical significance ($p = 0.061$). Regarding capillary flow area, only the outer retinal select area differed statistically significantly among groups, with ACS patients having the highest capillary flow ($p = 0.040$). There were no statistically significant differences in optic disk retinal nerve fiber layer thickness and VDs among groups ($p>0.05$ for both) (Table 1).

3.2. The SS-I analysis

The mean SS-I in CAD patients was 12.0 ± 7.95. The patients were further divided into two groups based on their mean SS-I, those with SS-$I<12$ and those with SS-$I \geq 12$, for comparative analysis. There were no statistically significant differences based on age ($p = 0.615$) or gender ($p = 0.655$). Despite the fact that there were no statistically significant differences in OCTA parameters among healthy controls, SS-$I<12$ and SS-$I \geq 12$ patients, CAD patients (SS-$I<12$ and SS-$I \geq 12$ patients) were associated with slightly lower capillary plexus VDs in all regions ($p>0.05$). Further, CAD patients had lower FD-300 levels that were close to statistical significance relative to healthy controls ($p = 0.066$). The optic disk retinal nerve fiber layer thickness ($p = 0.643$) and VDs ($p>0.05$) in SS-$I \geq 12$ patients were lower than in SS-$I<12$ patients and health controls, though the difference was statistically non-significant (Table 2).

3.3. The SS-II analyses based on PCI and CABG

3.3.1. The SS-II PCI analysis

The mean SS-II PCI score was 28.5 ± 9.3. There were no statistically significant differences based on age ($p = 0.816$) or gender ($p = 0.919$) A comparison of SS-II PCI<28.5 and SS-II PCI≥28.5 patients, and healthy controls revealed that CAD patients (SS-II PCI<28.5 and SS-II PCI≥28.5

Table 1
Comparative analysis of optical coherence tomography angiography parameters based on coronary artery disease status.

Parameters			Healthy controls, $n = 37$	CCS, $n = 32$	ACS, $n = 35$	p value
			Mean±Standard deviation			
SCP VD (%)		Whole **	51.45±2.76	49.48±4.27	48.35±6.09	0.073
		Foveal**	21.75±8.48	21.37±8.04	19.96±6.16	0.488
		Parafoveal**	53.58±3.15	49.24±8.61	50.16±7.08	0.052
		Perifoveal**	51.84±2.86	50.21±4.53	48.70±6.38	0.084
DCP VD (%)		Whole**	53.00±5.23	50.72±6.55	50.73±7.39	0.324
		Foveal*	36.35±8.63	34.87±6.73	34.15±7.21	0.461
		Parafoveal**	55.81±3.67	53.64±5.96	53.59±6.34	0.284
		Perifoveal**	54.55±5.42	51.81±7.22	52.12±8.12	0.327
FAZ parameters		FAZ area (mm^2)**	0.29±0.12	0.30±0.13	0.29±0.11	0.787
		PERIM (mm)*	2.07±0.47	2.15±0.51	2.11±0.46	0.758
		FD-300 (%)**	54.25±3.51	51.99±5.59	50.21±8.17	0.061
Capillary flow area (mm^2)	Outer retinal	Select area**	28.28±0.05[ab]	28.27±0.05[a]	28.34±0.26[b]	**0.040**
		Flow area**	8.10±1.80	9.52±2.87	9.15±3.62	0.112
	Choriocapillaris	Select area**	28.26±0.04	28.26±0.05	28.25±0.04	0.564
		Flow area**	19.34±1.16	19.36±1.12	19.14±1.06	0.430
OD	Retinal nerve fiber layer thickness (μm)	Global*	114.16±13.81	113.19±10.91	110.80±15.04	0.557
	VD (%)	Whole*	48.97±2.62	49.15±2.95	47.45±3.98	0.062
		Inside disk**	50.95±6.53	50.13±5.20	50.00±4.54	0.379
		Peripapillary**	52.12±2.22	52.06±3.87	49.82±4.62	0.090

CCS=Chronic coronary syndrome, ACS=Acute coronary syndrome, SCP=Superficial capillary plexus, DCP=Deep capillary plexus, VD=Vessel density, FAZ=Foveal avascular zone, PERIM=FAZ perimeter, FD-300= Foveal VD 300 μm around FAZ, OD=Optic disk, mm^2=Millimeter square, mm=Millimeter,%=Percentage, n=Number of participants,.

* =ANOVA test,.

** =Kruskal Wallis-H test. Note: Different letters in each line indicate the statistical difference among groups.

Table 2
The SS-I-based comparative analysis of optical coherence tomography angiography parameters.

Parameters			Healthy controls, $n = 37$	SS-I<12, $n = 33$	SS-$I \geq 12$, $n = 34$	p value
			Mean±Standard deviation			
SCP VD (%)		Whole **	51.45±2.76	49.72±4.19	48.08±6.13	0.066
		Foveal**	21.75±8.48	20.22±7.38	21.03±6.91	0.432
		Parafoveal**	53.58±3.15	50.12±8.32	49.34±7.37	0.060
		Perifoveal**	51.84±2.86	50.36±4.36	48.52±6.49	0.090
DCP VD (%)		Whole**	53.00±5.23	50.63±6.64	50.82±7.34	0.314
		Foveal*	36.35±8.63	33.51±5.52	35.45±8.05	0.287
		Parafoveal**	55.81±3.67	53.39±5.91	53.83±6.38	0.187
		Perifoveal**	54.55±5.42	51.86±7.32	52.08±8.06	0.347
FAZ parameters		FAZ area (mm2)**	0.29±0.12	0.31±0.11	0.28±0.12	0.635
		PERIM (mm)*	2.07±0.47	2.19±0.45	2.07±0.51	0.490
		FD-300 (%)**	54.25±3.51	51.30±7.05	50.82±7.17	0.066
Capillary flow area (mm^2)	Outer retinal	Select area**	28.28±0.05	28.32±0.27	28.29±0.04	0.256
		Flow area**	8.10±1.80	9.29±3.39	9.36±3.18	0.246
	Choriocapillaris	Select area**	28.26±0.04	28.26±0.05	28.25±0.04	0.391
		Flow area**	19.34±1.16	19.32±1.20	19.17±0.98	0.572
OD	Retinal nerve fiber layer thickness (μm)	Global*	13.81±2.27	13.92±2.42	12.59±2.16	0.643
	VD (%)	Whole*	48.97±2.62	48.84±3.27	47.70±3.87	0.213
		Inside disk**	50.95±6.53	50.47±4.93	49.67±4.76	0.337
		Peripapillary**	52.12±2.22	51.51±4.00	50.29±4.73	0.262

SS-*I*=SYNTAX I score, SCP=Superficial capillary plexus, DCP=Deep capillary plexus, VD=Vessel density, FAZ=Foveal avascular zone, PERIM=FAZ perimeter, FD-300=Foveal VD 300 μm around FAZ, OD=Optic disk, mm^2=Millimeter square, mm=Millimeter,%=Percentage, *n*=Number of participants,.
* =ANOVA test,.
** =Kruskal Wallis-H test. Note: Different letters in each line indicate the statistical difference among groups.

patients), the vast majority of whom were SS-II PCI≥28.5 patients, had the lowest VDs, particularly in whole ($p = 0.034$) and parafoveal ($p = 0.009$) SCPs. Also, SS-II PCI≥28.5 patients had the lowest FD-300 ($p = 0.019$). The remaining OCTA parameters, such as capillary flow areas, as well as optic disk retinal nerve fiber layer thickness and VDs, had no statistically significant differences among groups (p>0.05) (Table 3).

3.3.2. *The SS-II CABG analysis*

The mean SS-II CABG was 25.1 ± 11.8. There were no statistically significant differences based on age ($p = 0.778$) or gender ($p = 0.822$). A comparison of SS-II CABG<25.1 and SS-II CABG≥25.1 patients, and healthy controls showed that CAD patients, the vast majority of whom were SS-II CABG≥25.1 patients, had the lowest VDs, particularly in whole ($p = 0.021$), parafoveal ($p = 0.014$), and perifoveal ($p = 0.030$) SCPs, as well as whole ($p = 0.020$) and perifoveal ($p = 0.017$) DCPs. The SS-II CABG≥25.1 patients also had the lowest FD-300 ($p = 0.003$). The outer retinal flow area of SS-II CABG≥25.1 patients increased the most, followed by SS-II CABG<25.1 patients, when compared to healthy controls ($p = 0.020$). The optic disk retinal nerve fiber layer thickness and VDs had no statistically significant differences among groups (p>0.05) (Table 4).

4. Discussion

As far as we can tell, the current OCTA-based study is the first of its kind to investigate retinal and optic disk microvascular morphological

Table 3
The SS-II PCI-based optical coherence tomography angiography analysis.

OCTA parameters			Healthy controls, $n = 37$	SS-II PCI<28.5, $n = 36$	SS-II PCI≥28.5, $n = 31$	p value
			Mean±Standard deviation			
SCP VD (%)		Whole**	51.45±2.76[a]	49.56±5.38[ab]	48.10±5.16[b]	**0.034**
		Foveal**	21.75±8.48	21.71±7.88	19.38±5.96	0.405
		Parafoveal**	53.58±3.15[a]	50.21±9.01[a]	49.15±6.21[b]	**0.009**
		Perifoveal**	51.84±2.86	50.11±5.58	48.63±5.57	0.067
DCP VD (%)		Whole**	53.00±5.23	51.09±8.11	50.30±5.40	0.214
		Foveal*	36.35±8.63	35.00±6.80	33.91±7.17	0.419
		Parafoveal**	55.81±3.67	53.33±7.52	53.93±4.00	0.277
		Perifoveal**	54.55±5.42	52.46±8.77	51.40±6.20	0.230
FAZ		FAZ area (mm^2)**	0.29±0.12	0.29±0.10	0.30±0.12	0.792
		PERIM (mm)*	2.07±0.47	2.13±0.41	2.14±0.55	0.808
		FD-300 (%)**	54.25±3.51[a]	52.22±6.91[ab]	49.70±7.11[b]	**0.019**
Capillary flow area (mm^2)	Outer retinal	Select area**	28.28±0.05	28.33±0.25	28.28±0.05	0.705
		Flow area**	8.10±1.80	8.91±2.92	9.81±3.61	0.125
	Choriocapillaris	Select area**	28.26±0.04	28.25±0.04	28.26±0.05	0.549
		Flow area**	19.34±1.16	19.45±0.99	19.00±1.16	0.217
OD	Retinal nerve fiber layer thickness (μm)	Global*	114.16±13.81	111.53±14.32	112.42±11.95	0.698
	VD (%)	Whole*	48.97±2.62	48.23±4.02	48.31±3.12	0.583
		Inside disk**	50.95±6.53	51.06±4.41	48.90±5.10	0.078
		Peripapillary**	52.12±2.22	50.40±4.85	51.46±3.79	0.309

SS-II=SYNTAX II score, PCI=Percutaneous coronary intervention FAZ=Foveal avascular zone, PERIM=FAZ perimeter, FD-300=Foveal VD 300 μm around FAZ, mm^2=Millimeter square, mm=Millimeter,%=Percentage, SCP=Superficial capillary plexus, DCP=Deep capillary plexus, VD=Vessel density, OD=Optic disk,.
* =ANOVA test.
** =Kruskal Wallis-H test. Note: The different letters in each line indicate the statistical difference among groups.

Table 4
The SS-II CABG-based optical coherence tomography angiography analysis.

Parameters			Healthy controls, $n = 37$	SS-II CABG<25.1, $n = 35$	SS-II CABG≥25.1, $n = 32$	p value
			Mean±Standard deviation			
SCP VD (%)		Whole**	51.45±2.76[a]	49.98±4.28[ab]	47.70±6.06[b]	**0.021**
		Foveal**	21.75±8.48	20.52±6.94	20.75±7.38	0.559
		Parafoveal**	53.58±3.15[a]	50.51±8.50[ab]	48.86±7.00[b]	**0.014**
		Perifoveal**	51.84±2.86[a]	50.65±4.27[ab]	48.08±6.55[b]	**0.030**
DCP VD (%)		Whole**	53.00±5.23[a]	52.61±6.13[a]	48.66±7.30[b]	**0.020**
		Foveal*	36.35±8.63	34.73±6.98	34.24±7.00	0.481
		Parafoveal**	55.81±3.67	55.16±4.55	51.92±7.15	0.069
		Perifoveal**	54.55±5.42[a]	54.17±6.53[a]	49.57±8.14[b]	**0.017**
FAZ		Area (mm^2)**	0.29±0.12	0.30±0.08	0.28±0.15	0.431
		PERIM (mm)*	2.07±0.47	2.19±0.34	2.07±0.59	0.457
		FD-300 (%)**	54.25±3.51[a]	53.08±5.80[a]	48.84±7.73[b]	**0.003**
Outer retinal (mm^2)		Select area**	28.28±0.05	28.32±0.26	28.28±0.05	0.642
		Flow area**	8.10±1.80[a]	8.56±3.00[ab]	10.17±3.37[b]	**0.020**
Choriocapillaris (mm^2)		Select area**	28.26±0.04	28.24±0.04	28.27±0.05	0.109
		Flow area**	19.34±1.16	19.44±1.05	19.03±1.10	0.239
OD	Retinal nerve fiber layer thickness (μm)	Global*	114.16±13.81	112.49±12.74	111.34±13.84	0.682
	VD (%)	Whole*	48.97±2.62	47.80±3.89	48.76±3.26	0.289
		Inside disk**	50.95±6.53	51.09±4.25	48.94±5.22	0.079
		Peripapillary**	52.12±2.22	50.34±4.17	51.49±4.62	0.279

SS-II=SYNTAX II score, CABG=Coronary artery bypass graft score FAZ=Foveal avascular zone, PERIM=FAZ perimeter, FD-300= Foveal VD 300 μm around FAZ, mm^2=Millimeter square, mm=Millimeter,%=Percentage, SCP=Superficial capillary plexus, DCP=Deep capillary plexus, VD=Vessel density, OD=Optic disk,.
* =ANOVA test,.
** =Kruskal Wallis-H test. Note: Different letters in each line indicate the statistical difference among groups.

changes in CAD patients undergoing coronary angiography. In this context, prediction of atherosclerosis and related cardiovascular mortality risk in conjunction with the interventional SS system appeared feasible, allowing for earlier therapeutic and preventive measures.

Essentially, focal or generalized arteriolar narrowing and arteriovenous notching are signs of vascular retinopathy, especially hypertensive retinopathy, and are frequently associated with systemic diseases [23]. To track these posterior segment changes, a conventional biomicroscopy is required. In fact, the retina could be used to study the body's microvascular system because it is an excellent tissue for directly viewing microvascular structure [24]. With technological advances, it is now possible to comprehensively visualize and assess morphological structure of the retinal and optic disk microvasculature [25]. This method also allows for the detection of not only SCP but also DCP and choroidal vascularization, which are normally invisible to the naked eye during retonoscopy [12].

It has long been reported that there is an association between the retinal and heart microvascular structures, as well as risk factors associated with them [26,27]. Patients with central retinal artery occlusion are more likely to develop ACS [28]. A number of changes, particularly retinal sclerosis, have been associated with cardiac mortality, especially ACS [29]. Moreover, the thickness of coronary microvascular structures has been reported to be comparable to that of the retinal arteries [10]. Since retinal vessel diameters are related to CAD, it has been demonstrated that examining the retinal microvascular structure can shed light on the disease [30].

Consistent findings were also revealed in the current study, which found that CAD patients were associated with lower whole, foveal, parafoveal, and perifoveal SCP and DCP VDs, as well as FD-300 than healthy controls, despite statistically non-significant differences. This condition was accompanied by increased FAZ area and PERIM in these patients. Furthermore, compared to CCS patients and healthy controls, ACS patients had the highest outer retinal select area. However, no significant difference in the optic disk retinal nerve fiber layer thickness or VDs was found between CAD patients and healthy controls. Although there were non-significant differences, especially in capillary plexus VDs, the overall findings of posterior segment microvascular variations in CAD patients appeared to be a potential reflection of their cardiovascular status.

Likewise, VD analysis in hospitalized ACS patients in the Eye-MI Pilot study using OCTA revealed that SCP VDs were associated with a high cardiovascular risk profile and impaired left ventricular ejection fraction in high-risk patients [31]. This finding lends credence to the hypothesis underlying the relationship between microvascular structures of the ocular posterior segment and the heart in general. Additionally, despite the lack of clinical fundus involvement, CCS patients had significantly lower VDs and choriocapillary flow area in all retinochoroidal layers except the superficial and deep foveal regions in the OCTA study published by Wang et al. [32]., indicating that changes in the retinochoroidal microvasculature could be linked to stenosis of coronary artery and its branches. Lower VDs and flow area were associated with left main coronary artery, left circumflex/right coronary artery (proximal portion), and left descending artery (proximal portion). The same study concluded that OCTA could be a valuable non-invasive method for detecting early stage CCS. Overall, these findings corroborate the current study's findings, as did those of Hannappe et al. [33]., who revealed that ACS patients had significantly lower retinal inner perfusion density than controls.

In the current study, despite statistically non-significant differences in OCTA parameters between CAD patients (SS-*I*<12 and SS-*I* ≥ 12 patients) and healthy controls, the former were associated with slightly lower capillary plexus VDs in all regions, as well as lower FD-300 levels that were close to statistical significance. In addition, the optic disk retinal nerve fiber layer thickness and VDs in SS-*I* ≥ 12 patients were the lowest, though the difference was statistically non-significant. In general, higher SS-I levels were associated with lower ocular microcirculation, as measured by OCTA. Similarly, when CAD patients (SS-II PCI<28.5 and SS-II PCI≥28.5 patients) were compared to healthy controls, the former, the vast majority of whom were SS-II PCI≥28.5 patients, had the lowest VDs, particularly in whole and parafoveal SCPs, as well as in FD-300. Also, SS-II CABG≥25.1 patients had the greatest outer retinal flow area, followed by SS-II PCI<28.5 patients. From this perspective, the higher the SS-I and SS-II, especially among CABG patients, the lower the ocular microcirculation. This tended to create an increased outer retinal flow area, potentially allowing for widespread posterior segment nourishment, which could otherwise be compromised secondary to cardiovascular imbalance.

There are some limitations to the current study. First, there was a lack of standardization among groups in terms of patients with various systemic diseases. The SS-II was calculated with chronic obstructive

pulmonary disease comorbidity in mind. This evaluation, however, may have revealed a direct chronic obstructive pulmonary disease-induced change in the retinal and optic disk microvasculature. Further, while the possibility of retinal and optic disk microvascular changes directly caused by peripheral artery disease was considered when calculating the SS-II of peripheral artery disease patients, the possibility of these changes being caused by peripheral artery disease was ignored. Second, the OCTA procedure requires patient cooperation and coordination. As such, CAD patients who weren't fit enough to perform OCTA and whose health was only just recovering were not studied due to poor scan quality index of OCTA images. Inclusion of patients who died during or after coronary angiography, or who were referred to the cardiovascular surgery clinic for CABG but did not undergo OCTA procedure during the study period, could have yielded clinically significant results. Third, the electrocardiography and ejection fraction data needed to calculate SS-II were reviewed jointly and non-blindly by two senior cardiologists; however, even minor changes in SS-II could occur in such conditions, potentially influencing study results, despite independent ejection fraction measurement. The same could be true for lung disease diagnosis in chronic obstructive pulmonary disease patients, with some variation in their SS-II even after evaluation by two independent pulmonologists.

Despite these limitations, the current study may contribute clinically significant information to the literature. This is primarily due to the fact that it is the first of its kind to evaluate a large number of CAD patients using the interventional method (the SS) in conjunction with a novel non-invasive OCTA technology to predict atherosclerosis and related cardiovascular mortality risk, allowing for earlier preventive and/or therapeutic measures. Besides, OCTA findings differed statistically significantly among CAD patient groups, particularly in the SS-II. In the future studies, OCTA could be integrated into the SS system and used to predict prognosis in ACS and CCS patients. Hence, a stronger prognostic marker could well emerge when SS-II is calculated with the eyes, lungs, heart, kidneys, and peripheral arteries included in the SS system. Basically, in search of clinically useful outcomes, more large-scale prospective multidisciplinary studies on this "time-dependent life-or-death battle" against cardiovascular diseases might be worth trying.

5. Conclusions

Despite non-significant differences, particularly in capillary plexus VDs, the current study found a general decrease in posterior segment microcirculation using OCTA in CAD patients graded with the interventional SS system during coronary angiography. In the meantime, the vast majority of significant differences were associated with CAD patients who underwent SS-II PCI and SS-II CABG. The OCTA, a non-invasive imaging technique, appears to have the potential to yield significant clinical results in the early diagnosis or prognosis of cardiovascular diseases.

Financial interest

All authors certify that they have no association or participation with any organization or individual with any financial interest or non-financial interest in the subject matter or materials discussed in this article.

Ethics approval

This study, which was carried out in accordance with the Helsinki Declaration, was approved by the XX University Clinical Research Ethics Committee with the approval date and number: 2022/234.

Consent to participate

Informed consent was obtained from all study participants.

Availability of data and materials

The data supporting our study findings are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

İbrahim Ethem Ay: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **İbrahim Etem Dural:** Investigation, Methodology, Data curation, Writing – original draft. **Aynur Er:** Investigation, Methodology, Visualization. **Mustafa Doğan:** Investigation, Methodology, Writing – review & editing. **Hamidu Hamisi Gobeka:** Conceptualization, Data curation, Formal analysis, Validation, Visualization, Writing – review & editing. **Ömer Faruk Yilmaz:** Formal analysis, Investigation, Methodology, Visualization.

Declaration of Competing Interest

The authors declare that they have received no public or private financial support or involvement in the products, methods, or materials mentioned in this manuscript, and there is no conflict of interest to disclose.

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