Retinal changes in patients with angina pectoris and anginal equivalents: a study of patients with normal coronary angiography

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Background and aims. Approximately 10–30% of the patients with typical symptoms of angina pectoris have normal angiography showing normal macrovasculature. In these patients, however, the microvascular problems should be monitored. Hence, the main aim of this study is to evaluate retinal changes in normal angiographic patients.

Methods. In this descriptive cross-sectional study, 60 normal angiographic patients with typical chest pain or anginal equivalents visiting Modarres Hospital Cardiology Research Center between 2018 and 2019 were enrolled and retinal changes were determined in Labbafinejad Hospital by Optical Coherence Tomography Angiography using Foveal Avascular Zone (FAZ), Superficial Vascular Density (SVD), and Deep Vascular Density (DVD).

Results. The results of this study demonstrated that FAZ was normal in all subjects, but SVD and DVD were abnormal in 45% and 8.3%, respectively. Totally, 18.5% and 66.7% showed abnormal SVD among stable angina (SA) and unstable angina (UA) cases, respectively ($P < 0.001$). There was no statistically significant difference between abnormal DVD in SA and UA cases ($P = 0.058$). Abnormal SVD was significantly more common among diabetic patients ($P < 0.001$), while DVD was not related to diabetes presence in the study population ($P > 0.05$). Moreover, abnormal SVD was more common among patients with chest pain ($P = 0.036$), while there was no significant difference for DVD ($P = 0.371$). Interestingly, abnormal ECG was associated with both abnormal DVD and SVD.

Conclusions. The results of this study showed that nearly half of the patients with angina pectoris or anginal equivalents who revealed normal angiographic findings may suffer from retinal changes. Thus, retinal assessment is needed in these patients to evaluate microvascular changes.

Key words: retinal changes, angiography, microvascular involvement, coronary artery disease, angina pectoris.

INTRODUCTION

High burden of cardiovascular diseases (CVDs), especially coronary artery disease, is a global issue with extended rate of mortality and morbidity as well as health costs [1, 2]. It has been reported that there were 422.7 million cases of CVDs and 17.92 million related deaths worldwide in 2015 [3]. Also, ischemic heart disease (IHD) is believed to be the leading cause of CVD health loss globally. It is projected that IHD-related deaths will increase to more than 9 million global death in 2030 [4]. Recognition of high-risk subjects has some limitations and further studies are required to acknowledge the vital factors and at the same time rule out the effect of confounding factors [5, 6]. Such attempts to determine the high-risk groups are essential in all patients, especially in cases with insufficient number of known risk factors [7–9].

These methods for the determination of the risk factors should be easy and feasible [9].

It is assumed that retinal vessels may resemble microvasculature of coronary arteries and can reflect both the microvascular injuries and their course of progression [9]. Also, some studies have shown the association between macrovascular disease of coronary arteries and retinal small vessels [10]. These findings in micro-circulation alterations such as micro-aneurysm, focal and general stenosis, and arteriolar or venular nicking may predict the risk of cardiovascular events [11].

Retinopathy can be seen as cotton wool spots, hemorrhage, micro-aneurysm, macular edema, and exudates [12]. Despite proposed association between retinal disease and systemic artery diseases, the ophthalmoscopy is not accepted as a routine procedure because it is not a quantitative and objective method [12, 13]. Nevertheless, state-of-the-art methods

assessing retinal vessels and their structures are available and may have different applicability in this era [12, 13].

Macula is the main retinal part that can be assessed in terms of retinal function and structure evaluation by optical coherence tomography angiography (OCTA) and by reporting the dimensions of foveal avascular zone [14]. Nearly 10–20 % of patients with chest pain undergoing angiography may have normal findings [15]. Among them, subjects with exertion chest pain and ST-segment depression in ECG or impaired myocardial perfusion are considered as X-syndrome [15]. In these patients, however, the microvascular problems should be monitored, while there is no definite tool to assess these changes and predict future macrovascular problems. Hence, the main aim of this study was to evaluate retinal changes in patients with normal coronary angiography.

MATERIALS AND METHODS

In this descriptive cross-sectional study, 60 consecutive patients with normal coronary angiography or non-significant findings that had typical chest pain or anginal equivalents were enrolled. These patients, also, had abnormal non-invasive tests such as ECG, echocardiography, and exercise tests. All the patients referred to Modarres Hospital Cardiology Research Center (Tehran, Iran) between 2018 and 2019. We excluded the cases with slow-flow phenomenon, coronary ectasia or incomplete data.

This study was approved by local ethical committee of Shahid Beheshti University of Medical Sciences and written consent was obtained from all patients. All the research protocols were in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Complete history was taken and recorded in the checklists. Retinal changes including atherosclerosis and retinopathy were determined in Labbafinejad Hospital by optical coherence Tomography Angiography (OCTA). Accordingly, foveal avascular zone (FAZ), superficial vascular density (SVD), and deep vascular density (DVD) were assessed. The only ophthalmologist was blind to the study protocol during retinal assessments.

Normal coronary artery was defined by conventional angiography method; in other words, cases with no 'endoluminal irregularities' or 'no significant (< 20%) stenosis' were considered normal-angiographic. Also, mild coronary artery disease was defined as cases with stenosis between 20%

and 50% in coronary arteries. OCTA provides some depth-resolved images of the blood flow in the retina and choroid with definite details. This multimodal imaging methods is used for the evaluation of retinal diseases. FAZ was defined as the round/oval capillary-free region within the macula area. SVD was also defined as the proportion of the sample area occupied by vascular lumens after binary reconstruction of images. DVD was defined as deep capillary plexuses of the sample area occupied by vascular lumens following binary reconstruction of the images. Normal ranges were those in mean $\pm$ standard deviation in normal populations.

Data analysis was performed in SPSS version 26.0. Utilized statistical tests were Kolmogorov-Smirnov, Independent-Sample-T, Chi-Square, and Fisher tests. P-values under 0.05 were considered as statistically significant.

RESULTS

The mean age of patients (21 males, 39 females) was 66.2 ± 6.9 years. Patients' baseline characteristics are summarized in Table 1.

Retinal findings included FAZ, DVD, and SVD. FAZ and diameter were both normal in all subjects, and to better explain, it can be mentioned that it was in a range of mean $\pm$ standard deviation in all subjects. However, SVD and DVD were abnormal in 45% and 8.3% of patients, respectively. As shown in Table 2, older age was related to abnormal SVD ($P = 0.036$), but not to abnormal DVD ($P = 0.088$).

As shown in Table 3 and Table 4, sex was not associated with SVD and DVD findings ($P > 0.05$). Also, history of hypertension had no significant association with either SVD or DVD results ($P > 0.05$). Abnormal SVD was significantly more common among diabetic patients ($P < 0.001$), while DVD was not related to diabetes presence in patients ($P > 0.05$). Moreover, hyperlipidemia and smoking were not related to DVD and SVD results ($P > 0.05$).

Totally, 18.5% and 66.7% among stable angina (SA) and unstable angina (UA) cases revealed abnormal SVD with significant difference ($P < 0.001$). There was no statistically significant difference between abnormal DVD in SA and UA cases ($P = 0.058$). As shown in Table 5, abnormal SVD was more common among patients with chest pain ($P = 0.036$), while there was no significant difference for DVD ($P = 0.371$).

Table 1
Patients' baseline characteristics

	Number	Percent
Male	21	35%
Female	39	65%
HTN	47	78.33%
HTN (male)	14	23.33%
HTN (female)	33	55%
DM	27	45%
DM (male)	9	15%
DM (female)	18	30%
HLP	24	40%
HLP (male)	8	13.33%
HLP (female)	16	26.66%
Smoking	12	20%
Smoking (male)	8	13.33%
Smoking (female)	4	6.66%

Abbreviations: HTN, hypertension; DM, diabetes mellitus; HLP, hyperlipidemia.

Table 2
SVD and DVD results by age among patients

		Age		P-Value
		Mean	Standard Deviation	
SVD	Normal	64.8	7.1	0.036
	Abnormal	68.6	6.2	
DVD	Normal	66.1	6.5	0.088
	Abnormal	71.6	9.9	

SVD – Superficial Vascular Density; DVD – Deep Vascular Density.

Table 3
DVD results by categorical data

DVD						
		Normal		Abnormal		P-Value
		Count	Percent	Count	Percent	
Sex	Male	21	100.0%	0	.0%	0.152
	Female	34	87.2%	5	12.8%	
Hypertension	Positive	42	89.4%	5	10.6%	0.575
	Negative	13	100.0%	0	.0%	
Diabetes Mellitus	Positive	24	88.9%	3	11.1%	0.649
	Negative	31	93.9%	2	6.1%	
Hyperlipidemia	Positive	22	91.7%	2	8.3%	1.000
	Negative	33	91.7%	3	8.3%	
Smoking	Positive	12	100.0%	0	.0%	0.572
	Negative	43	89.6%	5	10.4%	

DVD – Deep Vascular Density.

Table 4
SVD results by categorical data

		SVD				P-Value
		Normal		Abnormal		
		Count	Percent	Count	Percent	
Sex	Male	15	71.4%	6	28.6%	0.061
	Female	18	46.2%	21	53.8%	
Hypertension	Positive	23	48.9%	24	51.1%	0.073
	Negative	10	76.9%	3	23.1%	
Diabetes Mellitus	Positive	7	25.9%	20	74.1%	0.001
	Negative	26	78.8%	7	21.2%	
Hyperlipidemia	Positive	14	58.3%	10	41.7%	0.672
	Negative	19	52.8%	17	47.2%	
Smoking	Positive	7	58.3%	5	41.7%	0.795
	Negative	26	54.2%	22	45.8%	

SVD – Superficial Vascular Density.

Table 5

SVD and DVD results by type of cardiac symptoms

		Symptom						
		CP		DOE		Both		
		Count	Percent	Count	Percent	Count	Percent	P Value
SVD	NL	21	47.7%	7	100.0%	5	55.6%	0.036
	ANL	23	52.3%	0	.0%	4	44.4%	
DVD	NL	39	88.6%	7	100.0%	9	100.0%	0.058
	ANL	5	11.4%	0	.0%	0	.0%	

NL – Normal; ANL – Abnormal; CP – Chest pain; DOE – Dyspnea on exertion; SVD – Superficial Vascular Density; DVD – Deep Vascular Density.

Percentage represent the prevalence normal and abnormal SVD or DVD in patients with each complaint. P-values are associated with the difference of abnormal SVD or DVD between columns.

As shown in Table 6, among those with abnormal and normal ECG, 73.3% and 35.5% showed abnormal SVD, respectively (P = 0.011). Also, among

those with abnormal and normal ECG, 26.7% and 2.2% had abnormal DVD with significant difference (P = 0.012).

Table 6

SVD and DVD results by ECG findings

		DVD		SVD		Abnormal		P-value
		Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	
		Count	Percent	Count	Percent	Count	Percent	
ECG	Normal	44	97.8%	1	2.2%	29	64.4%	0.012
	Abnormal	11	73.3%	4	26.7%	4	26.7%	

SVD – Superficial Vascular Density; DVD – Deep Vascular Density.

DISCUSSION

Totally up to one-third of cases with typical chest pain have normal angiography and determination of the risk factors for progression of vascular disease in these subjects is crucial [15]. In our study, SVD and DVD were abnormal and showed some differences by the type of symptoms and disease subtype. The abnormality was more common in unstable angina cases and those with chest pain.

Many studies have evaluated the correlation between coronary artery disease and retinal microvascular changes, but their findings are inconsistent. Van Hecke *et al.* found that there was no correlation between retinal microvascular abnormalities and endothelium-dependent flow-mediated vasodilation (a marker for endothelial function) or carotid intima-media thickness (a marker for early atherosclerosis) [16]. The most important difference between our study and Van Hecke's is that we included patients with related cardiac symptoms of IHD; in other words, we included patients with possible clinical dysfunction of cardiovascular system, while the others of the mentioned study included patients without any clinical symptoms, and this can justify this inconsistency. On the other hand, a Chinese study found significantly decreased central retinal artery blood flow in the patients with coronary artery disease, which underscores the role of endothelial

dysfunction as a mutual mechanism [17]. Possible shared mechanism proposed is systemic inflammation which affects not only coronary arteries but also retinal vessels [18].

Tedeschi-reiner *et al.* [19] assessed 109 Coronary Artery Disease (CAD) cases and reported that CAD severity and retinal vessel atherosclerosis were interrelated. In our study, however, we enrolled patients with normal coronary findings in angiography. Witt *et al.* [12] also performed a case-control study and reported that microvascular findings in retinal assessments may be utilized as a non-invasive method to predict the outcomes. However, our study was a cross-sectional one and further longitudinal studies should be carried out for outcome prediction.

Kreis *et al.* [20] assessed both coronary and retinal vessels angiography in 98 cases and found that there was no association between CAD severity and retinal findings. In our study, the type of coronary artery disease was related to retinal findings and unstable versus stable angina had different rate of abnormality in retinal assessments. Also, types of retinal findings were different among patients with diverse clinical symptoms. This may show that the level of coronary artery involvement may be also associated with the degree of involvement in retinal vessels.

Wang and colleagues [21] reported that among 472 suspected cases of CAD, assessed by

angiography, approved CAD cases had higher abnormalities in retinal evaluations with further severity. In our study, there were no comparison group and for this matter definite interpretation in this era is impossible.

A meta-analysis by Liu *et al.* suggests that only arteriolar caliber (but not venular) is associated with arterial function and this association become more prominent in cardiometabolic patients [22]. This may underscore the importance of shared mechanism of preclinical changes in large arteries and microcirculation. We also showed that in patients with CVD, there are some associations between CVD and retinal vessels. However, more studies are needed to clarify this association in patients with other vascular diseases, such as stroke.

Here, it should be mentioned that both retinal vessels anatomy and physiological functionality should be taken into account for risk stratification

in CAD [23]. Moreover, other related complication such as stroke, heart failure, and mortality has been shown to correlate with the structure of retinal vessels, but the results are diverse and further studies are needed to develop a risk-scoring system using retinal vessels [23].

CONCLUSION

The results of this study showed that nearly half of the patients with angina pectoris or anginal equivalents who revealed normal angiographic findings may suffer from retinal changes. Thus, retinal assessment may be needed in these patients to evaluate microvascular changes. However, further studies with larger sample size and further diagnostic methods are required to attain more definite comparable results in this era.

Introducere. 10–30% dintre pacienții cu simptome tipice de angină pectorală au angiografie normală. Acești pacienți prezintă însă afectare microvasculară care trebuie evaluată. Studiul evaluează modificările microvasculare la acești pacienți.

Metode. A fost realizat un studiu descriptiv transversal în care au fost evaluați 60 de pacienți cu angiografii normale, dar cu simptome de angina pectorală sau echivalente de angină ce s-au prezentat în spitalul Modarres între 2018 și 2019. Modificările retinale au fost evaluate la Spitalul Labbafinejad folosind tehnicile FAZ (Optical Coherence Tomography Angiography using Foveal Avascular Zone), SVD (Superficial Vascular Density) și DVD (Deep Vascular Density).

Rezultate. FAZ a fost normal la toți pacienții însă SVD și DVD au fost modificate la 45% respectiv 8,3% dintre pacienți. 18,5% și 66,7% dintre pacienții cu SVD modificat aveau angină stabilă (SA), respectiv angina instabilă (US) ($p < 0,001$). Nu s-a observat o diferență semnificativă între SA și UA privind modificările DVD. SVD anormal s-a observat mai degrabă la pacienții diabetici ($p < 0,001$), pe când DVD nu s-a observat a fi asociat cu diabetul. Modificările SVD au fost prezente mai degrabă la pacienții cu durere precordială ($p = 0,036$), dar nesemnificativă asocierea cu DVD ($p = 0,371$). Modificările ECG s-au asociat cu modificări ale DVD și SVD.

Concluzii. Aproape jumătate din pacienții cu angină și angiografii normale au avut modificări ale circulației retinei. Evaluarea retinei la acești pacienți ar putea fi utilă în vederea evaluării afectării microvasculare.

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Authors' contributions:

Vahid Eslami: Manuscript writing, analysis
 Simin Mojahedin: Data acquisition, manuscript writing
 Ramin Nourinia: Supervision, conceptualisation, final edit
 Mohammadreza Tabary: Manuscript editing, data acquisition
 Isa Khareshi: Manuscript editing, data acquisition

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