Acta Cardiol Sin 2023;39:733–741
Original Article
doi: 10.6515/ACS.202309_39(5).20230209A

Coronary Artery Disease

Evaluation of Arterial Stiffness and Subfoveal Choroidal Thickness in Patients with Coronary Slow Flow

Zekeriya Dogan,[1] Cigdem Ileri,[2] Beste Ozben,[1] Murat Sunbul,[1] M. Kursat Tigen,[1] Ozlem Sahin[3] and Osman Yesildag[1]

Background: Coronary slow flow may not only affect the coronary arteries, but it may also be a vascular problem affecting the rest of the arterial system.

Objective: The aim of this study was to determine peripheral arterial stiffness and the thickness of the choroid layer in patients with slow coronary flow.

Methods: Fifty consecutive patients (age, 54.3 ± 11.4 years, 38 male) with coronary slow flow and 25 consecutive patients (age, 50.5 ± 9.9 years, 16 male) with normal coronary arteries both documented by coronary angiography were included. Arterial stiffness parameters were measured noninvasively using a Mobil-O-Graph arteriography system. The choroidal thickness was assessed using the enhanced depth imaging optical coherence tomography method.

Results: The patients with coronary slow flow had significantly higher peripheral systolic blood pressure, peripheral pulse pressure, central pulse pressure, and pulse wave velocity (PWV) and significantly thinner choroidal thickness compared to the controls. Thrombolysis in myocardial infarction frame count was positively correlated with PWV (r: 0.237, p = 0.041) and negatively correlated with choroidal thickness (r: -0.249, p = 0.031). There was also a negative correlation between PWV and mean choroidal thickness (r: -0.565, p < 0.001). Linear regression analysis showed that coronary slow flow was an independent predictor of both PWV and choroidal thickness when adjusted by age and sex.

Conclusion: The acceleration of average peripheral arterial PWV with a thinning of choroidal thickness in patients with coronary slow flow may support the idea that this phenomenon may be a coronary presentation of a systemic microvascular disorder.

Key Words: Arterial stiffness • Choroidal thickness • Coronary slow flow phenomenon

Abbreviations

AIx	Augmentation index
Cx	Circumflex artery
hs-CRP	High sensitive C-reactive protein
LAD	Left anterior descending artery
NT-proBNP	N-terminal pro-brain natriuretic peptide
OCT	Optical coherence tomography
PWV	Pulse wave velocity
RCA	Right coronary artery
TIMI	Thrombolysis in myocardial infarction

Received: September 23, 2022 Accepted: February 9, 2023
[1]Department of Cardiology, Marmara University School of Medicine; [2]Department of Cardiology, Kosuyolu Heart Education and Research Hospital; [3]Department of Ophthalmology, Marmara University School of Medicine, Istanbul, Turkey.
Corresponding author: Dr. Beste Özben, Yildiz Caddesi Konak Apartmani No: 43/2, 34353 Besiktas, Istanbul Turkey. Tel: 90 535 3476231; Fax: 90 216 6570695; E-mail: besteozben@yahoo.com
The study was presented as an oral presentation at the European Society of Cardiology Congress 2017 in Barcelona (Spain).

INTRODUCTION

The coronary slow flow phenomenon is defined as delayed progression of the contrast medium in epicardial vessels during coronary angiography.[1] This condition is thought to be associated with a coronary microcirculation disorder. Generally, these patients are male and smokers with multiple risk factors and have frequent hospital admissions for recurrent chest pain.[2] Although it has a relatively good prognosis, there are cases of arrhythmias and sudden cardiac death.[3,4]

Coronary slow flow may be primary and associated with high resting microvascular resistance depending on the existence of diffuse hyperplastic fibromuscular thickening and microcalcification of small vessels. On the other hand, secondary coronary slow flow may be due to coronary ectasia, coronary spasm, or air embolism, or it may be seen after coronary reperfusion therapy, angioplasty, or coronary stenting in acute myocardial infarction, or residual stenosis in infarct-related arteries.[5,6] A systemic inflammatory state and abnormalities in autacoids such as endothelin-1 and thromboxane A have been implicated in the mechanism of coronary slow flow.[7]

Arterial stiffness plays a crucial role in the pathophysiology of cardiovascular diseases, and is related to cardiovascular risk factors such as aging, hypertension, hyperlipidemia, diabetes, obesity, and smoking.[8-11] It refers to structural features of the arterial wall, and progressive loss of arterial elasticity affects the blood flow, pressure, and arterial diameter change with each systole.[12] The development of arterial stiffness is a complex process related to interactions of endocrine factors and cytokines, as well as interactions between different vascular cellular components.[13-15] Inflammation, oxidative stress, extracellular matrix turnover, aging, sympathetic tone, and genetic polymorphisms are also associated with arterial stiffness.[16] It is a prognostic factor of cardiovascular morbidity and mortality.[10,17,18] Arterial stiffness may be evaluated noninvasively by pulse wave velocity (PWV) and augmentation index (AIx) methods, which can be used for cardiovascular risk assessment and early determination of vascular damage.[19,20]

The choroid is the most vascular layer of the eye and plays an important role in the physiology of the eye and various ocular diseases. It has the highest blood flow per tissue weight in the body. Because of its extensive vascular nature, diseases with vascular involvement may affect the choroid.[21] The structure of choroidal vessels can be revealed by spectral domain optical coherence tomography (OCT).

There is increasing evidence that coronary slow flow may be a component of systemic conditions affecting other arteries.[22] The aim of this study was to determine peripheral arterial stiffness and the choroidal thickness of patients with coronary slow flow.

METHODS

This investigation conformed to the principles outlined in the Declaration of Helsinki. The study was approved by the local ethics committee. All participants gave written informed consent.

Stable patients who had undergone coronary angiography for chest pain and/or documented ischemia in noninvasive stress tests were selected. Patients with a history of congestive heart failure, coronary artery disease including spasm, plaque, or ectasia, valvular heart disease, peripheral arterial disease, arrhythmia, active connective tissue diseases, previous cerebrovascular events, hormonal dysfunction, chronic liver or renal failure, and those taking medications known to alter retinochoroidal flow were excluded from the study. Patients with a history of ocular disease (glaucoma, diabetic retinopathy, any stages of hypertensive retinopathy, uveitis, high myopia, age-related macular degeneration, etc.) and/or a history of ophthalmic surgery that might affect the choroidal vascular network were also excluded.

Fifty consecutive patients who were shown to have coronary slow flow according to corrected thrombolysis in myocardial infarction (TIMI) frame count were included in the study. Twenty-five consecutive patients who had normal coronary arteries documented by coronary angiography were also included as the control group. The medical history and recent laboratory test results of the patients and controls including high sensitive C-reactive protein (hs-CRP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) were recorded. The presence of cardiovascular risk factors, including hypertension, diabetes mellitus, dyslipidemia, and smoking status were also assessed. Hypertension was defined as a systolic blood pressure of 140 mmHg and/or a diastolic

blood pressure greater than 90 mmHg orthe use of any antihypertensive drug. Diabetes mellitus was defined as fasting plasma glucose levels of more than 126 mg/dL in at least two consecutive measurements, previously diagnosed diabetes, or the use of any antidiabetic medication. Dyslipidemia was defined as serum total cholesterol ≥ 200 mg/dl, serum triglycerides ≥ 150 mg/dl, low-density lipoprotein cholesterol ≥ 130 mg/dl, previously diagnosed hyperlipidemia, or the use of any lipid-lowering medication.

Coronary angiography and assessment of coronary slow flow

All coronary angiographic evaluations were made using the same device (Siemens Artis Zee, Munich, Germany 2011). All patients underwent selective coronary angiography by the Judkins technique with 6 or 7 French catheters using the right or left femoral approach. By injecting an average of 5-9 ml of iohexol as opaque material for each exposure, the coronary arteries were visualized at 15 frames per second using cranial and caudal angles at right and left oblique positions. To measure the opaque material and detect coronary slow flow, the TIMI frame count method proposedby Gibson et al.[23] was used. The frame where the opaque material was delivered to the coronary artery ostium and the coronary artery was first seen was accepted as the first frame, while the frame with the first image of the distal point of the coronary artery was considered the last frame. The distal bifurcation for the left anterior descending artery (LAD), the end of the distal bifurcation for the circumflex artery (Cx), and the first lateral branch of the posterolateral artery for the right coronary artery (RCA) were taken as the distal points. The difference between the first and last frames was evaluated as the number of frames. Angiographies and the number of frames were evaluated twice by two different investigators who were blinded to the patient characteristics. In cases of different results, the mean value was taken.

Since the distance from the proximal to the distal bifurcation of the LAD artery was longer than the other coronary arteries, the LAD TIMI frame count was significantly higher than the TIMI frame counts of the RCA and Cx. Therefore, the LAD frame count was divided by 1.7 to obtain the corrected TIMI frame count.[24] In our study, coronary slow flow was defined as a corrected TIMI frame count greater than 24 frames for LAD, 26 for RCA, and 30 for Cx.[23]

Assessment of arterial stiffness

All patients and controls were asked to refrain from eating and drinking alcohol, coffee, or tea for at least 12 hours before the evaluation of arterial stiffness. After resting for 30 minutes, the test was performed in the supine position in a quiet, temperature-controlled room (22-24 °C) in the morning (between 08.00 and 10.00 am). PWV analysis was performed noninvasively using a Mobil-O-Graph arteriography system (Mobil-O-Graph NG, Stolberg, Germany) from the brachial artery by a single cardiologist blinded to the results of coronary angiography. After the blood pressure was measured by the device, the cuff was inflated to a value of at least 35 mmHg above the detected systolic pressure value, and blood flow was stopped during the measurement period (only 6-20 seconds, mean 8 seconds). The system detects signals from the brachial artery even though the cuff pressure is 35 mmHg higher than the systolic pressure in the brachial artery. This technique is based on the pulse wave (early systolic peak) running down the aorta which is initiated by myocardial contraction. This first wave is reflected from the aortic wall at the distal branching point and causes a reflected second wave (late systolic peak). The morphology of this second reflected wave depends on the stiffness of the large artery. Using amplitude and time difference between the first and the second wave, AIx (adjusted for heart rate 75 bpm) and PWV are calculated.[25-27] Systolic and diastolic blood pressure, central systolic and diastolic blood pressure, heart rate, pulse pressure, cardiac output, PWV, and AIx of the patients and controls were recorded.

Assessment of choroidal thickness

After a comprehensive ocular examination including best-corrected visual acuity (Snellen) testing, intraocular pressure measurement with Goldmann applanation tonometry, refraction, slit-lamp biomicroscopy, and color fundus photography, all eyes were imaged with OCT (RTVue-100 version 5.1 Fourier-domain optical coherence tomography; Optovue Inc., Fremont, CA, USA). Choroidal thickness was assessed by a single experienced ophthalmologist blinded to the results of coronary angiography while the patient was in a fixed straight look

position.[28] The choroidal thickness was measured as the distance between the outer border of the retinal pigment epithelium and the hyperreflective inner surface of the sclera (Figure 1). Choroidal thickness was measured manually at three points for each eye, including central, medial, and lateral points. Medial and lateral measurements were taken from 500 μm medial and lateral to the fovea.[29]

Statistical analysis

Statistical analyses were performed using SPSS (SPSS 11.0 for Windows, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as number and percentage. The chi-square test was used to compare categorical variables, while the Student's t-test or Mann-Whitney U test was used to compare parametric and nonparametric continuous variables, respectively. Normal distribution was assessed by the Kolmogorov-Smirnov test. Correlation analysis was performed using Pearson or Spearman's correlation tests. Linear regression analysis was performed to explore the independent predictors of PWV and choroidal thickness. A p value of < 0.05 was considered statistically significant.

RESULTS

The study included 50 consecutive patients with coronary slow flow (age, 54.3 ± 11.4 years, 38 male) and 25 patients with normal coronary arteries (age, 50.5 ± 9.9 years, 16 male). The characteristics and laboratory measures of the patients and controls are shown in Table 1.

Arterial stiffness parameters of the patients and controls are listed in Table 2. The patients with coronary slow flow had a significantly higher peripheral systolic blood pressure, peripheral pulse pressure, and central pulse pressure. While PWV was significantly higher in the coronary slow flow group, there were no significant differences in AIx values between the groups.

The choroidal thickness measurements are shown in Table 3. The patients with coronary slow flow had a significantly thinner choroidal thickness at all measured sites compared to the controls.

Correlation analysis revealed a positive correlation between TIMI frame count and PWV (r: 0.237, p = 0.041), and a negative correlation between TIMI frame count and choroidal thickness (r: -0.249, p = 0.031). Similarly, there was a negative correlation between PWV and mean

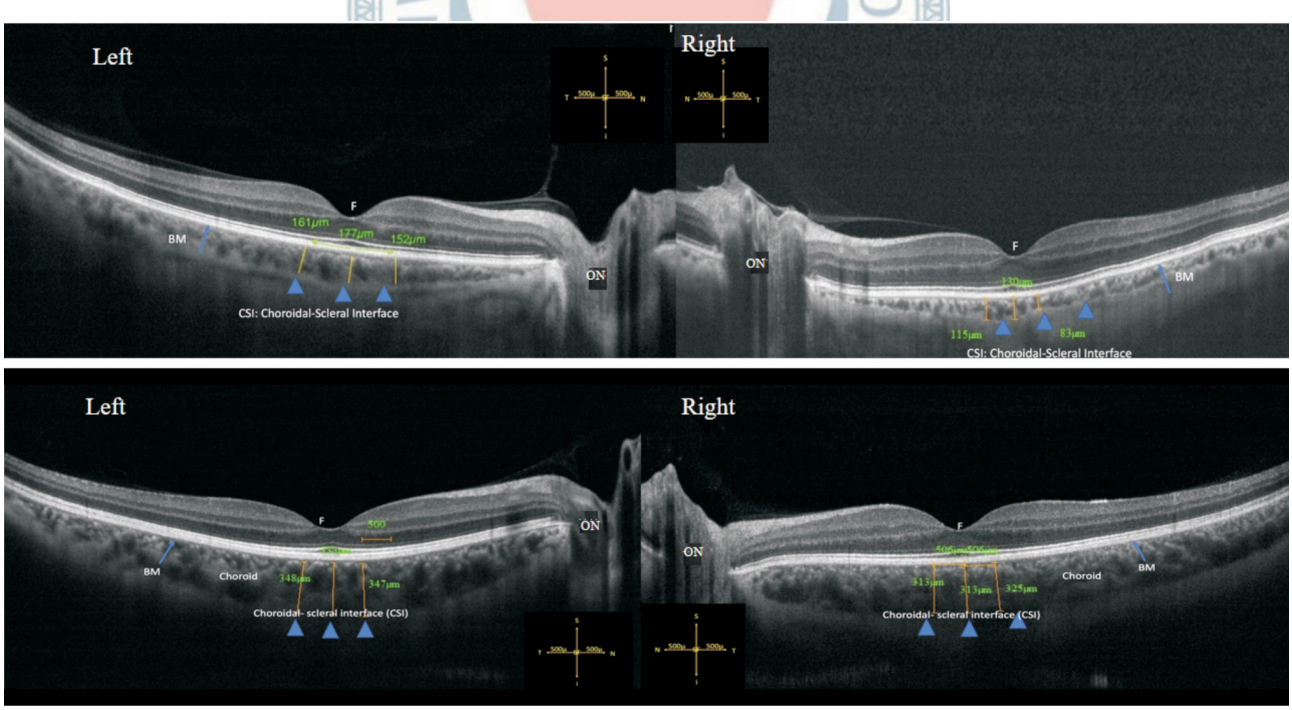

Figure 1. *Choroidal thickness measurements of a patient with coronary slow flow (up) and a control with normal coronary flow (down). Measurements were taken at three locations: subfoveal, nasal (500 μm medial to the fovea), and temporal (500 μm lateral to the fovea). BM, brunch's membrane; CSI, choroidal-scleral interface; F, fovea; ON, optic nerve.*

Table 1. General characteristics and laboratory parameters of the patients and controls

	Coronary slow flow group (n = 50)	Controls (n = 25)	p
Age (years)	54.3 ± 11.4	50.5 ± 9.9	0.165
Male sex (n, %)	38 (76%)	16 (64%)	0.275
Body mass index (kg/m^2)	30.5 ± 4.9	30.7 ± 3.7	0.868
Hypertension(n, %)	40 (80%)	17 (68%)	0.251
Dyslipidemia (n, %)	36 (72%)	14 (56%)	0.166
Diabetes (n, %)	10 (20%)	3 (12%)	0.524
Smoking (n, %)	21 (42%)	11 (44%)	0.869
Medications			
Aspirin (n, %)	29 (58%)	12 (48%)	0.412
ACEI/ARB (n, %)	38 (76%)	16 (64%)	0.275
Beta blocker (n, %)	17 (34%)	7 (28%)	0.600
Statin (n, %)	36 (72%)	13 (52%)	0.086
Creatinine (mg/dL)	0.82 ± 0.22	0.78 ± 0.16	0.418
NT-proBNP (pg/mL)	364.7 ± 950.5	296.5 ± 537.9	0.462
hs-CRP (mg/L)	4.2 ± 5.0	4.8 ± 5.7	0.695
LDL cholesterol(mg/dL)	129 ± 39	131 ± 32	0.826
HDL cholesterol (mg/dL)	46 ± 11	47 ± 7	0.226
Total cholesterol (mg/dL)	206 ± 50	200 ± 39	0.655
Triglyceride (mg/dL)	183 ± 130	121 ± 46	0.163
TIMI frame counts			
LAD	45.9 ± 12.0	25.3 ± 3.5	< 0.001
RCA	27.8 ± 7.5	14.0 ± 2.0	< 0.001
Cx	33.8 ± 12.0	17.1 ± 2.8	< 0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Cx, circumflex artery; HDL, high density lipoprotein; hs-CRP, high sensitive creactive protein; LAD, left anterior descending artery; LDL, low densitylipoprotein; NT-proBNP, N terminal pro-brain natriuretic peptide; RCA, right coronary artery.

Table 2. Arterial stiffness parameters of the patients and controls

	Coronary slow flow group (n = 50)	Controls (n = 25)	p
Peripheral systolic BP (mmHg)	127.9 ± 18.8	119.9 ± 12.7	0.032
Peripheral diastolic BP (mmHg)	82.5 ± 13.4	83.3 ± 11.7	0.790
Average peripheral BP (mmHg)	103.2 ± 14.8	99.7 ± 11.6	0.266
Peripheral pulse pressure (mmHg)	45.3 ± 12.9	36.7 ± 8.1	0.005
Central systolic BP (mmHg)	118.3 ± 17.2	112.9 ± 12.2	0.181
Central diastolic BP (mmHg)	84.0 ± 13.5	84.4 ± 11.9	0.919
Central pulse pressure (mmHg)	34.3 ± 10.2	28.7 ± 7.0	0.022
PWV (m/sn)	8.0 ± 1.6	7.1 ± 1.3	0.018
Augmentation index (%)	21.7 ± 11.5	20.2 ± 14.2	0.605
Heart rate (/min)	81.6 ± 13.1	80.4 ± 13.2	0.724
Cardiac output (L/min)	5.5 ± 1.3	5.3 ± 1.1	0.405
Cardiac index (L/min/m^2)	2.8 ± 0.7	2.7 ± 0.7	0.846

BP, blood pressure; PWV, pulse wave velocity.

Table 3. Choroidal thickness measurements of the patients and controls

	Coronary slow flow group (n = 50)	Controls (n = 25)	p
Left medial choroidal thickness (μm)	229.7 ± 63.7	272.6 ± 64.5	0.008
Left central choroidal thickness (μm)	256.7 ± 65.7	307.7 ± 70.4	0.003
Left lateral choroidal thickness (μm)	247.5 ± 69.1	290.0 ± 71.3	0.007
Right medial choroidal thickness (μm)	230.6 ± 59.6	289.4 ± 62.4	< 0.001
Right central choroidal thickness (μm)	247.4 ± 60.0	315.7 ± 65.4	< 0.001
Right lateral choroidal thickness (μm)	233.0 ± 57.7	301.4 ± 63.4	< 0.001
Mean choroidal thickness (μm)	240.8 ± 58.4	296.1 ± 64.6	0.001

choroidal thickness (r: -0.565, p < 0.001). Linear regression analysis showed that coronary slow flow was still an independent predictor of both PWV (p = 0.010, standardized beta: 0.132, T: 2.640) and choroidal thickness (p = 0.005, standardized beta: -0.262, T: -2.901) when adjusted by age, sex, hypertension, dyslipidemia and diabetes.

DISCUSSION

Coronary slow flow may be a coronary presentation of a systemic vascular disorder. In this study, we evaluated the arterial stiffness parameters and choroidal thickness of patients with coronary slow flow, and found that these patients had a significantly higher PWV and significantly thinner choroidal thickness compared to patients with normal coronary flow. Coronary slow flow was independently associated with higher PWV and thinner choroidal thickness. Our results suggest the possibility of a systemic vascular disorder in patients with coronary slow flow.

Endothelial dysfunction, atherosclerosis, inflammation, and imbalance of vasoactive substances have been suggested to be underlying mechanisms of coronary slow flow.[5,30] Several studies have reported correlations between corrected TIMI frame counts and endothelial dysfunction.[31,32] Endothelial dysfunction in patients with coronary slow flow may also be linked to arterial stiffness in these patients, as there is a relationship between endothelial function and arterial stiffness.[33] In addition, plasma levels of adrenergic system hormones have been shown to be higher in patients with coronary slow flow suggesting increased sympathetic system activity,[34] which may explain the higher PWV in our patients as increased sympathetic system activity and adrenergic hormone levels have been associated with arterial stiffness and increased PWV.[35] However, coronary slow flow and arterial stiffness are a very complex phenotype, and because of the complexity of underlying mechanisms, there are still conflicting results about the association between coronary slow flow and increased PWV. These inconsistencies may be explained by different methods used to assess arterial stiffness, comorbidities of the patients or phase of the disease process.[36-38]

Systemic microvascular dysfunction may be involved in the pathogenesis and progression of ocular diseases such as age-related macular degeneration and glaucoma.[39,40] The choroid is a highly vascularized tissue which can be affected by many systemic conditions and coronary risk factors.[41-45] Thus, the relationship between the choroid and cardiovascular diseases has become an interesting clinical question and may be a potential biomarker of cardiovascular diseases. A healthy choroid may be a sign of systemic health. OCT has improved the examination of choroidal structure and increased the number of studies exploring the relationship between systemic diseases and the choroid.[21]

Previous studies have shown changes in choroidal and retinal layer thickness in patients with cardiovascular diseases based on the microvascular dysregulation hypothesis.[46] The sympathetic system may play an important role in basal choroidal blood flow and choroidal thickness. Experimental models have shown vasoconstriction and a decrease in choroidal blood flow due to sympathetic innervation, which has been proposed to be a protective mechanism for the acute blood pressure increase caused by sympathetic system activation.[47] On the other hand, an increase in choroidal blood flow has been observed in parasympathetic system activation.[48] We found that the patients with coronary slow flow had a thinner choroidal thickness, which may be associated with the presence of increased sympathetic system in these patients. TIMI frame count has been shown to be positively correlated with retinal flow time and vascular resistance index.[49] Similarly, we found a negative correlation between PWV and mean choroidal thickness, suggesting that arterial stiffness may also be a possible cause of choroidal thinning.

Some studies have suggested systemic involvement in patients with coronary slow flow, such as endothelial dysfunction, changes in nitric oxide activity, and also inflammatory markers.[31,50] We found that corrected TIMI frame count was correlated with PWV and choroidal thickness in our study. In parallel with the underlying mechanisms suggesting systemic involvement in coronary slow flow, our results imply that coronary slow flow may be a generalized vascular disease rather than a local abnormality affecting only coronary blood flow.

In summary, the clinical implications of our study suggest that coronary slow flow may affect the whole arterial system. Although these patients do not have any

significant coronary artery stenosis, they have increased arterial stiffness, which has already been correlated with adverse cardiac events. Close follow-up of these patients may be warranted. Choroidal thickness in these patients was decreased; however, whether the decrease in choroidal thickness is associated with the prognosis of these patients is currently unknown. Large-scale studies with longer follow-up will help to elucidate the prognostic value of choroidal thickness changes in coronary slow flow patients.

Study limitations

The major limitations of this study are the relatively small sample size and being a single-center study. The inability to discontinue medications that might affect arterial stiffness and choroidal thickness was another limitation, although medications known to alter retinochoroidal flow were excluded. Medications such as statins may influence arterial stiffness parameters.[51] Failure to exclude cardiac syndrome X patients from the control group may be considered as another study limitation. In addition, we tested only hs-CRP levels as a marker of inflammation in our study. Novel indices and biomarkers of inflammation, oxidative stress or thrombosis may help to better understand the underlying mechanisms and associations between coronary slow flow and arterial stiffness.

NEW KNOWLEDGE GAINED

- Pulse wave velocity is increased in patients with coronary slow flow.
- Choroidal thickness is decreased in patients with coronary slow flow.
- Corrected TIMI frame count is correlated with pulse wave velocity and choroidal thickness.
- Coronary slow flow was independently associated with increased arterial stiffness and thinner choroidal thickness.

CONCLUSION

Coronary slow flow may be a coronary presentation of a systemic microvascular disorder affecting other vascular structures. PWV was increased in the patients with coronary slow flow, indicating increased arterial stiffness. The choroidal thickness was decreased in these patients, mostly due to increased sympathetic system activity and arterial stiffness. In the management of patients with coronary slow flow, it is reasonable to evaluate the rest of the arterial system with a multidisciplinary approach.

DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

REFERENCES

1. Tambe AA, Demany MA, Zimmerman HA, Mascarenhas E. Angina pectoris and slow flow velocity of dye in coronary arteries--a new angiographic finding. *Am Heart J* 1972;84:66-71.
2. Yilmaz H, Demir I, Uyar Z. Clinical and coronary angiographic characteristics of patients with coronary slow flow. *Acta Cardiol* 2008;63:579-84.
3. Saya S, Hennebry TA, Lozano P, et al. Coronary slow flow phenomenon and risk for sudden cardiac death due to ventricular arrhythmias: a case report and review of literature. *Clin Cardiol* 2008;31:352-5.
4. Amasyali B, Turhan H, Kose S, et al. Aborted sudden cardiac death in a 20-year-old man with slow coronary flow. *Int J Cardiol* 2006; 109:427-9.
5. Beltrame JF, Limaye SB, Horowitz JD. The coronary slow flow phenomenon--a new coronary microvascular disorder. *Cardiology* 2002;97:197-202.
6. Wang X, Nie SP. The coronary slow flow phenomenon: characteristics, mechanisms and implications. *Cardiovasc Diagn Ther* 2011; 1:37-43.
7. Chen Z, Chen X, Li S, et al. Nicorandil improves myocardial function by regulating plasma nitric oxide and endothelin-1 in coronary slow flow. *Coron Artery Dis* 2015;26:114-20.
8. Franklin SS. Beyond blood pressure: arterial stiffness as a new biomarker of cardiovascular disease. *J Am Soc Hypertens* 2008; 2:140-51.
9. Payne RA, Wilkinson IB, Webb DJ. Arterial stiffness and hypertension: emerging concepts. *Hypertension* 2010;55:9-14.
10. Mitchell GF, Hwang SJ, Vasan RS, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation* 2010;121:505-11.
11. Laurent S, Cockcroft J, Van Bortel L, et al.; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clini-

cal applications. *Eur Heart J* 2006;27:2588-605.
12. Townsend RR, Wilkinson IB, Schiffrin EL, et al.; American Heart Association Council on Hypertension. Recommendations for improving and standardizing vascular research on arterial stiffness: a scientific statement from the American Heart Association. *Hypertension* 2015;66:698-722.
13. Aroor AR, Demarco VG, Jia G, et al. The role of tissue renin-angiotensin-aldosterone system in the development of endothelial dysfunction and arterial stiffness. *Front Endocrinol (Lausanne)* 2013;4:161.
14. Candela J, Wang R, White C. Microvascular endothelial dysfunction in obesity is driven by macrophage-dependent hydrogen sulfide depletion. *Arterioscler Thromb Vasc Biol* 2017;37:889-99.
15. Jia G, Aroor AR, DeMarco VG, et al. Vascular stiffness in insulin resistance and obesity. *Front Physiol* 2015;6:231.
16. Cooper LL, Palmisano JN, Benjamin EJ, et al. Microvascular function contributes to the relation between aortic stiffness and cardiovascular events: the Framingham Heart Study. *Circ Cardiovasc Imaging* 2016;9:e004979.
17. Mattace-Raso FU, van der Cammen TJ, Hofman A, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation* 2006;113:657-63.
18. Seldenrijk A, van Hout HP, van Marwijk HW, et al. Depression, anxiety, and arterial stiffness. *Biol Psychiatry* 2011;69:795-803.
19. Mattace-Raso F, Hofman A, Verwoert GC, et al.; Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J* 2010;31:2338-50.
20. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010; 55:1318-27.
21. Tan KA, Gupta P, Agarwal A, et al. State of science: choroidal thickness and systemic health. *Surv Ophthalmol* 2016;61:566-81.
22. Wang X, Geng LL, Nie SP. Coronary slow flow phenomenon: a local or systemic disease? *Med Hypotheses* 2010;75:334-7.
23. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation* 1996;93:879-88.
24. Dodge JT Jr, Brown BG, Bolson EL, Dodge HT. Intrathoracic spatial location of specified coronary segments on the normal human heart. Applications in quantitative arteriography, assessment of regional risk and contraction, and anatomic display. *Circulation* 1988;78:1167-80.
25. Sunbul M, Tigen K, Ozen G, et al. Evaluation of arterial stiffness and hemodynamics by oscillometric method in patients with systemic sclerosis. *Wien Klin Wochenschr* 2013;125:461-6.
26. Van Bortel L. Focus on small artery stiffness. *J Hypertens* 2002; 20:1707-9.
27. Van Bortel LM, Duprez D, Starmans-Kool MJ, et al. Clinical applications of arterial stiffness, Task Force III: recommendations for user procedures. *Am J Hypertens* 2002;15:445-52.
28. Eraslan M, Cerman E, Yildiz Balci S, et al. The choroid and lamina cribrosa is affected in patients with Parkinson's disease: enhanced depth imaging optical coherence tomography study. *Acta Ophthalmol* 2016;94:e68-75.
29. Margolis R, Spaide RF. A pilot study of enhanced depth imaging optical coherence tomography of the choroid in normal eyes. *Am J Ophthalmol* 2009;147:811-5.
30. Mosseri M, Yarom R, Gotsman MS, Hasin Y. Histologic evidence for small-vessel coronary artery disease in patients with angina pectoris and patent large coronary arteries. *Circulation* 1986;74: 964-72.
31. Sezgin AT, Sigirci A, Barutcu I, et al. Vascular endothelial function in patients with slow coronary flow. *Coron Artery Dis* 2003;14: 155-61.
32. Anderson TJ, Uehata A, Gerhard MD, et al. Close relation of endothelial function in the human coronary and peripheral circulations. *J Am Coll Cardiol* 1995;26:1235-41.
33. Wright CI, Brouwer-de Cock KA, Kroner CI, et al. The relation of arterial stiffness to endothelial function in healthy subjects. *Physiol Meas* 2007;28:573-82.
34. Yazici M, Demircan S, Durna K, Sahin M. The role of adrenergic activity in slow coronary flow and its relationship to TIMI frame count. *Angiology* 2007;58:393-400.
35. Petrák O, Strauch B, Zelinka T, et al. Factors influencing arterial stiffness in pheochromocytoma and effect of adrenalectomy. *Hypertens Res* 2010;33:454-9.
36. Akkaya H, Güntürk EE. The relationship between coronary slow flow phenomenon and carotid femoral pulse wave velocity and aortic elastic properties. *JRSM Cardiovasc Dis* 2020;9:20480040 20973094.
37. Kim BS, Kim HJ, Han SW, et al. Slow coronary flow is related to increased carotid intima-media thickness but not pulse wave velocity. *Korean Circ J* 2011;41:666-70.
38. Hussein O, Zidan J, Plich M, et al. Arterial elasticity in obese subjects with coronary slow flow phenomenon. *Isr Med Assoc J* 2013;15:753-7.
39. Mudassar Imran Bukhari S, Yew KK, Thambiraja R, et al. Microvascular endothelial function and primary open angle glaucoma. *Ther Adv Ophthalmol* 2019;11:2515841419868100.
40. Lipecz A, Miller L, Kovacs I, et al. Microvascular contributions to age-related macular degeneration (AMD): from mechanisms of choriocapillaris aging to novel interventions. *Geroscience* 2019; 41:813-45.
41. Schuster AK, Leuschner A, Feretos C, et al. Choroidal thickness is associated with cardiovascular risk factors and cardiac health: the Gutenberg Health Study. *Clin Res Cardiol* 2020;109:172-82.
42. Ahmad M, Kaszubski PA, Cobbs L, et al. Choroidal thickness in patients with coronary artery disease. *PLoS One* 2017;12:e0175691.
43. Regatieri CV, Branchini L, Carmody J, et al. Choroidal thickness in patients with diabetic retinopathy analyzed by spectral-domain optical coherence tomography. *Retina* 2012;32:563-8.
44. Querques G, Lattanzio R, Querques L, et al. Enhanced depth imaging optical coherence tomography in type 2 diabetes. *Invest*

Ophthalmol Vis Sci 2012;53:6017-24.
45. Wong IY, Wong RL, Zhao P, Lai WW. Choroidal thickness in relation to hypercholesterolemia on enhanced depth imaging optical coherence tomography. *Retina* 2013;33:423-8.
46. Flammer J, Konieczka K, Bruno RM, et al. The eye and the heart. *Eur Heart J* 2013;34:1270-8.
47. Bill A, Sperber GO. Control of retinal and choroidal blood flow. *Eye (Lond)* 1990;4:319-25.
48. Fitzgerald ME, Vana BA, Reiner A. Control of choroidal blood flow by the nucleus of Edinger-Westphal in pigeons: a laser Doppler study. *Invest Ophthalmol Vis Sci* 1990;31:2483-92.
49. Taha NM, Asklany HT, Mahmoud AH, et al. Retinal fluorescein angiography: a sensitive and specific tool to predict coronary slow flow. *Egypt Heart J* 2018;70:167-71.
50. Camsarl A, Pekdemir H, Cicek D, et al. Endothelin-1 and nitric oxide concentrations and their response to exercise in patients with slow coronary flow. *Circ J* 2003;67:1022-8.
51. Alidadi M, Montecucco F, Jamialahmadi T, et al. Beneficial effect of statin therapy on arterial stiffness. *Biomed Res Int* 2021;2021:5548310.