Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci

February 2023; 9(1): 1-13

RESEARCH ARTICLE **DOI:** 10.19127/mbsjohs.1155632

The Relationship Between Coronary Slow Flow and Myocardial Ischaemia Evaluated with Timi Frame Count and Myocardial Perfusion Scintigraphy

Mehmet Zeki Yılmaztekin[1(ID)], Osman Kayapinar[2(ID)], Gülşah Aktüre[2(ID)], Gökhan Coşkun[2(ID)], Muhammed Aşık[1(ID)], Hamdi Afşin[3(ID)]

[1]Department of Nuclear Medicines, Harran University Faculty of Medicine, Urfa, Turkey
[2]Department of Cardiology, Düzce University Faculty of Medicine, Düzce, Turkey
[3]Department of Nuclear Medicines, Aban İzzet Baysal University Faculty of Medicine Bolu, Turkey

Received: 11 August 2022, Accepted: 05 January 2023, Published online: 28 February 2023

Abstract

Objective: Coronary slow flow (CSF) is known as a form or early stage of common atherosclerotic disease. Myocardial perfusion scintigraphy (MPS) is a valuable technique in the diagnosis of coronary artery disease and prediction of prognosis. The aim of this study was to investigate the relationship between the myocardial defect score and ischaemia in patients with CSF.

Methods: A total of 168 patients who applied with the complaint of angina pectoris and underwent SPECT as a non-invasive test followed by coronary angiography were included in this retrospective study. 9 patient was excluded from the study for various reasons. The study population comprised determined with CSF and no obstructive stricture in the coronary arteries and with normal flow. The mean age of the patients was 56±12 years. The scores obtained from Quantitative Perfusion SPECT (QPS) and Quantitative Gated SPECT (QGS) software were used in the myocardial perfusion evaluation. The TIMI frame counts were compared with the myocardial defect and ischaemia scores. The TIMI frame count method was used in the determination of CSF.

Results: In patients with slow flow in the circumflex (Cx) coronary artery, the stress total perfusion defect Cx (sTPD-Cx) was found to be 0.1 (range, 0.0-1.3), and in those with normal flow, it was 0.0 (range, 0.0-0.28) (p=0.002). The stress score Cx (sscore-Cx) was found to be 1.0 (range, 0.0-3.0) in patients with slow flow and 0.0 (range, 0.0-2.0) in those with normal flow (p=0.031). A linear correlation was determined between the Cx TIMI frame count and the sTPD-Cx and sscore-Cx values (r=0.207, p=0.009; r=0.159, p=0.045). No relationship was found between slow flow and the defect and ischemia scores in other myocardial regions.

Conclusion: In patients with slow flow in the Cx coronary artery, the sTPD-Cx and the sscore-Cx values were found to be significantly high. Although at a weak level, a linear correlation was found between the Cx TIMI frame count and the sTPD-Cx and the sscore-Cx values

Key words: Coronary slow flow, TIMI frame count, myocardial perfusion scintigraphy

Suggested Citation: Yılmaztekin MZ, Kayapinar O, Aktüre G, Coşkun G, Aşık M, Afşin H. The Relationshıp Between Coronary Slow Flow And Myocardıal Ischaemia Evaluated Wıth Tımı Frame Count And Myocardial Perfusion Scintigraphy. Mid Blac Sea Journal of Health Sci, 2023;9(1):1-13.

Address for correspondence/reprints:

Osman Kayapinar

Telephone number: +90 (532) 419 07 00

E-mail: osmankayapinar@gmail.com

INTRODUCTION

It is a common clinical problem to explain the cause of chest pain in patients with anginal complaints suggestive of myocardial ischemia and with normal coronary arteries on angiography. Some patients with chest pain and myocardial ischemia detected by noninvasive testing but with normal coronary anatomy have been termed 'cardiac syndrome X' (1).

In 1972, despite normal coronary anatomy, it was noticed for the first time that the contrast medium progressed slowly in the coronary arteries, and this situation was named as coronary slow flow. Although many studies have been conducted on the etiological factors that may cause slow coronary flow, this issue has not yet been fully elucidated (2).

Although the pathophysiological cause of coronary slow flow (CSF) is not exactly known, previous studies have shown that microvascular dysfunction, endothelial and vasomotor dysfunction and occlusive disease could be underlying causes (3-6). Recent studies have determined intimal thickening in coronary arteries, widespread calcification and atheroma plaques not creating lumen irregularity in a significant proportion of CSF patients (7-9). Based on this information, it would be more accurate to evaluate CSF as another type of coronary artery disease (CAD) rather than the previous evaluation as a subgroup of cardiac syndrome X. (10).

The aim of this study was to investigate the relationship between coronary slow flow and myocardial ischaemia by retrospectively evaluating the TIMI (Thrombolysis In Myocardial Infarction) frame count and myocardial perfusion scintigraphy results.

METHODS

In this retrospective study, the TIMI frame counts were calculated for patients who presented with anginal complaints and were applied with SPECT and then coronary angiography. The TIMI frame counts, calculated separately for LAD, Cx, and RCA, were determined using the scintigraphic method for the perfusion defects and ischaemia scores corresponding to these vascular beds. A total of 159 patients were included in the study, comprising determined with CSF on angiography and normal coronary arteries, and with normal flow. Patients were excluded from the study if they had hypertension, left ventricle hypertrophy, diabetes mellitus, connective tissue disease, arrhythmia, sick sinus syndrome, or congenital or acquired valve disease.

Access to the coronary arteries was obtained with 7F sheath cannulation of the right femoral artery with the Judkins technique, and selective coronary angiography was performed with a G2100 device (*make and model**). The TIMI frame count (TFC) method was used to determine a CSF pattern (9). The normal frame counts corrected for

coronary artery length required for filling the coronary arteries were accepted as 36.2±2.6 for LAD, 22.2±4.1 for Cx, and 20.4±3.0 for RCA and values above these were evaluated as CSF.

ECG Gated Myocardial Perfusion SPECT Imaging was applied as stress-rest imaging with a myocardial perfusion scintigraphy single day protocol. The images were taken 30 mins after completing the Efor test and at 45-60 mins after finishing the infusion in the pharmacological stress test. The images were obtained with a single-head gamma camera (Siemens E. CAM) synchronised with ECG. The Gated Single Positron Emission Computed Tomography (SPECT) images were taken using a general purpose parallel hole collimator with a 64 x 64 imaging matrix, 180° circular orbit and 6-angle sampling. Processing of the images was performed on a Siemens e. soft computer system using QGS software (Cedar's Sinai, ENTEGRA View Workstation Version 2: Siemens Medical System). Following reconstruction with the filtered back projection method by the software, short axis, vertical, and long axis cross-sectional myocardial perfusion images and functional gated images were formed (Figure 1).

The ischaemia and defect scores were obtained separately by totalling the scores of the segments corresponding to the vascular beds of LAD, Cx, and RCA (Table 1). The scores in the segments shown with 1-2-3-7-8-13-14-19-20 for LAD, the scores in the segments 5-6-11-12-17-18 for Cx, and the scores in the segments 4-9-10-15-16 for RCA were totalled and the stress scores (sscore-LAD, sscore-Cx, sscore-RCA) and rest scores (rscore-LAD, rscore-Cx, rscore-RCA) were formed.

The ischaemia score was calculated by subtracting the rest score from the stress score, and a score of ≥2 was accepted as significant in respect of myocardial ischaemia.

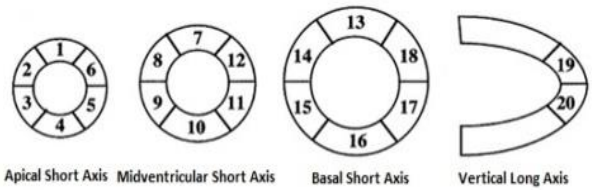

Figure 1. The scores in the segments and axial images

The total perfusion defect (TPD) was automatically calculated in the Cedars-Sinai QPS software using the following formula:

$$TPD = 100 \times \frac{\sum_{a=0}^{a<A} \sum_{p=0}^{p<P} score(a,p)}{4AP}$$

a, p; Radial coordinates on the polar map
A, P; Maximum sample count in each dimension
Score (a, p); Pixel score on the polar map (11).

Statistical Analysis

Statistical analyses were conducted with SPSS for Windows version 19.0 software (IBM SPSS Inc, Chicago, IL, USA). The Shapiro Wilk test was employed to assess the normal distribution of data. Numerical variables with normal distribution were presented as mean ± standard deviation, while

those without normal distribution were expressed as median (interquartile range) values. Categorical variables were stated as number (n) and percentage (%). Comparison of two-sample numerical variables was conducted using the Mann–Whitney U test. The relation between the variables was analyzed through Spearman's rank correlation analysis. The Pearson Chi-square test was also used to compare categorical variables. A two-tailed p value of <0.05 was considered statistically significant.

RESULTS

Evaluation was made of a total of 168 patients, comprising 113 (67.3%) females and 55 (32.7%) males, with a mean age of 56±12 years.

Table 1. Baseline Characteristics of Patients with determined with CSF and no obstructive stricture in the coronary arteries and with normal flow

Characteristics	n (%)
Age (years)	56 ± 12
Cender (Female/Male)	113/55 (67.3%)
Weight (Kg)	86.2 ± 9.3
Height (cm)	174.3 ± 11.2
BMI (kg/m2)	28.37 ± 7.6

In the LAD, normal flow was determined in 81% (129) and CSF in 19% (30), in the Cx normal flow was determined in 42% (68) and CSF in 58% (91), and in the RCA normal flow was determined in 49% (78) and CSF in 51% (Figure 2).

No significant correlation was found between the LAD frame count and the sTPD-LAD, sscore-LAD, iscore-LAD (p=0.249). A weak positive linear correlation was found between the Cx TIMI frame count and the sTPD-Cx and sscore-Cx (r= 0.207 p= 0.009; r= 0.159 p= 0.045, respectively). No significant correlation was determined between the Cx TIMI frame count and the iscore-Cx (p=0.505). No significant correlation was determined between the RCA frame count and the sTPD-RCA, sscore-RCA, iscore-RCA (p>0.05 for all). A weak positive correlation was determined between sESV and RCA-TFC (r=0.204, p=0.028) (Table1).

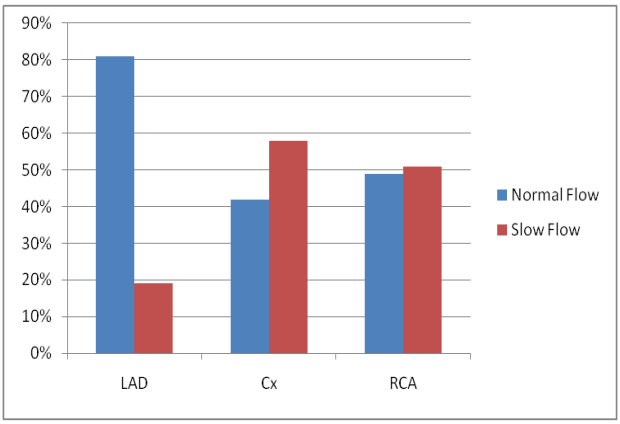

Figure 2. Graphic representation of the distribution of normal flow and slow flow of the coronary arteries.

The stress score of ≥4 was considered significant for myocardial perfusion defect and in the comparison of the normal flow groups with the slow flow groups for each vessel (LAD, Cx, RCA), no statistically significant difference was determined (p>0.05 for all) (Table 2).

The ischaemia score of ≥2 was considered significant for ischaemia and in the comparison of the normal flow groups with the slow flow groups for each vessel (LAD, Cx, RCA), no statistically significant difference was found (p>0.05 for all) (Table 3).

Table 2. Correlations between the parameters related to LAD, Cx and RCA TIMI Frame Counts

LAD-TFC			Cx-TFC			RCA-TFC		
	r	**p**		**r**	**p**		**r**	**p**
sTPD-LAD	0.093	0.249	sTPD-Cx	**0.207**	**0.009**	sTPD-RCA	0.041	0.605
fTPD-LAD	0.056	0.488	fTPD-Cx	0.015	0.850	fTPD-RCA	0.002	0.981
sscore-LAD	0.026	0.744	sscore-Cx	**0.159**	**0.045**	sscore-RCA	0.08	0.316
iscore-LAD	-0.039	0.631	iscore-Cx	0.053	0.505	iscore-RCA	0.073	0.358
~~s~~EF	-0.011	0.911	~~s~~EF	-0.055	0.559	~~s~~EF	-0.156	0.094
~~s~~ESV	0.037	0.693	~~s~~ESV	0.041	0.665	~~s~~ESV	**0.204**	**0.028**
~~s~~EDV	0.111	0.242	~~s~~EDV	0.04	0.671	~~s~~EDV	0.179	0.055

Cx, circumflex coronary artery; Cx-TFC, Cx TIMI frame count; sEF, post exercise left ventricle ejection fraction; sEDV, stress left ventricle diastolic end volume; sESV, stress left ventricle systolic end volume, fTPD- Cx, difference between total perfusion defect and Cx; fTPD- LAD, difference between total perfusion defect and LAD; fTPD-RCA, difference between total perfusion defect and RCA; iscore-Cx, ischaemia score Cx; iscore-LAD; ischaemia score LAD; iscore-RCA, ischaemia score RCA; LAD, left anterior descending coronary artery; LAD-TFC, LAD TIMI frame count; RCA, right coronary artery; RCA-TFC, RCA TIMI frame count; sscore-Cx, stress score Cx; sscore-LAD, stress score LAD; sscore-RCA, stress score RCA; sTPD-Cx, stress total perfusion defect-Cx; sTPD-LAD, stress total perfusion defect-LAD; sTPD-RCA, stress total perfusion defect-RCA; TFC, TIMI frame count; TIMI, thrombolysis in myocardial infarction.

Table 3. Comparison of the stress scores according to the flow characteristics of LAD, Cx and RCA

			LAD		***p***
			Normal Flow	Slow Flow	
sscore-LAD	<4	Count	82 (65%)	17 (56%)	
	≥4	Count	45 (35%)	13 (44%)	
Total		Count	127 (100%)	30 (100%)	p= 0.42
			Cx		
			Normal Flow	Slow Flow	
sscore-Cx	<4	Count	63 (92.6%)	77 (84.6%)	
	≥4	Count	5 (7.4%)	14 (15.4%)	
Total		Count	68 (100%)	91 (100%)	P= 0.122
			RCA		
			Normal Flow	Slow Flow	
sscore-RCA	<4	Count	72 (92.3%)	73 (90.1%)	
	≥4	Count	6 (7.7%)	8 (9.9%)	
Total		Count	78 (100,0%)	81 (100.0%)	P= 0.627

Cx, circumflex coronary artery; LAD, left anterior descending coronary artery; RCA, right coronary artery; sscore-Cx, stress score Cx; sscore-LAD, stress score LAD; sscore-RCA, stress score RCA.

Table 4. Comparğiğşison of the ischaemia scores according to the flow characteristics of LAD, Cx, and RCA

			LAD		***p***
			Normal Flow	Slow Flow	
iscore-LAD	<2	Count	49 (38%)	19 (63%)	
	≥2	Count	78 (62%)	11 (37%)	
Total		Count	127 (100%)	30 (100%)	P= 0.014
			Cx		
			Normal Flow	Slow Flow	
iscore-Cx	<2	Count	61 (89.7%)	75 (82.4%)	
	≥2	Count	7 (10.3%)	16 (17.6%)	
Total		Count	68 (100,0%)	91 (100.0%)	P= 0.196
			RCA		
			Normal Flow	Slow Flow	
iscore-RCA	<2	Count	69 (88.5%)	68 (84.0%)	
	≥2	Count	9 (11.5%)	13 (16.0%)	
Total		Count	78 (100.0%)	81 (100.0%)	P= 0.410

Cx, circumflex coronary artery; iscore-Cx, ischaemia score Cx; iscore-LAD, ischaemia score LAD; iscore-RCA, ischaemia score RCA; LAD, left anterior descending coronary artery; RCA, right coronary artery.

Table 5. Comparison of the parameters of the groups with normal flow and slow flow in LAD

	LAD-Normal Flow (N=127)	LAD-Slow Flow (N=30)	*p*
sTPD-LAD	3.0 (1.6-5.0)	2.85 (1.220-5.95)	0.909
fTPD-LAD	1.9 (0.3-3.4)	1.15 (0.0-4.55)	0.688
Sscore-LAD	3.0 (1.0-4.0)	3.0 (0.0-5.0)	0.751
iscore-LAD	2.0 (0.0-3.0)	1.0 (0.0-3.25)	0.225
sEF	67.0 (57.0-78.0)	62.0 (52.75-74.25)	0.255
sESV	21.5 (13.0-34.75)	27.0 (16.5-40.75)	0.167
sEDV	66.0 (53.25-80.75)	79.0 (61.75-96.5)	0.066

fTPD- LAD, difference between total perfusion defect and LAD; iscore-LAD, ischaemia score LAD; sEF, post exercise left ventricle ejection fraction; sEDV, stress left ventricle diastolic end volume; sESV, stress left ventricle systolic end volume; sscore-LAD, stress score LAD; sTPD-LAD, stress total perfusion defect-LAD.

Table 6. Comparison of the parameters of the groups with normal flow and slow flow in RCA

	RCA-Normal Flow (N=78)	RCA-Slow Flow (N=81)	*p*
sTPD-RCA	0.1(0.0-0.85)	0.0(0.0-1.4)	0.901
fTPD-RCA	0.0(0.0-0.5)	0.0(0.0-0.5)	0.960
sscore-RCA	0.0(0.0-2.0)	0.0(0.0-3.0)	0.965
iscore-RCA	0.0(0.0-1.0	0.0(0.0-2.0)	0.657
stEF	70.0(57.5-79.0)	64.0(54.0-77.0)	0.109
stESV	20.0(11.5-28.5)	25.0(14.0-40.0)	0.058
stEDV	66.0(52.5-79.0)	70.0(57.0-89.0)	0.106

fTPD-RCA, difference between total perfusion defect and RCA; iscore-RCA, ischaemia score RCA; sEF, post exercise left ventricle ejection fraction; sEDV, stress left ventricle diastolic end volume; sESV, stress left ventricle systolic end volume; sscore-RCA, stress score RCA; sTPD-RCA, stress total perfusion defect-RCA.

Table 7. Comparison of the parameters of the groups with normal flow and slow flow in Cx

	RCA-Normal Flow (N=78)	RCA-Slow Flow (N=81)	*p*
sTPD-Cx	0.0(0.0-0.28)	0.1(0.0-1.3)	**0.002***
fTPD-Cx	0.0(0.0-0.1)	0.0(0.0-0.4)	0.186
sscore-Cx	0.0 (0.0-2.0)	1.0(0.0-3.0)	**0.031***
iscore-Cx	0.0(0.0-1.0)	0.0(0.0-2.0)	0.177
stEF	67.0(55.5-78.0)	66.0(56.0-77.0)	0.780
stESV	22.0(13.5-34.5)	23.0(13.0-38.0)	0.984
stEDV	0.0(0.0-0.28)	0.1(0.0-1.3)	**0.002***

Cx, circumflex coronary artery; sEF, post exercise left ventricle ejection fraction; sEDV, stress left ventricle diastolic end volume; sESV, stress left ventricle systolic end volume; fTPD- Cx, difference between total perfusion defect and Cx;

No statistically significant difference was found between the LAD and RCA normal flow and slow flow groups in respect of the median values of the sTPD, sscore and iscore (Tables 4, 5). The sTPD and sscore median values of the patients with slow flow in Cx were found to be significantly higher than those of the patients with normal flow in Cx (p=0.002, p=0.031). No statistically significant difference was found between the Cx normal flow and slow flow groups in respect of the median iscore value (p=0.177) (Table 6,7).

DISCUSSION

Recent studies have shown that CSF is a type of coronary artery disease and could be associated with increased mortality (14-16). Although the etiopathogenesis of CSF has not been fully determined, the clinical and pathological characteristics have been defined (17). Clinical presentation may sometimes be

in the form of angina occurring with effort but is more often in the form of angina at rest. Patients may sometimes present with clinical acute coronary syndrome requiring admission to the coronary intensive care unit (18, 19). In patients with stable angina, coronary ischaemia can be shown with the exercise stress test or myocardial perfusion scintigraphy (20). There is no visible atherosclerotic lesion on coronary angiography, but invasive studies have shown that resting coronary artery resistance is abnormally high in these patients, consistent with delayed opaque transition (8). IVUS studies in recent years have shown that the coronary arteries are not normal in these patients, and there are widespread atherosclerotic changes and widespread calcifications (7, 8).

In a study by Yaymaci et al, (21) in which cardiac ischaemia was created with atrial pacing in patients with CSF, using as measures the lactate production and the difference in coronary arteriovenous oxygen content, which are measures of metabolic ischaemia, it was reported that although anginal complaints were seen in the majority of patients with atrial pacing, metabolic ischaemia was determined in only 17%. In 83.4% (n:5) of the patients determined with metabolic ischaemia, a perfusion defect was found on myocardial perfusion scintigraphy (MPS), anatomically consistent with the vessel determined with CSF. Consequently, it was emphasized that anginal complaints in patients determined with CSF did not originate from myocardial ischaemia. However, as the number of patients determined with ischaemia on MPS was extremely low in that study, the relationship between myocardial ischaemia or defect and CSF was not directly examined. In the current study with a larger patient population, the myocardial ischaemia/defect scores were compared with the CSF data with quantitative measurements. In contrast to the previous study, only the sTPD-Cx and sscore-Cx were found to be significantly high in the patients with slow flow in the Cx coronary artery. These differences between CSF patients could be due to changes in the coronary flow reserve, which is itself a marker of microvascular function (22).

Cesar et al. (23) investigated the relationship between CSF and hemodynamic factors, and reported that of 17 patients with CSF, perfusion defect was observed in 13 (76%) patients on exercise thallium-201 MPS. In the same study, when coronary blood flow was evaluated according to heart rate, 74 patients were included with heart disease and normal coronary blood flow. The hemodynamic factors of the patients with CSF were found to be normal at a significant rate compared to the group with heart disease and normal coronary blood flow. Therefore, it was concluded that there was no correlation

between hemodynamic factors and the detection of CSF in patients thought to have ischaemia on MPS.

In another study, Demirkol et al. (24) examined 60 patients determined with CSF and 50 subjects with normal coronary flow with technetium 99m-MIBI SPECT imaging given at rest and in stress condition. Ischaemia was determined on MPS in 17 (28.3%) of the patients with CSF, and no significant correlation was determined between CSF patients with and without ischaemia in respect of TIMI frame count. MPS was then applied with dipyridamole to the patients with CSF and perfusion was seen to be corrected in all 17. As a result, it was emphasized that CSF in vessels with a diameter of <200µm was associated with pathology, and it was reported that no significant correlation was found between coronary blood flow rate and ischaemia

Dağdelen et al. (25) investigated whether there was any relationship between TIMI frame count and myocardial ischaemia with intracoronary ultrasound and MPS. The study included 24 patients determined with CSF and 13 with normal coronary flow. The patients were examined in 3 groups as CSF patients with ischaemia on MPS, CSF patients with no ischaemia on MPS and subjects with no ischaemia and normal coronary flow. The study results showed reduced coronary lumen change in cases with CSF, but no difference was found between the CSF patients with and without ischaemia. As a result of the study, there was reported to be no correlation between flow change and coronary area of ischaemia in those with CSF, the basic pathology was at the microvascular level, and the disruption in microvascular circulation was thought to lead to ischaemia. In the same study, no significant difference was determined between the two groups of CSF patients with and without ischaemia in respect of TIMI frame count. Similarly, in the current study, no significant correlation was determined between TIMI frame counts and ischaemia scores. In the previously mentioned study, only a regional comparison for LAD was made, whereas in the current study, comparisons were made by matching the scores of the regions fed by the related vessels with coronary flow rate. Thus, the confounding effect on the results of defect and ischaemia scores originating from other regions was avoided. Demirkol et al. (24) only compared the relationship between the presence of ischaemia and slow flow. Using quantitative score values together with the presence of ischaemia in the current study, it was attempted to apply a more objective evaluation. In the study by Dağdelen et al, by IVUS evaluation of IMA phasic changes, a different perspective was examined and while the results supported a relationship between atherosclerosis and slow flow, no correlation

was determined between ischaemia and slow flow. In the current study, no significant correlation was determined between CSF and the TMI frame counts and ischaemia scores.

Mangieri et al. (26) administered intracoronary infusions of 0.56 mg/kg dipyridamole and 100 µg nitroglycerine to patients determined with CSF, and reported that while nitroglycerine had no significant effect on TIMI frame count, dipyridamole resulted in a significant decrease (5). Such a result may have been due to dipyridamole having a dilation effect on vessels smaller than 200µm, rather than nitroglycerine having no effect on coronary arteries larger than 200µm, and this supports the view that the event is at the microvascular level.

Von Lierde et al. (27) measured the coronary flow reserve in a CSF patient with intracoronary Doppler ultrasound and despite very evident CSF, the coronary flow reserve was seen to be within normal limits. This was thought to be a result of epicardial coronary disease such as coronary ectasia, and not to originate from the microvascular system. Using fractional flow reserve (FFR) and IVUS, Pekdemir et al. investigated the relationship between CSF and epicardial resistance in a study of 19 patients. A significant negative correlation was found between TIMI frame count and FFR in CSF patients, and although there was a reduction in FFR in the epicardial coronary arteries of CSF patients, with IVUS in the same coronary artery, there was determined to be an increase in intimal thickness and massive calcification extending longitudinally along epicardial coronary arteries. Consequently, this was attributed to an increase in resistance in epicardial coronary arteries associated with diffuse atherosclerosis (8). In another IVUS study by Cin et al. to investigate epicardial coronary artery pathology in CSF patients, similar to the previous study, coronary angiography demonstrated widespread intimal thickening, widespread calcifications along the vessel wall and atheroma plaque not causing luminal irregularity. Flow rate was measured along the coronary vessels and there was determined to be a pressure gradient between the proximal and distal segments. It was concluded that the abnormal flow pattern observed in CSF could be a form or early stage of common atherosclerotic disease involving both the microvascular system and the epicardial coronary arteries (9).

De Bruyne et al. (28) reported that in normal coronary arteries, the gradient between distal and proximal coronary arteries was no more than 1 mmHg, and although there was no significant obstructive lesion, the gradient between the distal and proximal coronary arteries was determined to be >10mmHg, and this increase in epicardial resistance was associated with diffuse atherosclerotic disease. In addition, previous autopsy studies have

often shown the combination of small vessel disease and epicardial coronary involvement (29, 30). This has been supported in several IVUS studies with the angiographic observation of the presence of diffuse atherosclerotic disease such as intimal thickening and reduced distensibility in normal coronary arteries (31, 32). Intravascular pathologies have been evaluated in these studies with the IVUS method, which is accepted as advanced technology. In addition to the pathologies evaluated anatomically within the vessels, evaluation with scintigraphy of the functional response of the myocardial wall can be considered a contribution to these studies.

There were some limitations to this study, primarily the relatively small study population. Studies with larger patient populations would provide higher statistical power. Another basic limitation was the observational nature of the study, which did not allow for the determination of cause and effect relationships. Intravascular ultrasonography (IVUS) was not performed to determine the atherosclerotic changes in the coronary arteries of the patients, and therefore, diffuse CAD combination could not be determined as the gold standard in patients with CSF. Finally, the microvascular perfusion phenomenon was examined using the TIMI frame count method to angiographically determine the filling of epicardial coronary arteries with contrast material. This method is relatively operator-dependent. Therefore, although the angiographic contrast material was administered manually, great care was taken to provide a fixed injection speed.

CONCLUSION

When all these data are taken into consideration, it seems to be insufficient to hold only microvascular dysfunction, regardless of epicardial involvement, responsible for the explanation of the etiopathogenesis of CSF. The results of this study demonstrated that although weak, a significant correlation was determined between slow flow in the Cx coronary artery and the sTPD-Cx and sscore-Cx values reflecting the stress perfusion defect, but no significant relationships were found for LAD and RCA. As advanced technology methods such as IVUS were not available in the hospital for this study, it was not possible to evaluate on scintigraphy the functional reflection of anatomic impairments determined with IVUS in CSF.

Ethics Committee Approval: This prospective study was approved by the ethical review committee of Düzce University (OMU) Hospital (2014/94)

Peer-review: Externally peer-reviewed.

Author Contributions: Concept -O K, M Z Y, Design –G A, M Z Y, Audit– M A, H A, Data Collection and/or Processing – H A, M A, Analysis and/or Interpretation –M Z Y, O K

Writing– M Z Y, Critical Review – M Z Y, O K, M A

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study hasn't received no financial support.

REFERENCES

1. Kemp HG, Vokoanas PS, Cohn PF, Gorlin R. The anginal syndrome associated with normal coronary arteriograms. Report of a six-year experience. *Am J Med* 1973; 54: 735-42.
2. Tambe AA, Demany MA, Zimmerman HA, Mascarenhas E. Angina pectoris and slowflow velocity of dye in coronary arteries-A new angiografic finding. *Am Heart J* 1972; 84 66-71.
3. Sezgin AT, Sigirci M, Barutcu I. Vascular endothelial function in patients with slow coronary flow. *Coron Artery Dis* 2003; 14: 155-161. Mosseri M, Yorom R, Gotsman MS, Hasin Y. Histologic evidence for small vessel coronary artery disease in patients with angina pectoris and patent large coronay arteries. *Circulation* 1986; 7: 964-972.
4. Mangieri M, Machiarelli G, Ciavolella M, Barilla F, Avella A, Martinotti A, et al. Slow coronary flow: Clinical and histopatological features in patients with otherwise normal epicardial coronary arteries. *Cathet Cardiovasc Diag* 1996; 37: 375-381.
5. Kurtoğlu N, Akcay A, Dindar I. Usefulness of oral dypridamole therapy for angiographic slow coronary artery flow. *Am J Cardiol* 2001; 87(Suppl 8A): 777-779.
6. Pekdemir H, Polat G, Cin VG, Camsari A, Cicek D, Akkus MN, Doven O, Katircibasi MT, Muslu N. Elevated plasma endothelin-1 levels in coronary sinus during rapid rate atrial pacing in patients with coronary slow flow. *İnt J Cardiol* 2004;97(1):35-41.
7. Pekdemir H, Cin VG, Cicek D, Camsari A, Akkus MN, Doven O, Parmaksiz HT. Slow coronary flow may be a sign of diffuse atherosclerosis. Contribution of FFR and IVUS. *Acta Cardiol* 2004; 59(2):127-33
8. Pekdemir H, Cin VG, Cicek D, Camsari A, Akkus MN, Doven O, Parmaksiz HT. Slow coronary flow may be a sign of diffuse atherosclerosis. Contribution of FFR and IVUS. *Acta Cardiol* 2004; 59(2):127-33.
9. Cin VG, Pekdemir H, Camsari A, Cicek D, Akkus MN, Parmaksiz HT, Katircibasi MT, Doven O. Diffuse İntimal Thickening of Coronary Arteries in Slow Coronary Flow. *Japan Heart J.* 2003; 44: 907,919
10. Goel PK, Gupta SK, Agarwal A, Kapoor A. Slow coronary flow: A distinct angiographic subgroup in Syndrome X. *Angiology*. 2001; 52(8): 507-14.

11. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. *N Engl J Med.* 1985 Apr 4;312(14):932-6.

12. Gibson CM, Cannon CP, Daley WL, Dodge JT, Jr., Alexander B, Jr., Marble SJ, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation*. 1996 Mar 1;93(5):879-88.

13. Slomka PJ, Berman DS, Germano G, Quantification of myocardial perfusion. In: Germano G, Berman DS, eds. Clinical Gated Cardiac SPECT, 2nd Edition. *Los Angeles: Blackwell;* 2006: 69-91.

14. Turhan H, Sezgin AT, Yetkin O, Senen K, Đleri M, Sahin O, Karabal O, Yetkin E, Kutuk E, Demirkan D. Effects of slow coronary artery flow on QT interval duration and dispersion. *Ann Noninvasive Electrocardiol* 8(2):107-111, 2003

15. Koç S, Ozin B, Altın C, Altan Yaycıoğlu R, Aydınalp A, Müderrisoglu H. Evaluation of circulation disorder in coronary slow flow by fundus fluorescein angiography. Am J Cardiol. 2013; 111:1552-6.

16. Wang X, Geng LL, Nie SP. Coronary slow flow phenomenon: A local or systemic disease? Med Hypotheses. 2010; 75:334-7

17. Hawkins BM, Stavrakis S, Rousan TA, Mazen Abu-Fadel, Eliot Schecther. Coronary slow flow prevalence and clinical correlations. Circ J 2012;76(4):936-42

18. Ayhan E, Uyarel H, Isık T, Ergelen M, Cicek G, Altay S et al. Slow coronary flow in patients undergoing urgent coronary angiography for ST elevation myocardial infarction. Int J Cardiol. 2012; 156:106–8

19. Sen T. Coronary slow flow phenomenon leads to ST elevation myocardial infarction. Korean Circ J. 2013; 43:196–8.

20. Cesar LA, Ramires JA, Serrano Junior CV, Meneghetti JC, Antonelli RH, da-Luz PL, Pıgellı FC. Slow coronary run-off in patients with angina pectoris: clinical significance and thallium-201 scintigraphic study. Braz J Med Biol Res. 1996 May;29(5):605-13.

21. Yaymacı B, Dagdelen S, Bozbuga N, Demirkol O, Say B, Guzelmeric F, Dindar I. The response of the myocardial metabolism to atrial pacing in patients with coronary slow flow. Int J Cardiol. 2001 Apr;78(2):151-6

22. Erdoğan D, Çalışkan M, Güllü H, Sezgin AT, Yıldırır A, Müderrisoğlu H. Coronary flow reserve is impaired in patients with slow coronary flow. Atherosclerosis. 2007 Mar;191(1):168-74.

23. Cesar LA, Ramires JA, Serrano Junior CV, Meneghetti JC, Antonelli RH, da-Luz PL, et al. Slow coronary run-off in patients with angina pectoris: clinical significance and thallium-201 scintigraphic study. Braz J Med Biol Res. 1996 May;29(5):605-13.

24. Demirkol MO, Yaymaci B, Mutlu B. Dipyridamole myocardial perfusion single photon emission computed tomography in patients with slow coronary flow. Coron Artery Dis 13(4):223-229, 2002.

25. Dağdelen S, Yaymacı B, İzgi A. Evaluation of the relationship between coronary slow flow and myocardial ischemia with TIMI frame count and intracoronary ultrasound measurements. Turkish Cardiol Association Research 2000:28: 747-51.

26. Sellke FW, Myers PR, Bates JN, Harrison DG. Influence of vessel size on the sensitivity of porcine coronary microvessels to nitroglycerin. Am J Physiol 258:H51S-H520, 1990.

27. Van Lierde J, Vrolix M, Sionis D, De Geest H, Piessens J. Lack of evidence for small vessel disease in a patient with "slow dye progression" in the coronary arteries. Cathet Cardiovasc Diagn. 1991 Jun;23(2):117-20.

28. De Bruyne B, Hersbach F, Pijls NH, Bartunek J, Bech JW, Heyndrickx GR, Gould KL, Wijns W. Abnormal epicardial coronary resistance in patients with diffuse atherosclerosis but "Normal" coronary angiography. Circulation. 2001 Nov 13;104(20):2401-6.

29. James TN. Small arteries of the heart. Circulation 1977; 56: 2-14.

30. Ratcliffe HL, Redfield E. Atherosclerotic stenosis of the extramural and intramural coronary arteries of man. Related lesions. Virchows Arch A Pathol Pathol Anat 1972; 357: 1-10.

31. Nakatani S, Yamagishi M, Tamai J, Goto Y, Umeno T, Kawaguchi A, et al. Assessment of coronary artery distensibility by intravascular ultrasound. Application of simultaneous measurements of luminal area and pressure. Circulation. 1995 Jun 15;91(12):2904-10.

32. Tuzcu EM, Kapadia SR, Tutar E, Ziada KM, Hobbs RE, McCarthy PM, et al. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: evidence from intravascular ultrasound. Circulation. 2001 Jun5;103(22):270510