The effects of endothelial dysfunction and inflammation on slow coronary flow

Endotel disfonksiyonu ve enflamasyonun yavaş koroner akım üzerine etkisi

Hasan Arı, M.D., Selma Arı, M.D., Ercan Erdoğan, M.D., Osman Tiryakioğlu, M.D.,[#] Kağan Huysal, M.D.,[†] Vedat Koca, M.D., Tahsin Bozat, M.D.

Departments of Cardiology, [#]Cardiovascular Surgery, and [†]Biochemistry,
Bursa Yüksek İhtisas Heart-Education and Research Hospital, Bursa

Objectives: We evaluated the effects of endothelial dysfunction and inflammation on slow coronary flow (SCF).

Study design: The study included 26 patients (group 1; 13 females, 13 males; mean age 58.8 years) who had normal coronary arteries but SCF in three coronary vessels and 25 subjects (group 2, 14 females, 11 males; mean age 62.7 years) with normal coronary arteries and normal flow. Coronary flow was quantified according to the TIMI (Thrombolysis In Myocardial Infarction) frame count method for the left anterior descending (LAD), circumflex (Cx), and right coronary (RCA) arteries. Endothelial function was assessed by plasma asymmetric dimethylarginine (ADMA) levels, brachial artery endothelium-dependent flow-mediated dilatation (FMD), and nitroglycerin-mediated dilatation (NMD). Inflammation was assessed by high-sensitivity C-reactive protein (hs-CRP) levels.

Results: TIMI frame count was significantly higher in group 1 compared to group 2 for each artery (p<0.001). In group 1, the mean FMD was significantly lower (6.6±1.6% *vs.* 11.2±1.6%, p<0.001) and the mean ADMA level was significantly higher (0.8±0.2 μmol/l *vs.* 0.5±0.1 μmol/l, p=0.002), whereas NMD and hs-CRP levels did not differ significantly between the two groups (p>0.05). There was a significant correlation between plasma ADMA level and TIMI frame count (RCA: r=0.50, p=0.001; cLAD: r=0.46, p=0.004; Cx: r=0.32, p=0.04) and a significant negative correlation between FMD and TIMI frame count (cLAD: r=-0.68, p=0.0003; Cx: r=-0.54, p=0.0004; RCA: r=-0.46, p=0.004), but hs-CRP level was not correlated with TIMI frame count. In multivariate analysis, only ADMA (p=0.009) and FMD (p=0.02) were significant parameters to predict SCF.

Conclusion: Our results suggest that endothelial dysfunction as determined by increased ADMA level and impaired FMD, rather than inflammation, plays a role in the etiopathogenesis of SCF.

Key words: Blood flow velocity; C-reactive protein; coronary angiography; endothelium, vascular; N,N-dimethylarginine.

Amaç: Endotel disfonksiyonu ve enflamasyonun yavaş koroner akım (YKA) üzerine etkileri araştırıldı.

Çalışma planı: Çalışmaya anjiyografide üç koroner arterinde de YKA dışında patoloji bulunmayan 26 hasta (grup 1, 13 kadın, 13 erkek; ort. yaş 58.8) ve koroner akımı normal olan 25 hasta (grup 2, 14 kadın, 11 erkek; ort. yaş 62.7) alındı. Koroner akım, sol ön inen (LAD), sirkumfleks (Cx) ve sağ koroner (RCA) arterler için TIMI (Thrombolysis In Myocardial Infarction) kare sayısı yöntemine göre hesaplandı. Endotel fonksiyonları, her iki grupta plazma asimetrik dimetilarginin (ADMA) düzeyleri, brakiyal arter endotel bağımlı akıma dayalı dilatasyon (FMD) ve nitrogliserin ile oluşturulan endotel bağımsız dilatasyon (NMD) ile değerlendirildi. Enflamasyonu değerlendirmek için yüksek duyarlıklı C-reaktif protein (hs-CRP) düzeyleri ölçüldü.

Bulgular: Her koroner arter için TIMI kare sayısı grup 1'de grup 2'den anlamlı derecede yüksek bulundu (p<0.001). Grup 1'de ortalama FMD değeri anlamlı derecede düşük (%6.6±1.6 ve %11.2±1.6, p<0.001), ADMA düzeyi ise anlamlı derecede yüksek (0.8±0.2 μmol/l ve 0.5±0.1 μmol/l, p=0.002) bulunurken, NMD ve hs-CRP düzeyi açısından iki grup arasında anlamlı fark saptanmadı (p>0.05). Plazma ADMA düzeyi ile koroner TIMI kare sayıları arasında anlamlı pozitif ilişki (RCA: r=0.50, p=0.001; cLAD: r=0.46, p=0.004; Cx: r=0.32, p=0.04), FMD değerleri ile TIMI kare sayıları arasında anlamlı negatif ilişki saptandı (cLAD: r=-0.68, p=0.0003; Cx: r=-0.54, p=0.0004; RCA: r=-0.46, p=0.004); hs-CRP düzeyi ise TIMI kare sayıları ile anlamlı ilişki göstermedi. Çokdeğişkenli analizde, sadece ADMA (p=0.009) ve FMD (p=0.02) parametreleri YKA varlığını göstermede anlamlı bulundu.

Sonuç: Bulgularımız, enflamasyondan ziyade, artmış ADMA düzeyleri ve bozulmuş FMD değerleri ile belirlenen endotel disfonksiyonunun YKA etyopatogenezinde rol oynadığını göstermektedir.

Anahtar sözcükler: Kan akım hızı; C-reaktif protein; koroner anjiyografi; endotel, vasküler; N,N-dimetilarginin.

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Correspondence: Dr. Hasan Arı. Bursa Yüksek İhtisas Eğitim ve Araştırma Hastanesi, 1. Kardiyoloji Kliniği, 16320 Yıldırım, Bursa, Turkey. Tel: +90 224 - 360 50 50 e-mail: hasanari03@yahoo.com

The slow coronary flow (SCF) phenomenon is an angiographic observation characterized by angiographically normal coronary arteries with delayed opacification of the distal vasculature.

Nitric oxide (NO) is synthesized from L-arginine, a precursor in endothelial cells, by activation of NO synthase (NOS), thereby playing a key role in providing vascular homeostasis and its maintenance. Asymmetric dimethylarginine (ADMA), an endogenous competitive inhibitor of NOS, has been shown to decrease both the production and bioavailability of endothelium-derived NO.[1] Therefore, elevated plasma concentrations of ADMA have been considered to be an indicator of endothelial dysfunction and a risk factor for cardiovascular disease.[1-3] Flow-mediated dilatation (FMD) is a frequently used non-invasive measure of endothelial function. It may not only reflect function of the endothelium, but also local mechanical and anatomical properties of the artery.

High-sensitivity C-reactive protein (hs-CRP) is an acute phase protein and a marker of systemic inflammation. Recent studies have demonstrated increased CRP levels and a positive correlation between CRP and TIMI (Thrombolysis In Myocardial Infarction) frame count in patients with SCF.[4]

Several mechanisms have been proposed for the SCF phenomenon, including microvascular vasomotor dysfunction, diffuse atherosclerosis, small-vessel inflammation, and endothelial dysfunction.[5-11] However, the mechanism responsible for the SCF phenomenon remains controversial. The aim of this study was to evaluate the most important two factors affecting SCF, namely, endothelial dysfunction and inflammation.

PATIENTS AND METHODS

The study included 26 consecutive patients (group 1; 13 females, 13 males; mean age 58.8 years) who had normal coronary vessels with SCF in three coronary vessels and 25 consecutive subjects (group 2, 14 females, 11 males; mean age 62.7 years) with angiographically normal coronary arteries without associated SCF. All the patients with SCF underwent coronary angiography in our clinic for the evaluation of coronary artery disease and were diagnosed as having angiographically normal coronary arteries. The control subjects presented with atypical chest pain for which elective coronary angiography was performed and subsequently were found to have normal coronary arteries.

Exclusion criteria were coronary artery disease, coronary plaque, any coronary stenosis, coronary ectasia, previous history of myocardial infarction, left ventricular dysfunction, echocardiographically proven left ventricular hypertrophy, uncontrolled hypertension, renal dysfunction, acute infection, chronic inflammatory disease, the presence of ischemia on noninvasive tests, and the presence of metabolic syndrome. Hyperlipidemia was defined as high levels of low-density lipoprotein cholesterol (≥160 mg/dl) or total cholesterol (≥220 mg/dl) and/or triglyceride (≥200 mg/dl). Hypertension was defined as systolic or diastolic blood pressure measurements of ≥140 mmHg and ≥90 mmHg, respectively. Diabetes mellitus was defined as the fasting glucose level exceeding 126 mg/dl or active use of antidiabetic treatment. Current use of cigarettes was identified as smoking.

The study protocol was approved by the ethical committee of our hospital and written informed consent was obtained from each patient.

Documentation of slow coronary flow. All the patients underwent selective coronary angiography and left ventriculography with the standard technique. We used Iohexol (Omnipaque) as the contrast agent for coronary angiography in all patients and control subjects. Coronary flow rates of all subjects were documented by the TIMI frame count method. TIMI frame count was determined for each major coronary artery in each patient and control subject according to the method first described by Gibson et al.[12] Briefly, the number of cineangiographic frames, recorded at 25 frames/sec, required for the leading edge of the column of radiographic contrast to reach a predetermined landmark is determined. Since the left anterior descending (LAD) coronary artery is usually longer than the other major coronary arteries and the TIMI frame count for this vessel is often higher, TIMI frame count for the LAD coronary artery was divided by 1.7 to obtain corrected TIMI frame count.[12] TIMI frame counts for the LAD and left circumflex (LCx) arteries were assessed in the right anterior oblique projection with caudal angulation and for the right coronary artery (RCA) in the left anterior oblique projection with cranial angulation. Patients with a corrected TIMI frame count greater than two standard deviations from the normal range reported for the particular vessel were considered to have SCF.

Plasma ADMA and hs-CRP measurements. Blood samples were drawn from an antecubital vein before coronary angiography. Serum concentrations of hs-CRP were measured by a nephelometry assay using

Table 1. Baseline characteristics of patients with (group 1) and without (group 2) slow coronary flow

	Group 1 (n=26)			Group 2 (n=25)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			58.8±10.5			62.7±8.7	N S
Sex							N S
Male	13	50.0		11	44.0		
Female	13	50.0		14	56.0		
Body mass index (kg/m^2)			29.7±3.6			28.7±1.6	N S
Diabetes mellitus	2	7.7		1	4.0		N S
Hypertension	11	42.3		8	32.0		N S
Hyperlipidemia	9	34.6		6	24.0		N S
Smoking	6	23.1		4	16.0		N S
Systolic blood pressure (mmHg)			118.5±17.4			120.9±12.2	N S
Diastolic blood pressure (mmHg)			77.7±10.7			77.2±6.5	N S
Heart rate (beats/min)			78.8±13.8			76.9±7.8	N S
Ejection fraction (%)			68.0±6.6			64.0±6.1	N S
Biochemical findings							
Glucose (mg/dl)			102.3±21.8			92.5±13.4	N S
Urea (mg/dl)			37.3±6.6			44.2±15.4	N S
Creatinine (mg/dl)			0.9±0.1			1.0±0.2	N S
Creatine kinase (U/l)			75.6±26.9			65.5±23.6	N S
Creatine kinase MB (U/l)			13.3±4.1			13.7±2.6	N S
Total cholesterol (mg/dl)			188.8±34.3			178.9±18.5	N S
LDL-cholesterol (mg/dl)			123.2±27.8			109.3±17.6	N S
HDL-cholesterol (mg/dl)			34.6±5.0			34.2±7.7	N S
Triglyceride (mg/dl)			153.2±56.1			136.6±32.9	N S
High-sensitivity CRP (mg/dl)			4.7±3.5			2.7±0.6	0.06
Asymmetric dimethylarginine (μmol/l)			0.8±0.2			0.5±0.1	**0.002**
TIMI frame count							
(Corrected) Left anterior descending			41.8±7.4			27.8±4.3	**<0.001**
Circumflex			39.5±11.0			21.2±6.0	**<0.001**
Right coronary artery			45.6±16.4			17.2±4.5	**<0.001**
Flow-mediated dilatation (%)			6.6±1.6			11.2±1.6	**<0.001**
Nitroglycerin-mediated dilatation (%)			13.1±2.5			14.4±1.2	N S
Medications							
Aspirin	21	80.8		17	68.0		N S
Nitroglycerin	26	100.0		25	100.0		N S
Beta-blocker	6	23.1		5	20.0		N S
ACE inhibitor	6	23.1		8	32.0		N S
Statin	4	15.4		3	12.0		N S
Calcium channel blocker	7	26.9		6	24.0		N S

NS: Not significant.

a commercial kit (BN ProSpec, Behring Diagnostics, Westwood, MA, USA). Blood samples for ADMA were spun at 3000 g for 3 minutes and stored at -25 °C until analyzed. ADMA levels were assayed in fasting sera by a validated ELISA kit (DLD Diagnostika GmbH, Hamburg, Germany).[13]

Measurement of flow-mediated dilatation. We used a 10-MHz linear transducer echocardiography/ultrasonography system. Endothelial functions of all subjects were assessed by a single ultrasonographer blinded to the coronary flow groups, in a temperature-controlled room (22 °C) in the morning and after 8-12 hours of a fasting period. Ingestion of substances that might affect measurements, such as caffeine, high-fat foods, and vitamin C was not allowed for 12 hours before the study. Any vasoactive medication was discontinued at least five serum half-lives before the brachial studies. The right brachial artery was imaged above the antecubital fossa in the longitudinal plane. Upon acquiring an appropriate image, the surface of the skin was marked. The arm and the ultrasound probe were kept at the same position by the ultrasonographer during the entire study and the electrocardiogram was monitored continuously. The diameter of the brachial ar-

Table 2. The predictors of slow coronary flow in univariate analysis

	OR	95% confidence interval	*p*
Age	1.04	0.96 - 1.12	0.28
Body mass index	0.89	0.70 - 1.14	0.36
Diabetes mellitus	16.7	0.01 - 39.6	0.86
Hypertension	1.28	0.30 - 5.49	0.73
Smoking	2.99	0.31 - 28.4	0.33
Systolic blood pressure	1.01	0.96 - 1.05	0.66
Diastolic blood pressure	0.99	0.92 - 1.07	0.90
White blood cell count	1.00	0.99 - 1.00	0.74
Platelet count	1.00	0.99 - 1.01	0.63
Glucose	0.95	0.89 - 1.02	0.18
Total cholesterol	0.97	0.94 - 1.00	0.09
LDL-cholesterol	0.97	0.94 - 1.09	0.14
High-sensitivity CRP	0.73	0.52 - 1.00	0.056
Asymmetric dimethylarginine	0.002	0.0006 - 0.16	**0.008**
Flow-mediated dilatation	5.78	1.58 - 21.9	**0.01**
Nitroglycerin-mediated dilatation	1.48	1.06 - 2.09	**0.02**

tery was measured from longitudinal images in which the lumen-intima interface was visualized on the anterior and posterior walls at end-diastole (the onset of R wave on the electrocardiogram) and the mean of three highest measurements from five consecutive cardiac cycles was taken. After the basal lumen diameter and blood flow were noted at rest, a sphygmomanometer cuff was placed on the forearm and the cuff was inflated to 250 mmHg for arterial occlusion. After 5 minutes, the cuff was deflated and the lumen diameter was recorded one minute after to assess endothelium-dependent FMD. Flow-mediated dilatation was defined as both the maximum absolute change and maximum percentage change in vessel diameter during reactive hyperemia. After 10 minutes of rest following reactive hyperemia, 0.4 mg nitroglycerin was given sublingually to determine nitroglycerin-mediated vasodilation (NMD), in other words, endothelium-independent vasodilation. The lumen diameter was measured 4-5 minutes after nitroglycerin administration to assess the NMD. Nitroglycerin-mediated vasodilation was expressed as both the maximum absolute change and maximum percentage increase in vessel diameter after sublingual nitroglycerin.

Statistical analysis. Continuous variables were expressed as mean± standard deviation (SD) and categorical variables were expressed as percentages. Categorical and continuous variables were compared between the two groups using the chi-square test and unpaired t-test, respectively. Correlations between plasma ADMA and hs-CRP levels, FMD, and the mean TIMI frame count were assessed by the bivariate Pearson correlation test. The predictors of SCF were assessed by univariate analysis. Parameters that showed statistical significance in the univariate analysis were then compared with hs-CRP using multivariate logistic regression analysis. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Baseline demographic and clinical characteristics of the two groups were similar (Table 1). TIMI frame count was significantly higher in group 1 compared to group 2 for each artery (p<0.001, Table 1). In group 1, FMD was significantly lower (p<0.001) and ADMA level was significantly higher (p=0.002), compared to group 2, but NMD and hs-CRP level were similar in both groups (p>0.05, Table 1). In univariate analysis, ADMA, FMD, and NMD were significantly correlated with SCF (Table 2). Among these, ADMA and FMD were found to be significant predictors of SCF in multivariate logistic regression analysis (Table 3). Moreover, we found a significant positive correlation between plasma ADMA level and coronary TIMI frame count (RCA: r=0.50; p=0.001; LCx: r=0.32, p=0.04; cLAD: r=0.46, p=0.004) and a significant negative correlation between FMD and TIMI frame count (cLAD: r=-0.68, p=0.0003; LCx: r=-0.54, p=0.0004; RCA: r=-0.46, p=0.004), whereas hs-CRP level and coronary TIMI frame count were not correlated (RCA: r=0.03, p=0.83; LCx: r=0.06, p=0.69; cLAD: r=0.01, p=0.94) (Fig. 1).

DISCUSSION

The main findings of this study can be summarized as follows: *(i)* Plasma ADMA levels were significantly higher in patients with SCF than in those with normal coronary flow (NCF); *(ii)* brachial artery FMD was im-

Table 3. Multivariate logistic regression analysis for determination of slow coronary flow including endothelial dysfunction parameters in comparison with hs-CRP

	hs-CRP	ADMA	hs-CRP	NMD	hs-CRP	FMD
OR	0.61	0.001	0.74	1.20	0.63	4.85
95% CI	0.36 - 1.04	0.0007 - 0.12	0.53 - 1.03	0.87 - 1.64	0.38 - 1.02	1.45 - 18.5
p	0.07	**0.009**	0.08	0.26	0.068	**0.02**

hs-CRP: High-sensitivity C-reactive protein; ADMA: Asymmetric dimethylarginine; FMD: Flow-mediated dilatation; NMD: Nitroglycerin-mediated dilatation.

paired in patients with SCF; *(iii)* there was a significant positive correlation between the ADMA level and TIMI frame count, but there was no correlation between the hs-CRP level and TIMI frame count; *(iv)* ADMA and FMD were significant parameters for prediction of SCF.

Normal functioning endothelium is the key regulator of coronary blood flow through the synthesis and secretion of vasodilating and vasoconstricting substances.[14] Endothelium-derived NO is an important regulator of coronary blood flow with potent vasodilatory effects.[15] Asymmetric dimethylarginine has been shown to decrease both the production and bioavailability of endothelium-derived NO. It reduces vascular compliance, increases vascular resistance, and limits blood flow by inhibiting NO synthesis.[16,17] Thus, ADMA may play an important role in the regulation of coronary circulation.[18-21] In this study, we found that plasma ADMA levels were higher in patients with SCF than in those with NCF and were positively correlated with the TIMI frame count. These findings apparently support the concept that endothelial function is impaired in patients with SCF.

The correlation between impaired brachial artery FMD and increased TIMI frame count and the independent relationship between serum ADMA level and brachial artery SCF establish the role of ADMA in endothelial function-related coronary blood flow modulation. Selcuk et al.[22] found that ADMA levels and ADMA/L-arginine ratio were increased in patients with SCF and that both were correlated with TIMI frame count. Their results, similar to ours, showed a clear relationship between endothelial dysfunction and SCF.

Several mechanisms have been proposed in the development of endothelial dysfunction and SCF. One study suggested that insufficient NO response in coronary sinus blood after atrial pacing might be associated with coronary microvascular dysfunction in patients with SCF.[23] Two studies emphasized the role of homocysteine in the development of endothelial dysfunction and reported a close relationship between homocysteine and SCF.[9,24] Homocysteine is thought to impair endothelial function by causing ADMA accumulation and to inhibit NO synthesis by reducing the enzyme dimethylarginine dimethylaminohydrolase (DDAH) activity, which is responsible for the degradation of ADMA. Thus, ADMA-induced endothelial dysfunction plays an important role in the pathogenesis of SCF.

Inflammation has been shown to be a contributing factor for many cardiovascular events, and to be associated with different clinical settings of coronary artery disease. Inflammation has also been suggested in the pathogenesis of SCF. Turhan et al.[25] found in-

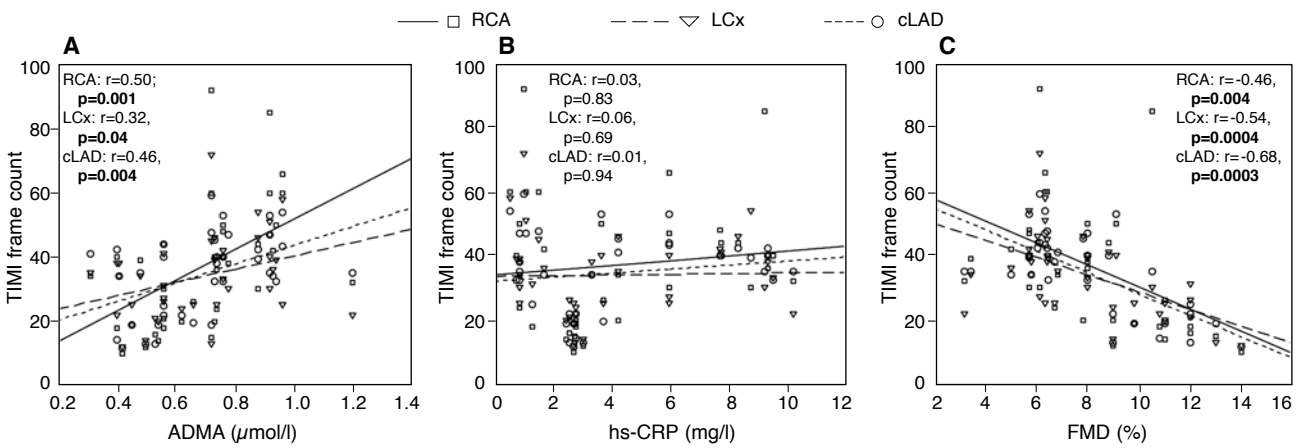

Figure 1. Corelations of **(A)** ADMA, **(B)** hs-CRP, and **(C)** FMD with TIMI frame counts for RCA, LCx, and LAD. hs-CRP: High-sensitivity C-reactive protein; ADMA: Asymmetric dimethylarginine; FMD: Flow-mediated dilatation; RCA: Right coronary artery; LCx: Circumflex artery; cLAD: (Corrected) Left anterior descending artery.

creased levels of plasma soluble adhesion molecules as possible indicators of endothelial activation or inflammation in patients with SCF having angiographically normal coronary arteries. In our study, the mean hs-CRP level was higher in SCF patients without reaching significance and, in univariate analysis, hs-CRP was not a contributing factor for SCF. Yazıcı et al.[26] also found normal CRP levels in patients with SCF and NCF and reported no relationship between CRP and TIMI frame count. Unfortunately, we could not study other inflammatory markers such as serum adhesion molecules and interleukins. If these had been studied, they might have provided much more informative data on the role of inflammation in the etiopathogenesis of SCF.

Several limitations of this study should be considered. Angiographic diagnosis of normal coronary arteries was based on axial contrast angiograms of the vessel lumen, which underestimate the presence of atherosclerotic plaques.[27] Prior studies have shown that heart rate, nitrate use, and coronary catheter size have confounding effects on the frame count.[28] In our study, coronary catheter size was the same in all participants and all patients were using nitrates. Heart rate was similar in subjects with and without SCF.

In conclusion, the presence of a positive correlation between the ADMA level and coronary TIMI frame count and impaired FMD in SCF patients support the role of endothelial dysfunction in the etiopathogenesis of SCF. We found endothelial dysfunction as a more prominent factor than inflammation in the etiopathogenesis of SCF. However, further large-scale studies with more sophisticated methods are needed to elucidate the etiology of SCF.

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