Left ventricular function in patients with coronary slow flow: a tissue Doppler study

Koroner yavaş akımı olan hastalarda sol ventrikül fonksiyonları: Doku Doppler çalışması

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Objectives: This study, was designed to assess left ventricular systolic and diastolic functions with conventional and tissue Doppler echocardiography in patients with the coronary slow flow phenomenon (CSFP).

Study design: The study included 22 patients (12 males, 10 females; mean age 48±12 years) with angiographically diagnosed CSFP but with otherwise normal epicardial coronary arteries. Twenty-two subjects (14 males, 8 females; mean age 47±11 years) with angiographically normal coronary arteries constituted the control group. Left ventricular systolic and diastolic functions were assessed by conventional and tissue-Doppler echocardiography before angiography. The diagnosis of CSFP was made using the TIMI frame count (TFC) method. TIMI frame counts were determined for the left anterior descending (LAD), circumflex (Cx), and right coronary (RCA) arteries.

Results: Patients with CSFP had significantly higher values of corrected TFC for the LAD, TFC for Cx and RCA, and the mean TFC ($p<0.001$). There were no significant differences in ejection fraction and mitral annular peak systolic velocity between the two groups. Conventional echocardiography showed significantly lower maximal velocity of early diastolic filling (E), ratio of maximal early to late diastolic filling (E/A), and longer isovolumetric relaxation time (IVRT) in the patient group ($p<0.01$, $p<0.001$, and $p=0.001$, respectively). Maximal velocity of atrial diastolic filling (A) and deceleration time of early diastolic filling (DT) were similar. Among tissue Doppler parameters, Em and Em/Am were significantly lower ($p<0.001$); IVRTm ($p=0.001$) and DTm ($p=0.02$) were significantly higher in the patient group. TIMI frame counts were negatively correlated with E, E/A, Em, and Em/Am, and positively correlated with DT, IVRT, DTm, IVRTm, and E/Em.

Conclusion: Coronary slow flow phenomenon is associated with left ventricular diastolic and systolic dysfunctions, requiring a close follow-up in this patient group.

Key words: Blood flow velocity; coronary circulation; echocardiography, Doppler/methods; myocardial ischemia; ventricular function, left.

Amaç: Bu çalışmada, koroner yavaş akım fenomeni olan hastalarda sol ventrikül sistolik ve diyastolik fonksiyonları konvansiyonel ve doku Doppler ekokardiyografi ile değerlendirildi.

Çalışma planı: Çalışmaya, anjiyografik olarak koroner yavaş akım tanısı konan ve epikardiyal koroner arterleri normal bulunan 22 hasta (12 erkek, 10 kadın; ort. yaş 48±12) alındı. Anjiyografik olarak koroner arterleri normal bulunan 22 hastadan (14 erkek, 8 kadın; ort. yaş 47±11) kontrol grubu oluşturuldu. Her iki grupta, anjiyografiden hemen önce, konvansiyonel ve doku Doppler ekokardiyografi ile sol ventrikül sistolik ve diyastolik fonksiyonları değerlendirildi. Koroner yavaş akım tanısı TIMI kare sayısı yöntemiyle kondu. Sol ön inen, sirkumfleks ve sağ koroner arterler için TIMI kare sayıları hesaplandı.

Bulgular: Koroner yavaş akım olan grupta sol ön inen arter için düzeltilmiş TIMI kare sayısı, sirkumfleks ve sağ koroner arterler için TIMI kare sayıları ve ortalama TIMI kare sayısı anlamlı derecede yüksek bulundu ($p<0.001$). İki grup arasında ejeksiyon fraksiyonu ve mitral annular pik sistolik hız açısından farklılık yoktu. Konvansiyonel ekokardiyografide, koroner yavaş akım grubunda erken diyastolik doluş maksimum hızı (E), erken ve geç diyastolik doluş maksimum hızlarının oranı (E/A) anlamlı derecede düşük, izovolümetrik gevşeme zamanı (IVRT) anlamlı derecede uzun bulundu (sırasıyla $p<0.01$, $p<0.001$ ve $p=0.001$). Atriyal diyastolik doluş maksimum hızı (A) ve erken diyastolik doluş deselerasyon zamanı (DT) açısından farklılık yoktu. Doku Doppler parametreleri açısından, koroner yavaş akım grubunda Em ve Em/Am anlamlı derecede düşük ($p<0.001$); IVRTm ($p=0.001$) ve DTm ($p=0.02$) yüksek bulundu. TIMI kare sayıları E, E/A, Em ve Em/Am ile negatif; DT, IVRT, DTm, IVRTm ve E/Em ile pozitif ilişki gösterdi.

Sonuç: Koroner yavaş akım fenomeninde sol ventrikül sistolik ve diyastolik fonksiyonları bozulmaktadır; bu hastaların bu açıdan yakından izlenmesi gerekir.

Anahtar sözcükler: Kan akım hızı; koroner akım; ekokardiyografi, Doppler/yöntem; miyokard iskemisi; ventrikül fonksiyonu, sol.

Presented at World Congress of Cardiology, September 2-6, 2006, Barcelona, Spain.

Received: February 25, 2007 *Accepted:* June 14, 2007

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The coronary slow flow phenomenon (CSFP) is an angiographic finding characterized by delayed opacification of vessels in the absence of obstructive epicardial coronary disease.[1] It was first described by Tambe et al.[2] in 1972. The exact etiology and pathogenesis of CSFP is still unknown; microvascular dysfunction and occlusive disease of the small coronary arteries have been implicated.[3] A number of studies have been published concerning the etiology and treatment of CSFP, but data are limited on left ventricular function in patients with CSFP.

This study was designed to assess left ventricular systolic and diastolic functions with the use of conventional and tissue Doppler echocardiography in patients with CSFP.

PATIENTS AND METHODS

Subjects. The study consisted of 22 patients (12 males, 10 females; mean age 48±12 years) with angiographically diagnosed CSFP but otherwise normal epicardial coronary arteries. Twenty-two subjects (14 males, 8 females; mean age 47±11 years) with angiographically normal coronary arteries constituted the control group. All the study subjects were selected among those who underwent routine coronary angiography because of suspected coronary artery disease. Indications for coronary angiography were unstable angina pectoris (Braunwald classification class III) in 10 patients with coronary slow flow, unstable angina pectoris (Braunwald classification class II) in six patients, and stable angina pectoris in six patients. The patients were not subjected to any cardiovascular stress test before coronary angiography. Patients having the following features were excluded from the study: history of coronary artery disease, coronary ectasia, proximal lumen diameter of less than 3 mm, history of arrhythmia, heart failure, valvular dysfunction, hypertension, left ventricular hypertrophy, diabetes mellitus, and systemic disorders. All concomitant medications were stopped 48 hours prior to the procedure. The study protocol was approved by our institutional ethics committee, and all subjects gave written informed consent before the study.

Coronary angiography and analysis of TIMI frame count. All the images were evaluated by an experienced cardiologist. Coronary angiography was performed by the femoral approach using the standard Judkins technique. Coronary arteries on the left and right oblique planes, and cranial and caudal angles were demonstrated. In all the patients, iodixanol 320/100 ml was used as the contrast medium. The diagnosis of coronary slow flow was made using the TIMI frame count (TFC) method.[4] Frame count extended from the origin of the coronary artery to its most distal segments. The outset frame was selected as the frame in which the coronary artery ostium was completely filled with contrast. The distal reference points were the terminal bifurcations of the left anterior descending (LAD) and circumflex (Cx) arteries, and the first side-branch of the posterolateral artery and the right coronary artery (RCA). The final frame was selected as the frame in which the branch terminating distally had contact with the contrast matter. For evaluation, corrected TFC was calculated for the LAD by dividing TFC of the LAD by a factor of 1.7.[4] TIMI frame counts for the LAD and Cx arteries were assessed in the right anterior oblique projection with caudal angulation and for RCA in the left anterior oblique projection with cranial angulation. The mean TFC for each patient and control subject was calculated by adding the TFC for the LAD, Cx and RCA arteries, and then dividing the sum by 3. The cutoff values for TFC were taken from a previous study[4] in which 70 normal coronary arteries were evaluated (for LAD: 36.2±2.6 ; for Cx: 22.2±4.1; for RCA: 20.4±3.0). Any TFC above these levels was considered coronary slow flow.

Echocardiographic study. Echocardiographic evaluation was made just before the angiographic study. A Vingmed System Five Doppler echocardiographic unit (General Electric, Horten, Norway) with a 2.5-MHz flat phased-array probe was used. Echocardiography was performed in the left lateral decubitus position. All the measurements were performed according to the guidelines of the American Society of Echocardiography.[5] Two-dimensional echocardiography and the modified Simpson’s rule were used to determine ejection fraction (EF), left ventricular end-diastolic and end-systolic diameters. Mitral flow velocity was obtained from the apical four-chamber view with the pulsed-wave technique by placing the sample volume between the tips of the mitral leaflets for conventional diastolic parameters of the left ventricle. The following parameters were calculated: maximal velocity of early diastolic filling (E), maximal velocity of atrial diastolic filling (A), the ratio of maximal early to late diastolic filling (E/A), deceleration time of early diastolic filling (DT). Left ventricle isovolumetric relaxation time (IVRT) was also obtained from the apical five-chamber view through the continuous-wave technique by placing the sample vol-

Table 1. Demographic and clinical characteristics of patients with coronary slow flow phenomenon compared to controls

	Patients (n=22)			Controls (n=22)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			48±12			47±11	NS
Gender							NS
Male	12	54.6		14	63.6		
Female	10	45.5		8	36.4		
Smoking	5	22.7		11	50.0		<0.05
Family history	4	18.2		3	13.6		NS
Systolic blood pressure (mmHg)			114±11			111±13	NS
Diastolic blood pressure (mmHg)			71±8			71±9	NS
Heart rate (beat/min)			68±8			71±8	NS
Total cholesterol (mg/dl)			189±35			189±27	NS
Triglyceride (mg/dl)			216±137			182±95	NS
High density lipoprotein (mg/dl)			37±7			41±11	NS
Low density lipoprotein (mg/dl)			108±29			110±21	NS

NS: Not significant.

ume between mitral and aortic leaflets. Tissue Doppler imaging was performed using the same echocardiographic unit with the tissue Doppler mode of the device. In the apical four-chamber view, mitral annular peak systolic (Sm), early diastolic (Em), and late diastolic (Am) velocities, late to early velocity ratio (Em/Am), deceleration time (DTm), and left ventricle isovolumetric relaxation time (IVRTm) were measured at the lateral corner of the mitral annulus. The presence of left ventricular hypertrophy was defined as the thickness of the septum or posterior wall exceeding 1.2 cm. The TFC was evaluated by an experienced cardiologist. Echocardiographic recordings were analyzed by a cardiologist who was unaware of the TFC values.

Statistical analysis. All the data were expressed as mean ± standard deviation. Differences between the groups were evaluated with the Mann-Whitney U-test. Correlations between TIMI frame counts and echocardiographic parameters were evaluated using the Spearman's correlation test. A p value of less than 0.05 was considered statistically significant.

RESULTS

There were no differences between the two groups in terms of age, sex, and blood pressure (Table 1). The frequency of smoking was higher in the control group.

Patients with CSFP had significantly higher values of corrected TFC for the LAD (51±23 *vs* 18±4), TFC for Cx (47±17 *vs* 17±4) and RCA (51±29 *vs* 20±4), and mean TFC (55±25 *vs* 18±3) (p<0.001 for all).

The two groups were compared for systolic and diastolic parameters. For systolic function EF and Sm were used. For diastolic functions, both mitral inflow pulsed-wave (PW) Doppler (E, A, E/A, DT, IVRT) and mitral lateral tissue Doppler (Em, Am, E/Am, DTm, and IVRTm) parameters were used.

Left ventricular EF was similar in both groups. There were no significant differences between the two groups with respect to left ventricle and left atrium diameters. Sm was lower in the patient group (97±30 cm/s *vs* 105±14 cm/s; p=0.03) (Table 2).

Patients with CSFP exhibited significantly lower E (56±11 cm/s *vs* 65±11 cm/s, p<0.01), E/A (1.1±0.3 *vs* 1.3±0.2, p<0.001), but higher IVRT (94±11 ms *vs* 82±12 ms, p=0.001) than the controls. Deceleration time was higher in the patient group, but this did not reach significance (p>0.05). Maximal velocity of late diastolic filling was similar in the two groups (p>0.05).

Among tissue Doppler parameters, Em (77±13 cm/s *vs* 139±21 cm/s) and Em/Am (0.8±0.2 *vs* 1.5±0.3) were significantly lower (p<0.001); IVRTm (83±15 ms *vs* 68±8 ms, p=0.001) and DTm (194±52 ms *vs* 156±25 ms, p=0.02) were significantly higher in the patient group.

The presence of CSFP was significantly associated with a higher E/Em ratio (0.73±0.2 *vs* 0.47±0.8, p<0.001) (Table 2). Both PW Doppler and tissue Doppler findings suggested the presence of systolic and diastolic dysfunction in the patient group.

Table 2. Left ventricular echocardiographic parameters

	Patients	Controls	*p*
Left ventricular			
End-diastolic diameter (mm)	49±5	46±4	NS
End-systolic diameter (mm)	31±4	31±3	NS
Ejection fraction (%)	68±8	65±8	NS
Left atrium (mm)	36±3	34±4	NS
Mitral inflow			
Maximal velocity of early diastolic filling (E) (cm/s)	56±11	65±11	<0.01
Maximal velocity of atrial diastolic filling (A) (cm/s)	54±14	51±9	NS
E/A	1.1±0.3	1.3±0.2	<0.001
Deceleration time of early diastolic filling (DT) (ms)	210±38	188±29	NS
Mitral annulus			
Peak systolic velocity (Sm) (cm/s)	97±30	105±14	0.03
Early diastolic velocity (Em) (cm/s)	77±13	139±21	<0.001
Late diastolic velocity (Am) (cm/s)	103±22	91±13	NS
Em/Am	0.8±0.2	1.5±0.3	<0.001
Deceleration time (ms)	194±52	156±25	0.02
Left ventricle isovolumetric relaxation time			
Continuous-wave (ms)	94±11	82±12	0.001
Tissue Doppler (ms)	83±15	68±8	0.001
E/Em	0.73±0.2	0.47±0.8	<0.001

NS: Not significant.

Conventional Doppler echocardiography showed diastolic dysfunction in the form of relaxation disorder in eight patients with coronary slow flow. Tissue Doppler evaluation, however, revealed diastolic dysfunction in 14 patients.

TIMI frame count was significantly correlated with echocardiographic parameters of diastolic function. TIMI frame counts were negatively correlated with E, E/A, Em, and Em/Am, and positively correlated with DT, IVRT, DTm, IVRTm, and E/Em (Table 3).

Table 3. Correlations between TIMI frame count and echocardiographic parameters

	TIMI frame count (TFC)							
	cLAD		Cx		RCA		Mean TFC	
	r	*p*	r	*p*	r	*p*	r	*p*
Left ventricular								
End-diastolic diameter	0.166	0.283	0.156	0.312	**0.345**	**0.022**	0.254	0.096
End-systolic diameter	0.112	0.469	0.092	0.552	0.245	0.109	0.184	0.231
Ejection fraction	0.170	0.270	0.191	0.213	0.155	0.315	0.145	0.347
Left atrium	**0.317**	**0.036**	0.191	0.214	0.246	0.108	0.185	0.230
Mitral inflow								
Maximal velocity of early diastolic filling (E)	**-0.390**	**0.009**	**-0.425**	**0.004**	**-0.422**	**0.004**	**-0.427**	**0.004**
Maximal velocity of atrial diastolic filling (A)	0.086	0.579	0.120	0.439	0.111	0.473	0.127	0.410
E/A	**-0.557**	**0.000**	**-0.625**	**0.000**	**-0.579**	**0.000**	**-0.635**	**0.000**
Deceleration time of early diastolic filling (DT)	**0.356**	**0.018**	**0.318**	**0.036**	**0.391**	**0.009**	**0.350**	**0.020**
Mitral annulus								
Peak systolic velocity (Sm)	-0.265	0.082	**-0.335**	**0.026**	-0.250	0.101	-0.233	0.128
Early diastolic velocity (Em)	**-0.738**	**0.000**	**-0.760**	**0.000**	**-0.761**	**0.000**	**-0.766**	**0.000**
Late diastolic velocity (Am)	**0.328**	**0.030**	**0.315**	**0.037**	0.234	0.126	**0.299**	**0.049**
Em/Am	**-0.792**	**0.000**	**-0.816**	**0.000**	**-0.785**	**0.000**	**-0.814**	**0.000**
Deceleration time (DTm)	**0.348**	**0.021**	**0.388**	**0.009**	**0.406**	**0.006**	**0.359**	**0.017**
Left ventricle isovolumetric relaxation time								
Continuous-wave (ms)	**0.345**	**0.022**	**0.395**	**0.008**	**0.415**	**0.002**	**0.425**	**0.004**
Tissue Doppler (ms)	**0.464**	**0.001**	**0.499**	**0.001**	**0.522**	**0.000**	**0.523**	**0.000**
E/Em	**0.544**	**0.000**	**0.560**	**0.000**	**0.558**	**0.000**	**0.568**	**0.000**

cLAD: Corrected frame count for left anterior descending artery; Cx: Circumflex artery; RCA: Right coronary artery; Mean TFC: (LAD+Cx+RCA)/3.

DISCUSSION

In our study, diastolic functions of the left ventricle were significantly impaired in patients with coronary slow flow compared to the control group. Although conventional echocardiography showed no differences with respect to systolic functions, tissue Doppler echocardiography, a more sensitive method, could detect systolic dysfunction in patients with coronary slow flow. In addition, the diastolic functions of the left ventricle were correlated with coronary artery frame counts.

A large number of studies have demonstrated that CSFP is associated with myocardial ischemia, but data are limited on how the left ventricular functions are affected from this disease.[1,6-11] Tambe et al.[2] described six patients with coronary slow flow. Of these, three developed ischemia as a result of exercise test, three showed mild hemodynamic abnormalities, and two had moderate enlargement of the left ventricle with segmental dyskinesia indicating left ventricular systolic dysfunction. Cannon et al.[12] also showed both systolic and diastolic abnormalities in left ventricular function, which were highly suggestive of significant myocardial ischemia in patients with angina pectoris.

Some studies have demonstrated the presence of diastolic dysfunction without systolic dysfunction at an early stage of myocardial ischemia in patients with coronary artery disease, compatible with the fact that left ventricular diastolic functions are more susceptible to ischemia than systolic functions.[13] Although hemodynamic assessment is the gold standard in evaluating diastolic functions, noninvasive diagnostic methods with similar accuracy rates have been developed, and among these, tissue Doppler echocardiography is the most reliable one.[14]

Left ventricular functions of patients with coronary slow flow have also been evaluated through echocardiography. Barutçu et al.[15] evaluated left ventricular ejection fraction by conventional echocardiography and found no differences in left ventricular systolic function between patients with CSFP and the control group. In another study, Sezgin et al.[16] found diastolic filling abnormalities but normal left ventricular systolic function by conventional Doppler echocardiography in patients with CSFP.

The results of that study contradict with those of our study. While Barutçu et al have compared only the systolic parameters, Sezgin et al have evaluated both systolic and diastolic functions through conventional methods. Unlike these two studies performed by conventional echocardiography, we also performed tissue Doppler echocardiography and showed left ventricular diastolic dysfunction as well as systolic dysfunction. Tissue Doppler echocardiography is less influenced by several factors such as load condition and PW Doppler mitral inflow velocities.

In our study, conventional PW Doppler echocardiography showed diastolic dysfunction in eight patients with coronary slow flow; however, tissue Doppler echocardiography detected diastolic dysfunction in 14 patients, which suggests that the diastolic filling pattern detected in most of the patients with coronary slow flow is a pseudo-normal pattern. The E/Em values which were significantly higher in patients with coronary slow flow were lower than the values expected for the pseudo-normal group (E/Em >10). This might have resulted from the small size of the patient group and the coexistence of a relaxation disorder with the pseudo-normal pattern in patients with coronary slow flow. Furthermore, we did not seek correlations between end diastolic pressures and the E/Em values, which might have resulted in insufficient interpretation of the clinical value of E/Em.

In distinction with earlier studies, we showed correlations between the frame counts of the coronary arteries and echocardiographic parameters, in that increased frame counts were associated with left ventricular diastolic dysfunctions.

In conclusion, CSFP is associated with left ventricular diastolic and systolic dysfunctions, requiring a close follow-up of patients with slow coronary flow. Further studies with larger series and longer follow-up are needed to determine the effects of left ventricular systolic and diastolic dysfunctions on mortality. In addition, agents such as adenosine and mibefradil, which have been shown to have positive effects on coronary slow flow,[17,18] should be evaluated with respect to their effects on the left ventricle functions.

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