ARAŞTIRMA MAKALESİ/ ORIGINAL ARTICLE

Kocaeli Med J 2019; 8; 2:191-196

Kadın Hastalarda Koroner Yavaş Akımın Klinik Belirleyicileri

Clinical Predictors of Coronary Slow Flow in Female Patients

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ÖZ

GİRİŞ ve AMAÇ: *Önceden, koroner yavaş akışın (KYA) erkek cinsiyet, yüksek BMI ve sigara kullanımı ile ilgili olduğu bildirilmişti. Ancak KYA, kadınlarda da görülen bir klinik durumdur ve bu konuda herhangi bir çalışma yapılmamıştır. Bu çalışmada kadın hastalarda KYA 'nın belirleyicilerini araştırmayı amaçladık.*

YÖNTEM ve GEREÇLER: *40'ı normal (ortalama yaş: 51.9 ± 5.2 yıl) ve 40 'I KYA (ortalama yaş: 54.6 ± 7.7 yıl) toplam 80 kadın hasta seçildi. TIMI frame sayıları hesaplandı ve demografik özellikler, komorbiditeler ve ilaç kullanımı ile ilgili veriler toplandı. CSF, frame sayısı> 27 olarak tanımlandı.*

BULGULAR: *KYA grubunda diyabetes mellitus (DM) yüzdesi anlamlı olarak yüksekti (% 52.5'e karşılık% 22.5; p: 0.005). DM, çok değişkenli lojistik regresyon analizinde KYA 'lı kadın hastaların anlamlı belirleyicisi olarak bulundu (O.R: 3.44,% 95 CI: 1.14–10.36; p: 0.028).*

TARTIŞMA ve SONUÇ: *KYA 'lı kadın hastalarda DM'nin anlamlı derecede arttığını ve çok değişkenli analizde KYA 'nın bağımsız belirleyicisi olduğunu bulduk.*

Anahtar Kelimeler: *kadın hastalar, koroner yavaş akım, klinik belirleyiciler*

ABSTRACT

INTRODUCTION: *Previously, the coronary slow flow (CSF) has been reported to be related to male sex, high BMI, and smoking. However, CSF is a clinical condition seen in women and no studies have been conducted on this subject. We aimed to investigate predictors of coronary slow flow in female patients.*

METHODS: *A total of 80 female patients, 40 of whom were normal (mean age: 51.9±5.2 years) and 40 with coronary slow flow(mean age: 54.6 ±7.7 years) were selected. TIMI frame counts were calculated, and data on demographics, comorbidities, and medication use were collected. CSF was defined as frame count >27.*

RESULTS: *Percentage of diabetes mellitus (DM) was significantly higher in the CSF group (52.5 % vs. 22.5 %; p: 0.005). DM was found to be significant predictor of female patients with CSF in the multivariate logistic regression analysis (O.R: 3.44, 95%CI: 1.14–10.36; p: 0.028).*

DISCUSSION and CONCLUSION: *We found that DM was significantly increased and only independent predictor of CSF in female patients with CSF.*

Keywords: *clinical predictors, coronary slow flow, female patients*

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Başvuru Tarihi: 10.02.2019
Kabul Tarihi: 03.08.2019

INTRODUCTION

The coronary slow flow (CSF) is characterized by the slow passage of contrast medium in absence of significant epicardial coronary stenosis in coronary angiography. The CSF is observed in 1-7% of all coronary angiographic studies performed for the evaluation of patients with angina pectoris and is associated with recurrent acute coronary syndromes, life-threatening arrhythmias, and sudden cardiac death (1-4). Although it is well recognized by interventional cardiologist, the underlying mechanisms are incompletely exposed. Endothelial dysfunction, small-vessel disease, and diffuse atherosclerosis have been proposed for etiology of CSF (5, 6).

Many studies found that CSF is associated with male sex, obesity (7), and smoking (8). However, CSF is a clinical condition seen in women and no studies have been conducted on this subject. Therefore, we aimed to investigate predictors of coronary slow flow in female patients.

METHODS

This is a cross-sectional observational study. It was conducted between 2015-2018 in our center. A total of 80 female patients, 40 of whom were normal and 40 with coronary slow flow were selected by 2 different experienced cardiologists without knowledge of the patients' demographic and laboratory data. All study participants who have normal ejection fraction were referred for coronary angiography as outpatients due to the presence of typical angina, symptoms considered to represent angina equivalence or positive stress tests in non-invasive test evaluations.

Normal coronaries were defined as coronary arteries without any obstructive or non-obstructive lesions in any coronary artery. Coronary flow was defined by Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) method.

Medical history was obtained, and physical and echocardiographic examination was performed in all study population. Weight and height of the patients were measured without heavy outer garments and shoes, after a 12 h fasting period. Body-mass index (BMI) was calculated as body weight divided by the square of the height. Heart rate, systolic, and diastolic blood pressure of patients were recorded at the same time of coronary angiography.

Patients with coronary artery disease, acute coronary syndrome, coronary vasospasm, coronary artery ectasia, moderate-severe valvular heart disease, left ventricular dysfunction and left ventricular hypertrophy on echocardiography, bradycardia, atrioventricular conduction abnormalities, hypotension during coronary angiography, known malignancy or inflammatory-immunologic disease, hepatic or renal dysfunction, thyroid disease, acute, or chronic infections were excluded.

The study was approved by the local institutional ethics committee, and informed consent was obtained from all the patients.

Angiographic data and TIMI frame count

Coronary angiography was performed using the standard Judkins technique. Angiographic images were obtained in standard views using right and left, cranial and caudal angulations. All angiograms were recorded at 15 frames/s. We used Iohexol (Omnipaque ® 350) as the contrast agent in all the study groups. Coronary flow rates of all subjects were determined by the TFC method as described by Gibson et al. (9). TFC was evaluated for each coronary vessel by two trained cardiologists, blind to the patient's clinical information. The first frame was considered to be that at which $>70\,\%$ lumen opacification with antegrade filling was noted.

The final frames were determined when contrast opacification reached a certain distal landmark in each vessel. The distal bifurcation was used ("whale's tail") for the left anterior descending artery (LAD). The most distal bifurcation of the obtuse marginal branch furthest from the coronary ostium was used as the distal landmark for the left circumflex artery (LCx). The first branch of the posterolateral segment was used for the right coronary artery (RCA). Because LAD is usually longer than the other major coronary arteries, TFC for the LAD coronary artery was divided by 1.7 to obtain corrected TFC (9). TFCs for the LAD and LCx arteries were assessed in the right anterior oblique projection with caudal angulation and for the RCA in the left anterior oblique projection with cranial angulation. The mean TFC for each patient

and control participant was calculated by dividing the sum of the TFCs of LAD, LCx, and RCA by 3 (9).Any frame count exceeding 27 was considered to be abnormal and indicative of slow flow (9). The intra- and interobserver coefficients of variation were 3.7% and 5.4%, respectively.

Laboratory Analysis

Blood samples were withdrawn by venipuncture from all subjects following 12 h of fasting. Hematologic parameters and biochemical measurements including glucose, serum creatinine, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglyceride concentrations were determined by standard laboratory methods.

Statistical Analysis

SPSS statistical software (SPSS for Windows, Inc., Chicago, IL, USA) was used for all statistical calculations. Categorical variables were expressed as number and proportions while continuous variables were expressed as mean ± standard deviation. Chi-square test was used to compare the groups regarding categorical variables. The Kolmogorov-Smirnov test was used to evaluate whether the distribution of continuous variables was normal. Continuous variables were compared with Student T-test (while compari.ng parametric variables) or Mann-Whitney U test (while comparing nonparametric variables). The variables for which p value < 0.10 in the univariate analysis included in the full multivariate logistic regression model as covariates. A p value < 0.05 was considered as significant.

RESULTS

A total of 80 female patients, 40 of whom were normal and 40 with coronary slow flow were enrolled in the study. Table 1 summarizes the angiographic findings of our study population: 40 subjects had slow coronary flow in at least 1 vessel, and the LCX, LAD and RCA were involved in 72.5 %, 62.5 % and 37.5 % of the patients, respectively. Two-vessel involvement was the most common (32.5 %) and was followed by 3-vessel (27.5%) and single-vessel involvement (25 %). TIMI frame count rates were significantly increased for all three vessels in patients with CSF (p: <0.001).

Table 1. Angiographic And Catheterization Data For Subjects With Slow Flow

Artery Involvement	NORMAL (N=40)	SLOW FLOW (N=40)	P VALUE
LAD (%)		62.5	
LCX (%)		72.5	
RCA (%)		37.5	
Vessel İnvolvement			
1-VESSEL (%)		25	
2-VESSEL (%)		32.5	
3-VESSEL (%)		27.5	
Frame Count			
LAD	16.9±3.15	32.1±9.7	<0.0001
LCX	20.1±4.9	31.8±13.5	<0.0001
RCA	16.7±3.5	25.9±12.6	<0.0001

LAD, Left Anterior Descending Artery; LCX, Left Circumflex Artery; RCA, Right Coronary Artery

The demographic findings and laboratory values of the study groups are presented in Table 2. There were no significant differences between the two groups regarding BMI, percentage of hypertension, hyperlipidemia, family history of CAD and smoking. Mean age was found increased in CSF group but it was not statistically different. Percentage of DM was significantly higher in the CSF group (52.5 % vs. 22.5 %; p: 0.005). Laboratory measurements and medications were also similar in the two groups.

Table 3 shows the results of the multivariate logistic regression analysis including DM, B-blocker usage, age and serum glucose level. Among these, DM was found to be significant predictor of female patients with CSF in the multivariate logistic regression analysis (O.R: 3.44, 95%CI: 1.14–10.36; p: 0.028).

Table 2. Demographic And Clinical Characteristics Of Subjects With Slow Flow			
DEMOGRAPHİCS	**NORMAL (N=40)**	**SLOW FLOW (N=40)**	**P VALUE**
AGE (YEARS)	51.9±5.2	54.6±7.7	0.07
BMI (KG/M^2)	27.2±3.4	26.3±3.1	0.250
COMORBİDİTİES			
HT (%)	32.5	42.5	0.244
DM (%)	22.5	52.5	0.005
Hyperlipidemia (%)	20	27.5	0.30
Smoking (%)	12.5	15	0.50
Family History of CAD	12.5	17.5	0.755
QUANTİTATİVE MEASUREMENTS			
SBP (MMHG)	124±7.7	123.2±11.3	0.730
DBP (MMHG)	77.8±5.3	76±8.8	0.254
HR	74.7±6.7	73.7±6.6	0.502
LABORATORY FİNDİNGS			
GLUCOSE (MG/DL)	108.4±15.8	116.3±22.7	0.077
CREATİNİNE (MG/DL)	0.69±0.1	0.71±0.15	0.494
TC (MG/DL)	182.5±27.2	185.5±31.1	0.653
TG (MG/DL)	156.3±50.1	150.7±59.8	0.648
HDL (MG/DL)	39.9±8.3	41.4±10.6	0.503
LDL (MG/DL)	108.5±26.2	114.7±26.4	0.292
Hemoglobin (G/DL)	13.1±1.6	13.3±1.4	0.590
Platelets (X10^9/L)	238±55.5	250.1±54.7	0.326
WBC (X10^3 MG/DL)	8.3±1.6	8.2±3.7	0.965
MEDİCATİON USAGE			
Aspirin (%)	30	35	0.406
B-Blocker (%)	7.5	20	0.096
CCB (%)	17.5	17.5	NS
ACEI/ARB (%)	30	35	0.406
Statins (%)	15	25	0.201

Table 3. Independent Predictors Of Coronary Slow Flow			
	OR	**95%CI**	**P VALUE**
DM	3.44	1.14–10.36	0.028
B-Blocker USAGE	2.52	0.54–11.66	0.238
Age	1.05	0.98–1.12	0.198
Glucose	1.002	0.97–1.03	0.908

DISCUSSION

The main points of this study can be summarized as follows: (1) This is the first study to investigate predictors of CSF in female patients in the literature, (2) The percentage of DM was significantly increased and only independent predictor of CSF in the study group, (3) On the contrary of the previous reports , BMI and smoking were not found to associate with CSF in female patients in our study, although those studies conducted in the general population.

Coronary slow-flow phenomenon was identified as an exclusive clinical entity in 1972 (10) where the distal opacification of the coronary artery is delayed on angiography in the absence of significant coronary artery disease. Incidence of CSF is reported to be 1-7% of all coronary angiograms (7). The exact pathogenesis of CSF is still not clear and is probably multi factorial. Functional and morphological abnormalities in the microvasculature, endothelial dysfunction, raised inflammatory markers, occult atherosclerosis and anatomical factors of epicardial arteries have all been implicated (1) .

Endothelium plays an integral role in the regulation of vascular tone, platelet activity, leukocyte adhesion, vascular smooth muscle proliferation, and is intimately involved in the development of atherosclerosis. It has been reported that reduced endothelium dependent flow-mediated dilatation (FMD) of the brachial artery was detected in patients with CSF, suggesting that endothelial dysfunction is implicated in etiology of CSF (6). Some studies have observed that these patients are more likely to suffer from metabolic disorders, including impaired fasting glucose and high HbA1c, perhaps because these abnormalities enhance the progression of the microvascular or endothelial dysfunction (11, 12). Endothelial dysfunction is one of the precursor key steps in the development of atherosclerosis in diabetic subjects. Decreased nitric oxide (NO) production, increased oxidative stress and impaired function of endothelial progenitor cells are the main mechanisms involved in the accelerated atherosclerotic process observed in type 2 DM patients (13). In our study, as support of this findings, endothelial dysfunction and early phase of atherosclerosis precipitated by DM might be related to CSF in our female population.

Previously, Hawkins et al. found that male sex and obesity were independent predictors of CSF phenomenon (7). Gomaa et al reported that CSF was common in smokers and diabetic patients (8). In other study, Yilmaz et al. (14) represented the clinical and laboratory features of CSF compared to the control subjects without CSF. Metabolic syndrome was more frequent in CSF in the presence of higher total cholesterol, low-density lipoprotein-cholesterol, fasting glucose and body mass index levels. On the contrary of these results, increased BMI and smoking were not found to be associated in our female study group. These results might be explained as follows; small patient groups, low obesity and smoking rate in our study population compared the other studies or most importantly, it may have been caused by a gender difference.

Our study had some limitations. This is a case-control study having relatively small number of patients. All data were based on a single measurement and may not reflect changes over time.

CONCLUSION

We found that DM was significantly increased and only independent predictor of CSF in female patients with CSF. This result may strengthen the role of endothelial dysfunction and early phase of atherosclerosis in CSF irrespective of gender difference.

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