Impact of renal dysfunction on coronary blood flow

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Abstract:
Objectives: Slow coronary flow (SCF) has long been identified and endothelial dysfunction and atherosclerosis of epicardial coronary arteries and microvasculature were reported to be associated with SCF. Impact of renal functions on atherosclerosis and endothelial dysfunction has been reported. Consequently, we aimed to investigate the association between coronary blood flow by means of TIMI frame count (TFC) and renal functions and other laboratory parameters in patients with SCF compared to control cases.
Design and Methods: Ninety-two patients with SCF and 562 control cases with normal coronary flow were studied after quantifying coronary blood flow according to TFC. Estimated glomerular filtration rate (eGFR) was evaluated with Cockcroft-Gault equation. The association between TFC and eGFR and other clinical and laboratory parameters were evaluated.
Results: There were statistically significant differences between SCF and control groups in respect to gender, systolic blood pressure, heart rate, serum uric acid and creatinine levels, hematocrit and eGFR. Mean TFC was correlated with age (r=0.113, p=0.004), gender (r=0.152, p<0.001), heart rate (r=-0.158, p<0.001), serum uric acid (r=0.201, p<0.001) and creatinine levels (r=0.190, p<0.001), eGFR (r=-0.105, p=0.007), hemoglobin (r=0.181, p<0.001), hematocrit (r=0.170, p<0.001) and platelet count (r=-0.136, p=0.005). Systolic blood pressure (χ^2=5.453, ß=-0.015, p=0.038), hematocrit (χ^2=5.956, ß=0.076, p=0.045) and eGFR (χ^2=6.765, ß=-0.028, p=0.014) were independent predictors of SCF whereas independent predictors of mean TFC were serum uric acid level (β=0.120, p=0.049) and eGFR (β=-0.470, p=0.048).
Conclusions: These findings suggest that eGFR is independently associated with mean TFC and renal dysfunction might be an independent predictor of the presence of SCF.
Key Words: Atherosclerosis; coronary artery disease; coronary microvasculature; endothelial dysfunction; glomerular filtration rate; slow coronary flow.

Renal disfonksiyonun koroner kan akımı üzerine etkisi

Özet
Giriş: Yavaş koroner akım (YKA) uzun zamandır bilinmektedir ve endotel disfonksiyonu ve epikardiyal koroner arterler ve mikrovasküler yatağın aterosklerozu ile ilişkisi bildirilmiştir. Renal disfonksiyonun, ateroskleroz ve endotel disfonksiyonu üzerine etkili olduğu bildirilmiştir. Bu çalışma ile YKA ve kontrol gruplarında TIMI kare sayısı (TKS) ile ölçülen koroner kan akımı ile renal fonksiyonların ve diğer laboratuar parametrelerinin ilişkisini araştırmayı amaçladık.
Gereç ve yöntem: Design and Methods: Çalışmaya koroner kan akım hızları TKS ile değerlendirilmiş olan 92 YKA ve 562 kontrol olgusu dahil edildi. Tahmini glomerüler filtrasyon hızı (tGFH) Cockcroft-Gault eşitliği ile hesaplandı. TKS ve tGFH ve diğer klinik ve laboratuar parametreler arasındaki ilişki incelendi.
Bulgular: Kontrol ve YKA gruplarının kıyaslanmasında iki grup arasında cinsiyet, sistolik kan basıncı, kalp hızı, serum ürik asit ve kreatinin düzeyleri, hematokrit ve tGFH yönünden istatistiksel anlamlı farklılıklar mevcut idi. Ortalama TKS yaş (r=0.113, p=0.004), cinsiyet (r=0.152, p<0.001), kalp hızı (r=-0.158, p<0.001), serum ürik asit (r=0.201, p<0.001) ve kreatinin düzeyleri (r=0.190, p<0.001), tGFH (r=-0.105, p=0.007), hemoglobin (r=0.181, p<0.001), hematokrit (r=0.170, p<0.001) ve trombosit sayısı (r=-0.136, p=0.005) ile korale idi. Sistolik kan basıncı (χ^2=5.453, ß=-0.015, p=0.038), hematokrit (χ^2=5.956, ß=0.076, p=0.045) ve tGFH (χ^2=6.765, ß=-0.028, p=0.014) YKA varlığının bağımsız prediktörü iken serum ürik asit düzeyi (β=0.120, p=0.049) ve tGFH (β=-0.470, p=0.048) ortalama TKS'nin bağımsız prediktörü idi.
Sonuç: Bu çalışmada elde edilen bulgular tGFH'nin ortalama TKS ile bağımsız ilişkili olduğunu ve renal disfonksiyonun YKA varlığının bağımsız bir belirteci olabileceğini ortaya atmaktadır.
Anahtar Kelimeler: Ateroskleroz; endotel disfonksiyonu; glomerüler filtrasyon hızı; koroner arter hastalığı; koroner mikrovasküler yatak; yavaş koroner akım.

Introduction

Renal dysfunction was shown to be related with accelerated atherosclerosis and poor outcomes mainly determined by cardiovascular events. Since the first report of Lindler et al. [1] revealing accelerated atherosclerosis in long-term maintenance hemodialysis patients, plenty of studies have shown increased risk of atherosclerosis and increased coronary artery disease (CAD) related mortality in patients with renal dysfunction ranging from mild renal impairment to end stage renal failure. The American Heart Association published a Scientific Statement that details the strong evidence supporting that individuals with renal dysfunction should be included in the highest-risk group for cardiovascular disease and therefore receive aggressive preventive measures to reduce the prevalence and severity of cardiovascular disease [2]. Although whether renal dysfunction causes cardiovascular disease or is a marker of cardiovascular disease remains controversial, patients with renal dysfunction clearly have significantly increased cardiovascular morbidity and mortality.

Slow coronary flow (SCF) on coronary angiogram is a well-known clinical entity; however, precise pathophysiologic mechanisms of SCF have not been elucidated. Whatever the mechanism, atherosclerosis of epicardial coronary arteries [3] and microvasculature [4] and endothelial dysfunction [5–9] were reported to be associated with SCF. The Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) is a simple, objective and reproducible clinical tool for assessing coronary blood flow [10]. This technique counts the number of cineangiographic frames from initial contrast opacification of the proximal coronary artery to opacification of distal arterial landmarks.

To our knowledge, there are no published data assessing the impact of renal functions on coronary flow rate. We hypothesized that renal functions may influence coronary blood flow since renal dysfunction was shown to be associated with CAD and endothelial dysfunction. Therefore, in the present study, we aimed to assess the relationship between coronary blood flow by means of TFC and renal functions using estimated glomerular filtration rate (eGFR) measured with Cockcroft-Gault equation [11] in patients with slow SCF compared to cases with normal coronary flow.

Materials and methods

Study population

The study population included 654 patients (mean age=52.4±10.8 years, 314 men and 340 women) with angiographically proven normal (0% stenosis) coronary arteries. We have retrospectively evaluated coronary angiographies, electrocardiographies and laboratory parameters besides medical records regarding details of past medical history and medications and details of physical examination. All patients were selected from individuals who underwent elective coronary angiography in our institution with a suspicion of CAD and diagnosed as having angiographically normal (0% stenosis) coronary arteries. The indications for coronary angiography were the presence of atypical chest pain or typical angina pectoris.

Exclusion criteria included CAD, history of myocardial infarction, presence of ischemia on noninvasive tests, left ventricular dysfunction, left ventricular hypertrophy, atrial fibrillation, valvular, myocardial or pericardial disease. Patients with concomitant inflammatory diseases such as infections and autoimmune disorders, neoplastic diseases, major depression, liver disease, renal dysfunction (serum creatinine>1.5g/dl) and recent major surgical procedure and patients taking nitrates, angiotensin-converting-enzyme inhibitors, diuretics were also excluded from the study.

Baseline definitions and measurements

Hypertension was defined as diastolic blood pressure ≥ 90 mmHg or systolic blood pressure ≥ 140 mmHg or self reported use of antihypertensive drug(s). Diabetes mellitus was diagnosed if the fasting plasma glucose concentration was ≥ 126 mg/dL on two separate occasions, or if the patient was on treatment with insulin or oral hypoglycemic agent(s). Height, weight, waist and hip circumferences were measured according to a standardized protocol. Body mass index was calculated by dividing weight in kilograms by height in meters squared (kg/m^2).

We estimated the creatinine clearance for each participant using the Cockcroft-Gault equation [eGFR= (140 - age) x body mass/72 x creatinine] x 0.85 (in women) which has a correlation coefficient of 0.83 with measured GFR [11].

Evaluation of coronary blood flow

All patients underwent selective coronary angiography with the Judkins technique using the Philips Angioscop Xray (Integris HM3000 Philips Medical Systems, Best, the Netherlands). Two observers blinded to the clinical details of the individual case independently quantified coronary flow objectively using the TFC as previously described [10]. The TFC in the left anterior

descending coronary artery (LAD) and left circumflex artery (LCx) were assessed in a right anterior oblique projection with caudal angulation and the right coronary artery (RCA) was assessed in a left anterior oblique projection with cranial angulation. The number of cineangiographic frames, recorded at 25 frames per second, required for the leading edge of the column of radiographic contrast to reach a predetermined distal landmark is determined. The first frame is defined as the frame in which concentrated dye occupies the full width of the proximal coronary artery lumen, touching both borders of the lumen, and forward motion down the artery. The final frame counted was that in which contrast first reaches the distal predefined landmark branch without necessity of full opacification [10]. These landmarks are as follows [10]: the distal bifurcation of the LAD (i.e., the mustache, pitchfork, or whale's tail) for LAD, the distal branch of the lateral left ventricular wall artery with the longest total distance from the coronary ostium for the LCx, and the first branch of the posterolateral artery for the RCA. If one of these landmarks was not well visualized, another well-visualized landmark close to these landmarks was chosen. Since the normal frame counts for the LAD are 1.7 times greater than the mean for the LCx and the RCA [10], the LAD frame counts were corrected by dividing by 1.7 to derive the corrected TFC [10]. Study participants with a TFC greater than two SDs from the normal published range for anyone of the three vessels (40.6 frames for LAD, 29.8 frames for LCx, 27.3 frames for RCA) were accepted as having SCF [10]. Accordingly, 92 cases were grouped as SCF group and 562 cases were grouped as controls in our study. The mean TFC for each subject was calculated by adding the TFCs for the corrected LAD, LCx, and RCA and then dividing the sum by three.

Assessment of biochemical markers

Laboratory variables assessed, for routine preparation of coronary angiography, on the same day or on the day before coronary angiography were evaluated in the present study. Blood samples were withdrawn following an overnight fasting from cubital vein into blood tubes. Serum was immediately separated from the cells by centrifugation at 3000g for 10 minutes. The levels of uric acid, triglyceride (TG), total cholesterol, HDL-cholesterol, LDL-cholesterol, fasting glucose, urea and creatinine were determined using commercially available assay kits (Abbott, Illinois, USA) with Abbott Aeroset auto-analyzer (Abbott, Illinois, USA).

Statistical Analysis

All analyses were conducted using SPSS 11.5 (SPSS for Windows 11.5, Chicago, IL). Continuous variables were expressed as mean±SD and categorical variables were expressed as percentages. Comparison of categorical and continuous variables between the SCF and control groups was performed using the $\chi 2$ test and independent samples t test, respectively. The correlation between mean TFC and continuous parameters was assessed by the Pearson correlation test whereas the correlation between mean TFC and nominal variables such as gender, hypertension, diabetes mellitus and smoking were evaluated with Point-biserial correlation analysis. In order to determine independent predictors of SCF, multiple logistic regression analysis was performed by including the parameters, which were significantly different between patients with SCF and control cases. Multiple linear regression analysis was performed to identify the independent predictors of mean TFC by including the parameters, which were correlated with mean TFC in bivariate analysis. Standardized β-regression coefficients and their significance from multiple linear regression analysis were reported. A two-tailed $p<0.05$ was considered statistically significant.

Results

Clinical characteristics of the study population

The clinical characteristics, laboratory parameters and TFC values of SCF and control groups were presented on Table 1. Age, frequncy of hypertension, diabetes mellitus and cigarette smoking, body mass index, waist and hip circumferences, diastolic blood pressure, lipid profiles, levels of fasting glucose and urea, hemoglobin, leukocyte and platelet counts were not different among the SCF and control groups. Frequency of male subjects, heart rate, serum levels of uric acid and creatinine, hematocrit were significantly higher in the SCF group compared to controls whereas systolic blood pressure and eGFR were significantly lower in the SCF group than in the control group (Table 1). Independent predictor(s) of SCF were determined with multiple logistic regression analysis by including gender, systolic blood pressure, heart rate, serum levels of uric acid and creatinine, eGFR, hematocrit into the model. Systolic blood pressure (χ^2=5.453, ß=-0.015, p=0.038), hematocrit (χ^2=5.956, ß=0.076, p=0.045) and eGFR (χ^2=6.765, ß=-0.028, p=0.014) were independent predictors of SCF.

TIMI frame count of the study population

Slow coronary flow was present in LAD in 76 patients, in RCA in seven patients, in LAD and RCA in four patients, in LAD and LCx in two

patients, in LCx and RCA in one patient and in LAD, LCx and RCA in two patients. The TFC for all epicardial coronary arteries and mean TFC were significantly higher in the SCF group than in the control group ($p<0.001$ for all, Table 1). Interobserver and intraobserver variability for determination of TFC were 5% and 3% respectively. Relationship between mean TFC and clinical characteristics and laboratory data was presented on Table 2. The mean TFC was positively correlated with age, male gender, serum uric acid and creatinine levels, hemoglobin level and hematocrit ($p<0.05$ for all, Table 2). Additionally, the mean TFC was inversely correlated with heart rate, eGFR (Figure 1) and platelet count in bivariate analysis (Table 2). In order to determine independent predictors of mean TFC, a stepwise linear regression analysis was performed by including parameters that were correlated with the mean TFC in bivariate analysis. Serum uric acid level ($\beta=0.120$, $p=0.049$) and eGFR ($\beta=-0.470$, $p=0.048$) were independent predictors of the mean TFC (Table 2).

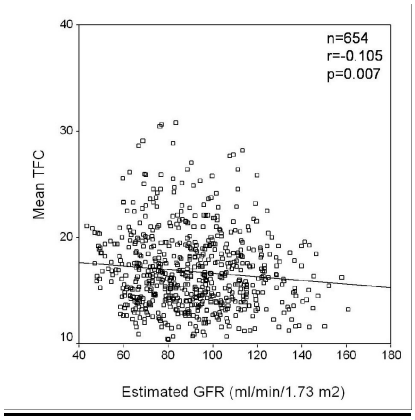

Figure 1
Graph demonstrating significant negative correlation -of moderate degree- between the mean Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) and estimated glomerular filtration rate (eGFR) (Pearson correlation coefficient [r]=-0.105, p=0.007). Multifactorial nature of coronary blood flow and exclusion of cases with evident renal dysfunction (serum creatinine>1.5mg/dL) might be the basis of the moderate degree of correlation. By any means whatsoever this graph implies that the impairment in renal functions might be the harbinger of impaired coronary blood flow.
Abbreviations: GFR: glomerular filtration rate, TFC: Thrombolysis in Myocardial Infarction (TIMI) frame count.

Table 1. Baseline clinical and laboratory characteristics of SCF and control groups

	Control group n = 562 (%)	SCF group n = 92 (%)	p Value
Clinical and Hemodynamic data			
Age (years)	52.3±10.9	53.5±10.8	0.343
Sex (Male/Female)	262/300	52/40	0.049
Hypertension [n (%)]	222 (39.5%)	36 (39.1%)	0.946
Diabetes Mellitus [n (%)]	78 (13.9%)	11 (12%)	0.618
Cigarette smoking [n (%)]	172 (30.6%)	35 (38.0%)	0.155
Body Mass Index (kg/m²)	26.2±4.6	25.7±4.6	0.356
Waist circumference (m)	0.94±0.11	0.94±0.11	0.816
Hip circumference (m)	0.88±0.11	0.89±0.10	0.427
Waist/hip ratio	1.07±0.09	1.06±0.06	0.193
Systolic Blood Pressure (mmHg)	132.5±24 .6	125.8±23.8	0.023
Diastolic Blood Pressure (mmHg)	77.4±12.4	74.7±13.8	0.072
Heart rate (beats/min)	80.0±11.7	76.1±11.1	0.006
Biochemical and hematological data			
Total cholesterol (mmol/L)	4.8±1.1	4.9±1.3	0.534
LDL cholesterol (mmol/L)	2.9±1.0	2.8±0.8	0.571
HDL cholesterol (mmol/L)	1.0±0.3	1.0±0.2	0.186
Triglyceride (mmol/L)	1.9±1.2	2.1±1.4	0.197
Fasting glucose (mg/dL)	114.7±47.1	111.3±52.7	0.516
Uric acid (mg/dL)	4.7±1.5	5.2±1.5	0.022
Urea (mg/dL)	35.0±13.2	37.7±22.2	0.117
Creatinine (mg/dL)	.87±.18	.94±.18	0.001
Estimated GFR (mL/min/1.73m^2)	91.6±22.9	85.2±18.3	0.01
Hemoglobin (g/dL)	13.8±1.6	14.2±1.4	0.098
Hematocrit (%)	39.4±4.6	41.2±7.0	0.01
WBC (/mL)	8186±2334	8326±1893	0.653
Platelets (/μL)	277.5±71.2	272.6±80.7	0.624
TFC			
LAD	28.0±5.7	45.0±6.9	<0.001
LAD*	16.5±3.3	26.5±4.1	<0.001
LCx	15.9 ±3.1	22.2±4.6	<0.001
RCA	15.1±3.0	20.3±5.8	<0.001
Mean TFC	15.8 ±2.6	23.0 ±3.0	<0.001

Abbreviations: GFR: glomerular filtration rate; HDL: high-density lipoprotein; LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; LDL: low-density lipoprotein; RCA: right coronary artery; SCF: slow coronary flow; TFC: TIMI frame count; WBC: white blood cells.
*Corrected TFC of LAD.

Table 2. Relationship between mean The Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) and clinical and laboratory parameters

	Correlation coefficient	*p* value	β regression coefficient[a]	*p* value
Age (years)[b]	0.113	0.004	-0.028	0.811
Sex (Male/Female)[c]	0.152	0.0001	0.143	0.159
Hypertension[c]	0.010	0.798		
Diabetes Mellitus[c]	-0.045	0.25		
Cigarette smoking[c]	0.066	0.091		
Body Mass Index (kg/m²)[b]	-0.004	0.921		
Waist circumference (m)[b]	0.062	0.141		
Hip circumference (m)[b]	0.063	0.138		
Waist/hip ratio[b]	0.010	0.821		
Systolic BP (mmHg)[b]	-0.062	0.133		
Diastolic BP (mmHg)[b]	-0.020	0.628		
Heart rate (beats/min)[b]	-0.158	<0.001	-0.087	0.076
Total cholesterol (mmol/L)[b]	-0.015	0.721		
LDL cholesterol (mmol/L)[b]	-0.079	0.099		
HDL cholesterol (mmol/L)[b]	-0.037	0.419		
Triglyceride (mmol/L)[b]	0.046	0.277		
Fasting glucose (mg/dL)[b]	0.038	0.397		
Uric acid (mg/dL)[b]	0.201	<0.001	0.120	0.049
Urea (mg/dL)[b]	0.068	0.083		
Creatinine (mg/dL)[b]	0.190	<0.001	0.189	0.319
Estimated GFR (mL/min/1.73m²)[b]	-0.105	0.007	-0.470	0.048
Hemoglobin (g/dL)[b]	0.181	<0.001	0.058	0.445
Hematocrit (%)[b]	0.170	<0.001	0.069	0.334
WBC (/mL)[b]	0.047	0.326		
Platelets (/μL)[b]	-0.136	0.005	-0.069	0.167

Abbreviations: BP: blood pressure; GFR: glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; WBC: white blood cells.

[a]From multiple linear regression analysis.

[b]From Pearson correlation analysis.

[c]From Point-biserial correlation analysis.

Discussion

The data of this study reveal, for the first time in the literature, that patients with SCF have significantly lower eGFR compared to subjects with normal coronary flow and eGFR is significantly and inversely correlated with mean TFC. Significant association between eGFR and coronary blood flow even in a study population without evident renal dysfunction (serum creatinine≤1.5g/dl) might suggest that the renal dysfunction would have great impact on coronary blood flow.

Impaired endothelial integrity, an early finding of atherosclerosis, was shown with findings of diffuse intimal thickening, calcification of the coronary vessel wall, and atheroma not leading to luminal irregularities in the coronary arteries on intra vascular ultrasound (IVUS) in patients with SCF [3]. Impaired renal functions might be the indicator of the presence of early atherosclerosis in the coronary circulation in the absence of gross atherosclerotic findings on coronary angiography in patients with SCF, in the present study, as the association between impaired renal functions and the presence and the severity of atherosclerosis was reported in previous studies. Impaired renal functions was reported to be associated with carotid artery intima media thickness [12,13], carotid artery plaque burden [13], peripheral arterial disease [14], coronary artery calcification [15] and occurence, extent and severity of coronary artery disease [16–20] especially in women [21–23]. Several pathophysiological mechanisms associated with the development of atherosclerosis such as increased oxidative stress and inflammation [24], insulin resistance [25], increased serum homocysteine levels [26], increased levels of asymmetric dimethylarginine [27], alterations in lipids and lipoproteins [28], and increase in serum lipoprotein(a) [29] have been elucidated during the course of renal dysfunction. Although the nature of vascular involvement with prominent thickening and calcification of the tunica media [30] in renal dysfunction is quite dissimilar to atherosclerotic process, renal dysfunction has significant impact on atherosclerosis and findings of the present study indicates the role of renal dysfunction on the early phase of coronary atherosclerosis.

Renal dysfunction was reported to be independently associated with the increased increased risk of death and cardiovascular events in previous large scale studies such as Valsartan in Acute Myocardial Infarction Trial (VALIANT) [31], the Studies of Left Ventricular Dysfunction (SOLVD) [32], and Survival and Ventricular Enlargement (SAVE) trials [33] beyond its significant association with the presence and the severity of CAD. Renal dysfunction was also shown to be independently associated with increased risk of death and cardiovascular events in patients with previous myocardial infarction

[34], and in patients undergoing percutaneous coronary intervention [35,36], coronary artery bypass grafting [37] and endovascular abdominal aortic aneurysm repair [38].

Endothelial dysfunction might be regarded as a major determinant of coronary blood flow based on the previous studies revealing increased markers of endothelial dysfunction such as homocysteine [6], uric acid [7], asymmetric dimethylarginine [8], C-reactive protein and interleukin-6 [9] in patients with SCF and by demonstrating significant correlation between increased TFC and increased levels of above-mentioned markers of endothelial dysfunction. Significantly reduced eGFR in cases with SCF and significant correlation between the eGFR and the mean TFC besides the independent relationship between serum uric acid level and both mean TFC and the presence of SCF might suggest endothelial dysfunction linked impact of renal dysfunction on coronary blood flow. Previous studies reporting the presence of endothelial dysfunction with markers of endothelial dysfunction such as hyperhomocysteinemia and hyperuricemia [26], increased levels of asymmetric dimethylarginine [27] and increased levels of inflammatory markers like C-reactive protein, fibrinogen, interleukin-6 [39] support our hypothesis. Impaired brachial artery flow mediated dilatation might represent another endothelial dysfunction based pathophysiological link between SCF and renal dysfunction since it is a common feature of both SCF [5] and renal dysfunction [40].

Coronary microvasculature, with small diameter and well-developed media, plays key role in regulation of coronary blood flow by controlling coronary vascular resistance [41] and atherosclerosis and dysfunction of coronary microvasculature is a well-known pathophysiologic mechanism of SCF [4] Coronary flow reserve, a non-invasive marker of coronary microvascular function, was reported to be impaired in patients with SCF and corrected TFC was correlated with coronary flow reserve [42]. Coronary microvascular dysfunction might be another pathophysiological mechanism of SCF development during the course of renal failure since impaired coronary flow reserve was reported in experimental acute renal failure [43], in mild renal insufficiency [44], in diabetic patients with end stage renal failure [45] and in hemodialysis patients [46].

Several limitations of this study should be concerned. We have used Cockcroft-Gault equation for determination of eGFR in the present study. Although previous reports have shown high accuracy and reliability of this equation in assessing GFR, assessment of GFR with 24-hour urine analysis would provide better GFR measurements.

Angiographic diagnosis of normal coronary arteries relies on axial contrast angiograms of the vessel lumen, which might underestimate the presence of atherosclerotic plaque [47]. Currently the IVUS provides accurate assessment of vessel lumen and wall for the presence and distribution of atherosclerosis [48]. Although IVUS is more sensitive technique than coronary angiography for detecting coronary atherosclerosis, we could not have the opportunity to perform IVUS in this study. Prior studies have shown that the heart rate, nitrate use and the coronary catheter size have effects on the frame count [49]. In the present study, coronary catheter size was the same in all participants and cases using nitrates were excluded from the study. Heart rate was lower in patients with SCF than in cases with normal coronary blood flow, and heart rate was correlated with mean TFC in bivariate analysis in our study supporting the previous findings [49]. However relationship between eGFR and mean TFC and the presence of SCF was independent from heart rate.

Study population continued taking previously prescribed medications before entry into the study. However, two groups did not differ with regard to the baseline medications, and no association was observed between these drugs and renal functions and mean TFC (data not shown).

In conclusion, though the underlying mechanism (s) of SCF is unknown, increased TFC of these patients suggests endothelial and/or microvascular regulation of coronary blood flow is impaired, and reduced eGFR may be a laboratory marker of SCF. However, further clinical studies are needed to clarify the physiopathological role of renal functions in regulation of coronary blood flow.

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