ORIGINAL ARTICLE

Coronary slow flow phenomenon and microalbuminuria: Is there any relationship?

Koroner yavaş akım fenomeni ve mikroalbüminüri: Herhangi bir ilişki var mı?

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ABSTRACT

Objective: The pathophysiology of coronary slow flow phenomenon (CSFP) is poorly understood. Evidence suggesting endothelial dysfunction in patients with slow coronary flow (SCF) led to this evaluation of a possible correlation between microalbuminuria (MAU), as an indicator of endothelial dysfunction, and CSFP in order to investigate a mutual pathophysiology.

Methods: In this case-control study, 15786 patients who presented between September 2016 and April 2018 were screened. All patients with CSFP had chest pain and coronary angiography was indicated due to a positive noninvasive test. All cases had a Thrombosis in Myocardial Infarction (TIMI) flow grade of 2 or a corrected TIMI frame count of >27 without any evidence of obstructive coronary artery disease. The patients used as controls had completely normal coronary angiograms. Fasting mid-stream urine samples were analyzed using an immunoturbidimetric assay to determine the albumin-creatinine ratio (ACR) as a surrogate of microalbuminuria (MAU) (ACR: 30–300 mg/g). The prevalence of MAU in the case and control groups was analyzed.

Results: A total of 154 individuals with a normal coronary angiogram and 46 patients with SCF were enrolled in the study. The prevalence of MAU was greater in patients with SCF than in the control group (8.7% vs 1.9%, respectively; p=0.048). Even after adjustment for major risk factors, the association between MAU and CSPF remained significant.

Conclusion: The results of this study indicated that there was a relationship between MAU and CSFP and confirmed that endothelial dysfunction is a contributing factor to CSFP. These findings are of utmost importance due to the prognostic value of MAU for both all-cause and cardiovascular mortality rates.

ÖZET

Amaç: Koroner yavaş akım fenomeninin fizyopatolojisi (KYAF) pek anlaşılmamıştır. KYAF olan hastalarda endotel disfonksiyonunu düşündüren kanıtlar bizi ortak fizyopatolojiyi aydınlatmak için endotel disfonksiyonunun bir göstergesi olan mikroalbüminüri (MAÜ) ile KYAF arasındaki ilişkiyi değerlendirmeye teşvik etti.

Yöntemler: Bu olgu kontrollü çalışmada Eylül 2016 ile Nisan 2018 arasında 15786 hasta tarandı. Tüm KYAF hastalarında göğüs ağrısı olup pozitif noninvaziv test nedeniyle koroner anjiyografi endikasyonu vardı. Hepsinde TIMI akım derecesi 2 veya düzeltilmiş TIMI kare sayısı >27 olup tıkayıcı koroner arter hastalığı kanıtı mevcut değildi. Kontrol grubunun koroner anjiyogramları tamamen normaldi. MAÜ'nün (AKO 30–300 mg/g) göstergesi olarak albümin kreatinin oranını (AKO) belirlemek için aç kalmış hastaların orta akım idrarları immünoturbidimetrik yöntemle analiz edildi. Olgu ve kontrol gruplarında MAÜ prevalansı karşılaştırıldı.

Bulgular: Koroner anjiyogramı normal 154 kontrol olgusu ve KYAF olan 46 hasta çalışmaya alındı. Kontrol grubuna göre KYAF olanlarda MAÜ prevalansı daha yüksekti (%1.9'a ve %8.7, p=0.048). Majör risk faktörleri için düzeltmeler yapıldıktan sonra bile MAÜ ile KYAF arasındaki ilişki anlamlı derecedeydi.

Sonuç: Çalışmamız MAÜ ile KYAF arasında ilişki olduğunu göstermiş ve endotel disfonksiyonunun KYAF'ye katkıda bulunduğunu doğrulamıştır. Hem tüm nedenli hem de kardiyovasküler mortalite açısından MAÜ'nün prognostik değeri nedeniyle bu bulgu son derece önemlidir.

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Coronary slow flow phenomenon (CSFP) was first described more than 4 decades ago in 6 patients who underwent coronary angiography (CAG) due to symptoms of acute coronary syndrome (ACS). It was characterized by the visibly decreased flow rate of contrast material in 1 or more coronary arterial bed during CAG despite no coronary stenosis justifying the slowed flow.[1,2] Since then, it has been defined quantitatively in most studies by assessing the Thrombolysis in Myocardial Infarction (TIMI) flow grade[3] or corrected TIMI frame count (CTFC).[4] It should be noted that secondary causes of coronary slow flow, e.g., valvular diseases, coronary artery spasm and ectasia, connective tissue disorders, and heart failure, must be excluded before a decisive diagnosis of CSFP can be made.[2,5]

The incidence of CSFP among patients undergoing CAG is 1%[6] to 5.5%.[7] This phenomenon is of paramount clinical importance due to recurrent angina, unnecessary hospital admissions, prolongation of QT interval, and life-threatening ventricular arrhythmias.[8–10]

Studies have shown that CSFP is associated with endothelial dysfunction.[11–19] Furthermore, a correlation between microalbuminuria (MAU) and endothelial dysfunction has been reported in the literature.[20–22] Therefore, it was hypothesized that there may be an association between CSFP and MAU. The aim of this study was to evaluate a possible correlation between MAU, as an indicator of endothelial dysfunction, and CSFP in order to investigate a mutual pathophysiology.

METHODS

Study design and population

This was a case-control study conducted in the Tehran Heart Center, a referral hospital in Iran.[23] The protocol of the study was approved by the research ethics committee of Tehran University of Medical Sciences (approval ID: IR.TUMS.MEDICINE.REC.1397.115). A total of 15786 patients who presented between September 2016 and April 2018 were screened for enrollment. All of the patients had chest pain and CAG was indicated due to a positive noninvasive test, such as an exercise stress test, stress echocardiography, or myocardial perfusion imaging. The cases included were patients with a TIMI-2 flow grade or a CTFC of >27 without any evidence of obstructive coronary artery disease (CAD). The controls had completely normal coronary angiograms. Coronary ectasia, history of myocardial infarction (MI) or percutaneous coronary intervention, presentation with ACS symptoms, diabetes mellitus, hypertension, non-sinus rhythm observed on electrocardiogram, congenital heart disease, chronic obstructive pulmonary disease, chronic systemic disease, fever or active infection, renal insufficiency [glomerular filtration rate (GFR) <90 mL/minute] or protein-losing nephropathies, albumin-creatinine ratio (ACR) >300 mg/g, neoplasms, or the consumption of alcohol or antioxidant drugs were exclusion criteria. In addition, all of the study patients underwent echocardiography and individuals with evidence of left ventricular hypertrophy, an ejection fraction <50% or diastolic dysfunction of more than grade 1, moderate to severe valvular heart disease, or cor pulmonale were excluded. The prevalence of MAU in the case and the control groups was compared. All of the participants were informed about the study and granted consent for the appropriate use of data.

Abbreviations:

ACS	*Acute coronary syndrome*
ACR	*Albumin-creatinine ratio*
CAD	*Coronary artery disease*
CAG	*Coronary angiography*
CTFC	*Corrected TIMI frame count*
CSFP	*Coronary slow flow phenomenon*
GFR	*Glomerular filtration rate*
MAU	*Microalbuminuria*
MI	*Myocardial infarction*
SCF	*Slow coronary flow*
TIMI	*Thrombolysis in Myocardial Infarction*

Coronary angiography

CAG was performed based on the Seldinger technique. Every single coronary artery was imaged with at least 4 views on the left and 2 on the right. The coronary artery flow was studied by an expert clinician who was blinded to the patients' clinical data. The TIMI frame count and the CTFC were calculated for the left and right coronary arteries (left anterior descending, left circumflex, and right coronary artery).

Urine analysis

A fasting mid-stream urine sample was collected and analyzed using an immunoturbidimetric assay (Cobas Integra 400 analyzer; Roche Diagnostics, GmbH, Risch-Rotkreuz, Switzerland). MAU was defined as an albumin-creatinine ratio (ACR) of 30-300 mg/g, and a quantitative measurement of urine albumin was performed.

Statistical analysis

The final data were analyzed using IBM SPSS Statistics for Windows, Version 23 (IBM Corp., Armonk, NY, USA). Normal distribution of data was evaluated with the Shapiro-Wilk test. Summary statistics of the quantitative variables without normal distribution and qualitative variables were shown as median (interquartile range) and number (proportion), respectively. Continuous variables with a skewed distribution were compared between 2 groups using the Mann-Whitney U test. A chi-square test or Fisher's exact test was employed for comparisons between 2 categorical variables. A p value <0.05 was considered significant.

RESULTS

After the exclusion of ineligible participants, 154 individuals with a normal coronary angiogram and 46 patients with SCF were enrolled. The baseline characteristics of both groups are depicted in Table 1. The case and control group participants were not statistically significantly different in age, sex, or GFR (Table 1). The distribution of age, CTFC, ACR, and GFR was not normal among the participants (All p<0.005 with the Shapiro-Wilk test). Therefore, nonparametric tests were used for comparisons.

The prevalence of MAU was greater in patients with SCF than in the control group: 8.7% vs 1.9%, respectively (p=0.048). Moreover, a statistically significant difference was found between the 2 groups in the mean ACR (Table 1).

Unadjusted and adjusted associations based on age, sex, and GFR between MAU and CSFP were evaluated. A logistic regression model using a backward likelihood ratio procedure was fitted to the data in order to predict MAU based on CSFP, age, gender, and GFR. Even after adjustment for important factors, the association between MAU and CSPF remained significant (Table 2).

Table 1. Baseline characteristics of the participants

	Coronary slow flow group (n=46)	Normal coronary group (n=154)	*p*
MAU-Number (Proportion), n (%)	4 (8.7)	3 (1.9)	0.048†
Age (years) -Median (IQR)	52.0 (13.0)	48.0 (14.0)	0.584‡
Sex –Number (Proportion), n (%)			
Male	30 (65.2)	84 (54.5)	0.266¥
Female	16 (34.8)	70 (45.5)	
CTFC (frames/second) - Median (IQR)	33.0 (7.0)	22.0 (6.0)	<0.001‡
ACR (mg/g) - Median (IQR)	5.0 (7.5)	4.0 (2.0)	0.010‡
GFR (mL/min) - Median (IQR)	93.0 (6.0)	93.0 (4.5)	0.809‡

†Fisher's exact test; ‡Mann-Whitney U test; ¥Continuity corrected chi-square test. ACR: Albumin-creatinine ratio; CTFC: Corrected Thrombolysis in Myocardial Infarction frame count; GFR: Glomerular filtration rate; IQR: Interquartile range; MAU: Microalbuminuria.

Table 2. Logistic regression analysis for prediction of microalbuminuria

	Variable univariate analysis†		Multivariate analysis†	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Coronary slow flow phenomenon	5.073 (0.908–28.351)	0.064	5.442 (1.102–26.872)	0.038
Age (years)	1.151 (0.995–1.332)	0.059	1.166 (1.007–1.350)	0.040
Sex	0.876 (0.134–5.714)	0.890	–	–
Glomerular filtration rate (mL/min)	0.824 (0.593–1.144)	0.247	–	–

†Backward logistic regression procedure. CI: Confidence interval; OR: Odds ratio.

DISCUSSION

The results of this study demonstrated an association between MAU, an indicator of endothelial dysfunction, and CSFP.

The pathophysiology of CSFP is poorly understood. Studies of cerebral blood flow velocity,[24] aortic distensibility,[25] and systemic atherosclerosis[26] in patients with CSFP have suggested that there is a systemic underlying pathology. There is evidence that endothelial function is disturbed in patients with SCF.[11–19] Histological studies of endomyocardial biopsies have reported evidence of endothelial dysfunction and microvascular pathology in the CSFP setting.[16] Investigators have reported that endothelium-dependent flow-mediated vasodilation is impaired in patients with SCF; however, nitroglycerin-induced endothelium-independent vasodilation was not deranged in these individuals.[11–15] In addition to arterial endothelial dysfunction, Signori et al.[12] observed that endothelium-dependent venodilation was also impaired in this population. These patients had an increased plasma level of asymmetric dimethylarginine,[11] endothelin-1,[17] and homocysteine,[18,19] and a decreased nitric oxide level in plasma[14,17] in comparison with individuals with normal coronary flow, all of which suggests that endothelial function is impaired in patients with SCF.

Yudkin et al.[27] first demonstrated an association between MAU, CAD, and peripheral vascular disease in non-diabetic individuals in 1988. Further studies demonstrated that MAU is associated with CAD[22,28,29] and endothelial dysfunction[20–22] regardless of diabetes mellitus, yet MAU has not been evaluated in patients with SCF. In comparison with other indicators of endothelial dysfunction, MAU has prognostic implications and more clinical significance. There is strong evidence showing that MAU is correlated with all-cause and cardiovascular mortality rates in patients with MI[30,31] and in the general population.[32,33]

To the best of our knowledge, this is the first study dedicated to determining a relationship between MAU and CSFP; however, it has several limitations, including a small sample size, and a small number of patients with MAU in both the case and control groups. We believe that further studies in the future addressing these weaknesses will help to further determine the role of MAU in CSFP.

Our study results indicated that MAU was associated with CSFP and confirmed endothelial dysfunction as a contributing factor to CSFP; however, our finding is of utmost importance due to the prognostic value of MAU in both all-cause and cardiovascular mortality rates.

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