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Usefulness of soluble endothelial protein C receptor combined with left ventricular global longitudinal strain for predicting slow coronary flow: A case-control study

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Abstract

Background: *Slow coronary flow (SCF) is an angiographic entity characterized by delayed coronary opacification without an evident obstructive lesion in the epicardial coronary artery. However, patients with SCF have decreased left ventricular (LV) global longitudinal strain (GLS). SCF is associated with inflammation, and soluble endothelial protein C receptor (sEPCR) is a potential biomarker of inflammation. Therefore, under evaluation herein, was the relationship between SCF and sEPCR and the predictive value of sEPCR and LV GLS for SCF was investigated.*

Methods: *Twenty-eight patients with SCF and 34 controls were enrolled. SCF was diagnosed by the thrombolysis in myocardial infarction frame count (TFC). The plasma level of sEPCR was quantified using enzyme-linked immunosorbent assay. LV GLS was measured by two-dimensional speckle-tracking echocardiography.*

Results: *Plasma sEPCR was significantly higher in patients with SCF than in controls and was positively correlated with the mean TFC ($r = 0.67$, $p < 0.001$) and number of involved vessels ($r = 0.61$, $p < 0.001$). LV GLS was decreased in patients with SCF compared to that in controls. sEPCR level (OR = 3.14, 95% CI 1.55–6.36, $p = 0.001$) and LV GLS (OR = 1.44, 95% CI 1.02–2.04, $p = 0.04$) were independent predictors of SCF. sEPCR predicted SCF (area under curve [AUC]: 0.83); however, sEPCR > 9.63 ng/mL combined with LV GLS > −14.36% demonstrated better predictive power (AUC: 0.89; sensitivity: 75%; specificity: 91%).*

Conclusions: *Patients with SCF have increased plasma sEPCR and decreased LV GLS. sEPCR may be a useful potential biomarker for SCF, and sEPCR combined with LV GLS can better predict SCF.*
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Key words: slow coronary flow, endothelial protein C receptor, global longitudinal strain, left ventricle

Introduction

Slow coronary flow (SCF) is an angiographic phenomenon characterized by delayed coronary opacification with normal or near-normal epicardial coronary arteries, which is different from the delay observed in other pathological conditions, such as acute myocardial infarction stenting, coronary

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artery ectasia, or myocardial dysfunction [1, 2]. Although SCF is only observed in 1–7% of patients undergoing coronary angiography because of suspected cardiovascular disease, it has been associated with recurrent chest pain, repeat coronary angiography, life-threatening arrhythmias, and even sudden cardiac death [3–5]. Therefore, patients with SCF should be closely monitored for any abnormalities.

Slow coronary flow has been reported to be related to clinical cardiovascular events, which significantly hamper the patient's quality of life [5]. Moreover, although there are no evident obstructive lesions in the epicardial coronary artery, several investigators have observed fibromuscular hyperplasia, medial hypertrophy, endothelial edema, thickening, and coronary microvessel degeneration in biopsy samples of patients with SCF [3]. However, because the precise pathophysiological mechanisms of SCF have not yet been elucidated, no standard and effective treatment approach exists for this condition. Therefore, it is vital to study the pathogenesis and pathophysiological processes involved in SCF, and, furthermore, identify novel biomarkers and therapeutic targets to halt disease progression in SCF.

Currently, the thrombolysis in myocardial infarction frame count (TFC) method using coronary angiography remains the only effective and accurate tool for the diagnosis and assessment of SCF [6]. However, due to its invasiveness and high cost, this method does not permit long-term follow-up and dynamic treatment evaluation. Therefore, an inexpensive, simple, and feasible alternative for SCF detection is warranted.

A previous study assessed left ventricular (LV) myocardial systolic function by noninvasive and inexpensive echocardiography and demonstrated that patients with SCF have decreased LV global longitudinal strain (GLS) [7]. Therefore, it was hypothesized that analyzing LV GLS may be an effective approach for predicting SCF.

Although several previous studies have hypothesized that inflammation, early-stage coronary atherosclerosis, endothelial dysfunction, or microvascular reserve anomalies may contribute to the etiopathogenesis of SCF, a clear pathophysiological mechanism has not been demonstrated, and a precise biomarker of SCF remains unknown [8, 9]. It has been reported that inflammation may be a major factor in many cardiovascular events, and may be associated with coronary artery disease. In the past few years, numerous studies have reported on the role of inflammation in SCF [10–12]. Therefore, it was further hypothesized that inflammation is involved in the development of SCF.

Endothelial protein C receptor (EPCR) is a 46-kDa, type 1 transmembrane glycoprotein, which has been observed in high concentrations in the endothelial membranes of the aorta, heart, and lungs. Soluble EPCR (sEPCR) is a molecule generated at the endothelial surface by cleavage of the extracellular portion of the protein C receptor, particularly due to inflammation, and has been suggested to be a potential biomarker of inflammation [13]. Elevated sEPCR levels are associated with the presence of coronary artery disease and myocardial infarction [14]. However, no study has, as yet, investigated the relationship between sEPCR levels and SCF.

Therefore, the aim of this study was to evaluate the correlation between sEPCR and SCF and investigate the predictive value of sEPCR and LV GLS for SCF.

Methods

Study population

This is a case-controlled study of the Department of Cardiology at the documented hospital between January 2018 and November 2018. Patients with normal or near-normal (less than 40% stenosis) epicardial coronary arteries were consecutively included in this study when coronary angiography was performed to determine the presence of obstructive coronary artery disease because of typical angina, coronary risk factors, or abnormal electrocardiography changes. Exclusion criteria were as follows: coronary artery spasm or ectasia; a previous history of myocardial infarction; LV ejection fraction (EF) $< 52\%$ in males or $< 54\%$ in females; abnormal heart structure (valvular dysfunction, cardiomyopathies, or congenital heart disease); pericardial effusion; any arrhythmia (atrioventricular conduction abnormalities, bundle branch block, ventricular pre-excitation, atrial fibrillation, or paced rhythm); uncontrolled hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 105 mmHg); hyperthyroidism or hypothyroidism; malignancy; autoimmune disease; infection; pulmonary, hepatic, or renal disorder; hematological disorder; positive results on an exercise test (to distinguish SCF from syndrome X), and poor echocardiographic images.

Based on the TFC, patients were divided into two groups: (1) the SCF group, with TFC > 27 in one or more vessels, and (2) the control group, with TFC ≤ 27 in all vessels [6]. Patients with in-

calculable TFC or any hemodynamic changes that might affect the TFC during coronary angiography were also excluded from the study.

All examinations were performed by investigators who were blinded to the clinical status of the patients. Written informed consent was obtained from all patients before enrollment. The study protocol was approved by the China Medical University Ethics Committee, and was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

Blood evaluations

Peripheral venous blood samples were obtained from a forearm vein after at least 12 hours of overnight fasting before coronary angiography. Routine blood tests were performed as routine procedures in the Laboratory Department of the hospital. The red blood cell count, red cell distribution width, platelet count, and platelet distribution width were analyzed using a Beckman Coulter LH 780 analyzer (Miami, FL, USA). Triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and fasting blood glucose were analyzed using a Siemens ADVIA 2400 analyzer (Tarrytown, NY, USA). The serum sEPCR level was measured by using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Lanji Biotech, Shanghai, China), in accordance with the manufacturer's instructions.

Coronary angiography and TFC calculation

Coronary angiography was performed using the General Electric Innova 3100 (Milwaukee, WI, USA). A femoral approach was used, with the standard Judkins technique and multiple angulated views. Iohexol (350/100 mL) was used as a contrast agent and was manually injected intravenously at the same rate of 3–4 mL/s for the left coronary artery and 2–3 mL/s for the right coronary artery (RCA). The same contrast medium was used in all patients.

In accordance with the method first described by Gibson et al. [6], the flow rate of each major coronary artery was quantitatively evaluated by TFC, including the left anterior descending artery (LAD), left circumflex coronary artery (LCx), and RCA. TFC, recorded at 30 frames per second, was the number of frames from the time (in seconds) at which the contrast medium filled > 70% the proximal coronary artery lumen to the time at which it reached the distal end. The distal end was defined as the distal bifurcation for the LAD, the distal bifurcation of the segment with the longest total distance for the LCx, and the first branch of the posterolateral artery for the RCA.

The TFC was assessed by two separate cardiologists and any disagreement was resolved by a third observer. Since the LAD is usually longer than are the LCx and RCA, the TFC of the LAD was divided by 1.7 to obtain the corrected TFC of the LAD (cLAD). The mean TFC for each patient was calculated by averaging of the TFCs for the RCA, LCx, and cLAD.

Echocardiography

A standard echocardiographic examination was performed using a Vivid E9 ultrasound system (GE Healthcare, Waukesha, WI, USA) equipped with a M5S phased-array probe within 72 hours after coronary angiography. Standard two-dimensional cine loops were recorded for offline analysis using an EchoPAC work station (GE Healthcare).

In accordance with the recommendations of the American Society of Echocardiography [15], the LVEF (by the biplane modified Simpson method), left atrial (LA) volume index, mitral E, mitral A, and mitral average e' were measured. Further, mitral E/A and mitral average E/e' were calculated. Two-dimensional speckle-tracking echocardiography (STE) was performed in accordance with the common standard from the consensus document of the EACVI/ASE/Industry Task Force [16]. LV GLS was obtained by averaging the end-systolic strains of all LV myocardial segments.

Statistical analysis

All statistical analyses were performed using the SPSS 17.0 software package (SPSS version 17, SPSS Inc., Chicago, IL). Data are presented as the mean ± standard deviation (SD) for continuous variables and as the frequency (percentage) for categorical variables. For independent-samples, the Student t-test was used to evaluate differences in continuous variables between the two groups. Categorical variables were compared using the χ^2 or Fisher exact test, as appropriate. The Spearman or Pearson correlation coefficients were obtained, as appropriate. Least squares linear regression was used to evaluate univariable and multivariable correlation with plasma sEPCR level. An enter multivariate logistic regression analysis was performed to identify independent predictors of SCF; results are expressed as the odds ratio (OR) and 95% confidence interval (CI). Receiver operating characteristic curve (ROC) analyses were performed to evaluate the diagnostic effects distinguishing patients with and without CSF and

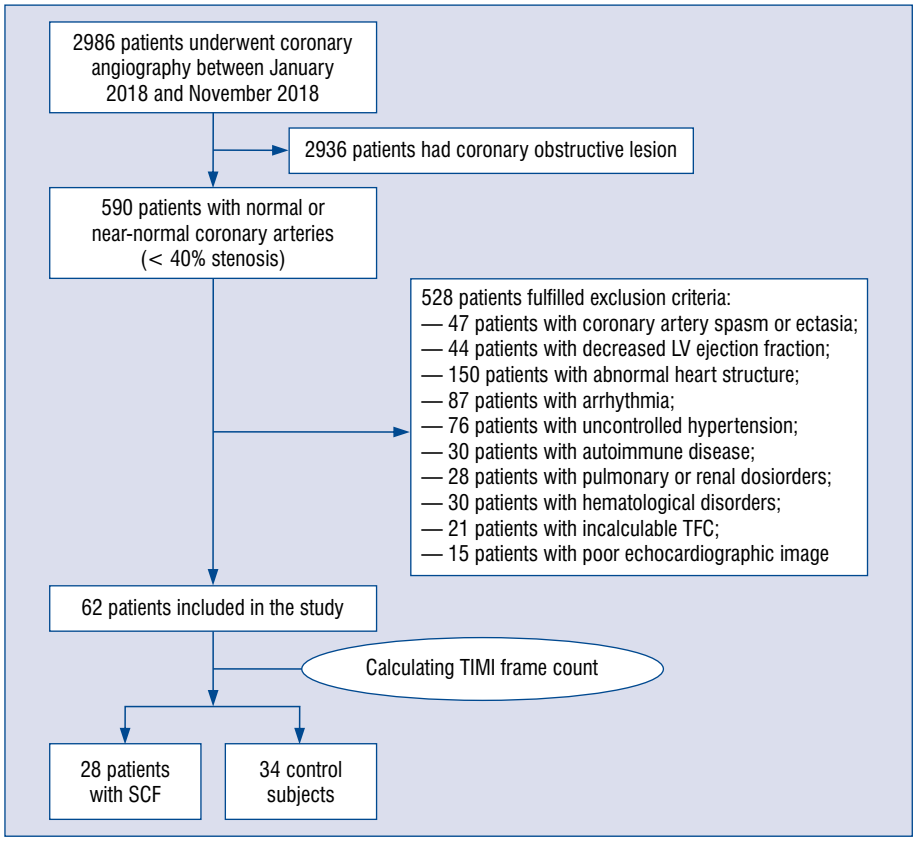

Figure 1. Patient recruitment flowchart; LV — left ventricle; TFC — thrombolysis in myocardial infarction frame count; SCF — slow coronary flow.

to determine appropriate cutoff values. For all parameters, $p < 0.05$ (two-tailed) was considered to indicate statistical significance.

Results

The study flowchart is shown in Figure 1. A total of 28 patients with SCF and 34 age- and sex-matched controls were enrolled in the study. The demographic, routine biochemical data, medications, and angiographic findings of the study population are shown in Table 1. There were no differences in baseline characteristics between the groups. Patients with SCF had significantly higher TFC values for the cLAD, LCx, and RCA, and a higher mean TFC, than those in controls. There was one-, two-, and three-vessel involvement in 14%, 57%, and 29% of the patients, respectively.

Although there was no difference in the LVEF between the groups, the LV GLS was decreased in patients with SCF compared to that in controls (–14.89% ± 2.94 vs. –16.97% ± 2.56, $p = 0.004$). Additionally, it was found that patients with SCF had decreased mitral average e' compared to that in controls, but the difference failed to reach significance (Table 2).

Plasma sEPCR levels were significantly higher in patients with SCF than in controls (10.39 ± 1.84 vs. 8.24 ± 1.20 ng/mL, $p < 0.001$). Moreover, the plasma sEPCR level was positively correlated with the mean TFC ($r = 0.67$, $p < 0.001$) and the number of involved vessels ($r = 0.61$, $p < 0.001$; Fig. 2). After adjusting for baseline covariates including age, sex, body mass index, systolic blood pressure, smoking history, fasting blood glucose and blood lipid, multivariate linear regression analysis showed the associations between plasma sEPCR level with mean TFC and the number of involved vessels were still significant (Table 3).

Logistic regression analysis confirmed that the plasma sEPCR level (OR = 3.14, 95% CI: 1.55–6.36, $p = 0.001$) and LV GLS (OR = 1.44, 95% CI: 1.02–2.04, $p = 0.04$) were independent predictors of SCF, after adjusting for age, sex, body mass index, and other variables with $p < 0.10$ on univariate analysis, including red blood cell count, statin use, and mitral average e' (Table 4).

Table 1. Comparison of baseline characteristics and angiographic findings.

	Controls (n = 34)	SCF (n = 28)	P
Demographics:			
Age [years]	56.24 ± 6.76	58.11 ± 6.58	0.28
Female sex	18 (53%)	10 (36%)	0.17
Body mass index [kg/m^2]	25.31 ± 3.67	24.63 ± 3.09	0.44
Medical history:			
Smoking	8 (24%)	11 (39%)	0.18
Hypertension	11 (32%)	5 (18%)	0.19
Diabetes mellitus	3 (9%)	4 (14%)	0.69
Laboratory values:			
Triglycerides [mmol/L]	1.44 ± 0.56	1.29 ± 0.58	0.31
Total cholesterol [mmol/L]	4.23 ± 0.84	4.01 ± 0.59	0.26
LDL cholesterol [mmol/L]	2.67 ± 0.72	2.52 ± 0.57	0.39
HDL cholesterol [mmol/L]	1.19 ± 0.25	1.15 ± 0.30	0.61
Fasting blood glucose [mmol/L]	5.36 ± 0.72	5.63 ± 1.02	0.23
Red blood cell count [10^{12}/L]	4.48 ± 0.39	4.66 ± 0.43	0.09
Red cell distribution width [%]	12.65 ± 1.07	12.60 ± 0.63	0.83
Platelet count [10^9/L]	230.44 ± 60.75	215.86 ± 57.61	0.34
Platelet distribution width [%]	11.75 ± 1.81	11.88 ± 1.48	0.78
Medications:			
ASA	23 (68%)	14 (50%)	0.16
ACEI	12 (35%)	6 (21%)	0.23
ARB	3 (9%)	2 (7%)	0.81
Beta-blockers	29 (47%)	14 (25%)	0.16
Calcium channel blocker	15 (60%)	19 (56%)	0.75
Statin	21 (62%)	11 (39%)	0.08
Nitrates	10 (29%)	6 (21%)	0.48
Levocarnitine/trimetazidine	17 (50%)	8 (29%)	0.10
TFC:			
cLAD	23.24 ± 3.71	44.25 ± 14.88	**< 0.001**
LCx	20.35 ± 3.67	32.64 ± 12.27	**< 0.001**
RCA	23.56 ± 3.83	38.32 ± 14.19	**< 0.001**
Mean	22.65 ± 3.28	40.26 ± 4.87	**< 0.001**
Vessel involved:			
1-vessel		4 (14%)	
2-vessel		16 (57%)	
3-vessel		8 (29%)	

Values are shown as means ± standard deviation or percentages. SCF — slow coronary flow; LDL — low-density lipoprotein; HDL — high--density lipoprotein; ASA — acetylsalicylic acid; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin II receptor blocker; TFC — thrombolysis in myocardial infarction frame count; cLAD — corrected left anterior descending coronary artery; LCx — left circumflex coronary artery; RCA — right coronary artery

Receiver operating characteristic curve analysis indicated that both sEPCR (area under curve [AUC]: 0.83) and LV GLS (AUC: 0.67) could predict SCF. However, sEPCR > 9.63 ng/mL combined with LV GLS > –14.36% demonstrated better predictive power (AUC: 0.89; sensitivity: 75%; specificity: 91%; Fig. 3).

Discussion

Under investigation was the relationship between the sEPCR level and SCF, and newly demonstrated the following: (1) the plasma sEPCR level was significantly higher in the SCF group than in controls, and was significantly correlated with

Table 2. Comparison of left ventricular function.

	Controls (n = 34)	SCF (n = 28)	P
LV end-diastolic volume [mL]	91.65 ± 22.07	96.51 ± 20.42	0.38
LV ejection fraction [%]	64.85 ± 4.21	64.00 ± 4.06	0.43
LV GLS [%]	–16.97 ± 2.56	–14.89 ± 2.94	**0.004**
LA volume index [mL/m^2]	28.06 ± 4.89	31.22 ± 6.33	0.11
Mitral E [cm/s]	62.79 ± 14.70	61.82 ± 17.30	0.81
Mitral E/A	0.90 ± 0.28	0.95 ± 0.31	0.56
Mitral average e' [cm/s]	9.12 ± 1.67	8.35 ± 1.75	0.09
Mitral average E/e'	7.02 ± 1.85	7.58 ± 2.26	0.29

Values are shown as means ± standard deviation. SCF — slow coronary flow; LV — left ventricle; GLS — global longitudinal strain; LA — left atrium; E — early diastolic flow velocity; A — late diastolic flow velocity; e' — early diastolic annular velocity

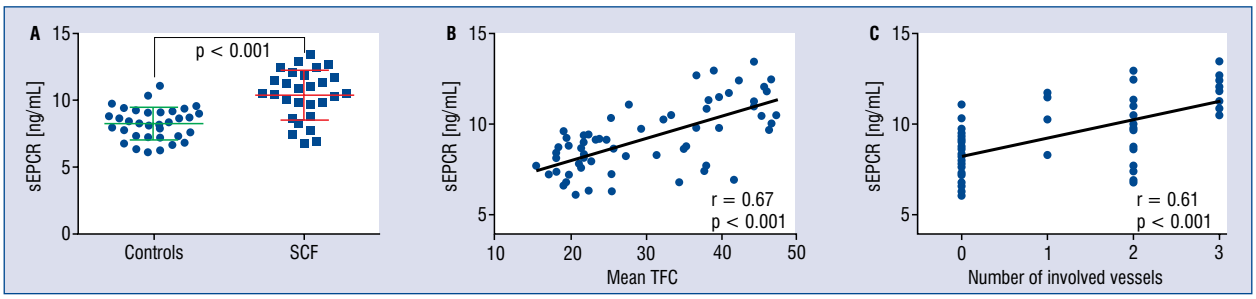

Figure 2. Relationship between soluble endothelial protein C receptor (sEPCR) level and slow coronary flow (SCF). The plasma sEPCR level was significantly higher in patients with SCF than in controls (**A**) and was positively correlated with the mean thrombolysis in myocardial infarction frame count (TFC) (**B**) and number of involved vessels (**C**).

Table 3. Associations between plasma soluble endothelial protein C receptor (sEPCR) level with mean thrombolysis in myocardial infarction frame count (TFC) and number of involved vessels on multivariate analysis.

	Mean TFC	Number of involved vessels
Model 1		
β [95% CI]	0.12 [0.09–0.16]	1.01 [0.68–1.33]
P	**< 0.001**	**< 0.001**
Model 2		
β [95% CI]	0.12 [0.09–0.16]	1.02 [0.68–1.35]
P	**< 0.001**	**< 0.001**
Model 3		
β [95% CI]	0.12 [0.08–0.16]	1.02 [0.68–1.37]
P	**< 0.001**	**< 0.001**
Model 4		
β [95% CI]	0.12 [0.08–0.16]	1.05 [0.67–1.42]
P	**< 0.001**	**< 0.001**

β —regression coefficient; CI — confidence interval. Model 1 — unadjust; Model 2 — adjust for model 1 plus age, sex, body mass index; Model 3 — adjust for model 2 plus systolic blood pressure and smoking history; Model 4 — adjust for model 3 plus fasting blood glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol

the mean TFC and number of involved vessels; (2) sEPCR and LV GLS were independent predictors for SCF; and (3) sEPCR combined with LV GLS can better predict SCF.

Li et al. [17] reported that patients with SCF have increased levels of C-reactive protein and interleukin-6. Moreover, elevations in leukocyte levels, neutrophil to lymphocyte ratio, and myeloperoxidase level in patients with SCF have also been reported [18, 19]. These findings suggest that inflammation might be a major contributing factor in SCF. However, although these inflammatory factors have excellent sensitivity, they lack specificity.

There are two forms of EPCR: membrane-bound EPCR (mEPCR) and sEPCR. On the one hand, mEPCR is bound to the endothelial layer, and can augment protein C activation to play a key role in anticoagulant, anti-inflammatory, and antiapoptotic activity [20]. On the other hand, sEPCR can attenuate mEPCR and inhibit the activities of activated protein C, and plays a major role in procoagulant activity and proinflammatory properties [14]. sEPCR is known to be involved in inflamma-

Table 4. Factors predicting slow coronary flow on multivariate analysis.

	Model 1		Model 2		Model 3	
	OR [95% CI]	P	OR [95% CI]	P	OR [95% CI]	P
Age	1.06 [0.97–1.15]	0.19	1.12 [0.99–1.26]	0.07	1.08 [0.94–1.26]	0.28
Sex	0.37 [0.12–1.13]	0.08	0.45 [0.09–2.22]	0.33	0.27 [0.04–1.90]	0.19
Body mass index	0.94 [0.80–1.10]	0.44	0.95 [0.76–1.19]	0.67	0.84 [0.64–1.11]	0.23
Red blood cell count			1.56 [0.22–11.05]	0.66	2.51 [0.24–26.88]	0.45
sEPCR			2.65 [1.50–4.68]	**0.001**	3.14 [1.55–6.36]	**0.001**
Statin			0.58 [0.13–2.63]	0.48	0.73 [0.13–4.03]	0.72
Mitral average e'					0.79 [0.48–1.31]	0.36
LV GLS					1.44 [1.02–2.04]	**0.04**

Data are presented as odds ratio (OR) and 95% confidence interval [95% CI]. Abbreviations — see Table 2 and 3. Model 1 included age, sex and body mass index; Model 2 included Model 1 plus red blood cell count, sEPCR and statin; Model 3 included Model 2 plus mitral average e' and LV GLS.

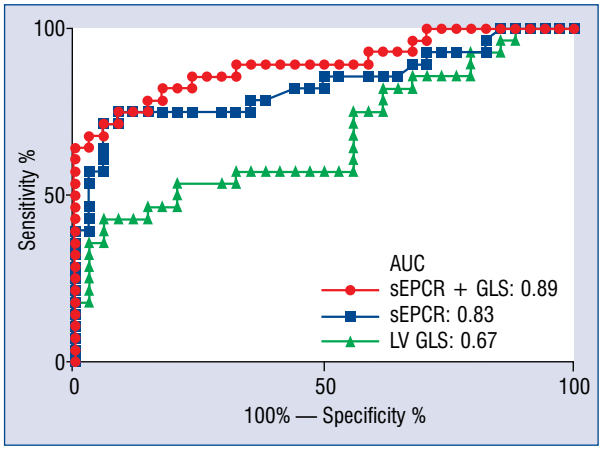

Figure 3. Receiver-operating characteristic curve analysis of soluble endothelial protein C receptor (sEPCR) and left ventricle global longitudinal strain (LV GLS) for predicting slow coronary flow; AUC — area under the curve.

tion, binding to activated neutrophils by neutrophil proteinase 3 and Mac-1 (CD11b/CD18a); activated neutrophils can contribute toward increased local thrombogenic activity, leading to distal embolization and microvascular plugging [13, 21]. The present study results show that patients with SCF have higher plasma sEPCR levels. These findings further strengthen the argument that inflammation plays a significant role in the development of SCF.

In the present study, the plasma sEPCR level had a strong positive correlation with the mean TFC and number of involved vessels. Thus, patients with SCF with greater TFCs and a greater number of involved vessels had higher plasma sEPCR levels. These findings suggest that slower coronary flow and a greater number of involved vessels represent more severe and diffuse inflammation in patients with SCF. Therefore, anti-inflammatory treatment may be considered as a potential approach in treatment for patients with SCF. However, whether such therapies can relieve symptoms and improve survival warrants further prospective investigations with larger sample sizes.

Speckle-tracking echocardiography-derived LV GLS can be considered as a noninvasive approach to detect early subclinical changes in LV global systolic function, even with normal LVEF. Moreover, it has been recommended by the American Society of Echocardiography. As with sEPCR, LV GLS were also found to be an independent predictor of SCF, and sEPCR combined with LV GLS demonstrated better predictive power than for that of sEPCR or LV GLS alone. Thus, the combination of serological testing and imaging examination may provide an inexpensive, simple, and feasible alternative for detecting SCF.

Limitations of the study

The major limitations of the present study are the small sample size and recruitment of patients from a single center. This might limit the generalizability of the present findings. Thus, large-scale, prospective, multicenter studies are warranted to verify and validate the role of sEPCR as a potential biomarker for SCF and confirm the predictive value of sEPCR combined with LV GLS for SCF.

Conclusions

Patients with SCF have an increased plasma sEPCR level and decreased LV GLS. sEPCR may

play an important role in the pathogenesis of SCF and is a potential biomarker for SCF. Moreover, sEPCR combined with LV GLS can better predict SCF. Further studies are warranted to analyze the clinical significance of an increased plasma sEPCR level and investigate the therapeutic efficacy of anti-inflammatory agents.

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Conflict of interest: None declared

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