Anatomic properties of coronary arteries are correlated to the corrected thrombolysis in myocardial infarction frame count in the coronary slow flow phenomenon

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Background **Coronary slow flow phenomenon (CSFP) is an important, angiographic clinical entity, but its etiology remains unclear. The purpose of this study was to explore the potential role of local coronary anatomic properties in the genesis of CSFP.**

Methods **One hundred and thirty-one consecutive patients with CSFP and 131 patients with angiographically normal coronary flow were prospectively enrolled after documenting coronary flow by corrected thrombolysis in myocardial infarction frame count (CTFC). Local anatomic parameters including the tortuosity index (TI), the ostial-to-middle diameter ratio, the ostial-to-middle cross-sectional area ratio, and the number of distal branches (NDB) of arteries at end-systole were compared between patients with CSFP and controls.**

Results **For each major coronary artery, CSFP patients had higher TI and NBD compared with controls (all $P<0.05$). The diameter ratio and cross-sectional area ratio of the three major coronary arteries were higher in the CSFP group ($P=0.004$ and 0.020, respectively). The TI ($r=0.476$, $P<0.001$) and NDB ($r=0.186$, $P=0.004$) were significantly correlated with CTFC. However, the higher TI ($\beta=0.424$, $P<0.001$) was the only independent correlate to CTFC. Multivariate logistic analysis revealed that TI (adjusted odds ratio 1.17, 95% confidence interval 1.11–1.23, $P<0.001$) and NDB (adjusted odds ratio 2.20, 95% confidence interval 1.50–3.21, $P<0.001$) were independent predictors of CSFP.**

Conclusion **The presence of CSFP was associated with higher tortuosity and more distal branches in coronary arteries, indicating that the anatomic properties of coronary arteries could also play a role in the pathogenesis of CSFP.** ***Coron Artery Dis*** **23:174–180** © **2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Coronary slow flow phenomenon (CSFP) is an angiographic entity characterized by the delayed progression of contrast dye injected into the coronary tree. CSFP is typically observed in patients presenting with acute coronary syndrome. More than 80% of patients experiencing recurrent chest pain undergo emergency room evaluations, hospitalizations, and repeat cardiac catheterizations [1]. Previous histopathologic studies have shown that small vessel disease, and microvascular and endothelial dysfunctions may be responsible for the occurrence of CSFP [2–4]. Pathophysiologic factors such as platelet activation [5], inflammation [6], diffuse atherosclerosis [7], and imbalance of vasoactive substances [8–12] have also been demonstrated to be responsible for the development of slow coronary flow. Recently, our group hypothesized that CSFP is not an isolated local observation but may be part of a generalized vascular disorder [13]. Clearly, the mechanisms involved in the manifestation of CSFP appear to be multifactorial and have yet to be fully determined.

Blood flow patterns in epicardial coronary arteries depend on the geometry and the motion of these vessels [14]. Disturbed laminar blood flow occurs in arterial segments with geometric irregularities such as curvatures, branches, and bifurcations [15]. It is in these complex regions that low blood velocity rates tend to occur. Confirming this theory, a very recent observation showed that in patients with CSFP, the angulations of the main coronary arteries from the aorta were smaller, determined with multidetector computed tomography coronary angiography, leading to bending head loss [16]. In addition, slow flow has often been seen in coronary ectasia [17]. It appears that abrupt changes in vessel diameter and direction can lead to slowing of blood flow. To date, only limited

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information is available regarding the local anatomic characteristics of coronary arteries that can potentially affect coronary blood flow. The purposes of this study were to describe parameters representing coronary geometry and to explore the correlation between the anatomic properties of coronary arteries and the occurrence of CSFP.

Methods

Patients and protocols

From August 2009 to April 2010, 113 consecutive patients with slow coronary flow in at least one major epicardial coronary artery detected by coronary arteriography were enrolled. In addition, 131 contemporary patients with angiographically normal coronary flow served as controls. All patients were referred for coronary angiography due to the presence of angina or angina-like chest pain. Patient demographics and laboratory data, including fasting lipid profile and serum glucose, were obtained. Patients with known coronary artery disease, valvular heart disease, cardiomyopathy, left ventricular systolic dysfunction (ejection fraction $< 50\%$), thyroid disease, autoimmune disease, malignancy, infection, and renal or hepatic insufficiency were excluded from the study. All patients provided written informed consent, and this study was approved by the institutional ethical committee of Beijing Anzhen Hospital. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the *International Journal of Cardiology* [18].

Coronary angiography and documentation of thrombolysis in myocardial infarction frame count

Left ventricular and selective coronary angiography was performed in all patients using the standard Judkins technique in multiple angulated views. Only angiograms with visually smooth contours and no wall irregularities were considered as normal. The contrast agent used in angiography was meglumine diatrizoate (Schering AG, Berlin, Germany).

Coronary flow was objectively quantified in a blinded manner by two independent observers (J.L. and L.-L.G.). Slow flow was diagnosed using the corrected thrombolysis in myocardial infarction (TIMI) frame count (CTFC) method [19]. Briefly, the number of cine frames required for the contrast to first reach the standardized distal coronary landmarks was measured, recorded at 30 frames/s. The first frame was defined as the frame in which concentrated dye extended across the entire width of the origin of the artery, touching both borders of the lumen. The final frame was defined as the frame in which the leading edge of the contrast column initially arrived at the distal landmark. The distal end was defined as the most distal branch of the left anterior descending (LAD) coronary artery and the left circumflex artery (LCX) and the first branch of the posterolateral artery for the right coronary artery (RCA). The LAD coronary artery is usually longer than the other major coronary arteries and the CTFC for this vessel is often higher. To obtain the CTFC for the LAD, the TIMI frame count was divided by 1.7. The TIMI frame counts in the LAD and LCX were assessed in a right anterior oblique projection with caudal angulation. In the RCA, the TIMI frame count was determined in the left anterior oblique projection with cranial angulation [19]. The mean TIMI frame count for each patient and control participant was calculated by adding the TIMI frame counts for the LAD, LCX, and RCA and then dividing the sum by 3. All participants with a CTFC greater than 27 were diagnosed as having CSFP [19].

Anatomic properties of epicardial coronary arteries

Quantitative analysis of coronary anatomy was performed with a computerized coronary angiography analysis system (Philips Medical System, Philips, the Netherlands). To specify anatomic factors that could influence coronary blood flow, four variables were introduced: the diameter ratio (DR, %), cross-sectional area ratio (CSAR, %) of the ostial segment to the middle segment, tortuosity index (TI, %) [20], and the number of distal branches (NDB) in each major coronary artery at end-systole. DR and CSAR were two novel variables signifying changes in coronary diameter. TI was defined as the percent ratio of the shortest distance divided by the total length of the coronary artery [20]. NDB was defined as the number of vessels with diameter at least 1 mm away from the middle LAD, first obtuse marginal branch of the LCX, and trifurcation of the RCA, respectively. Thus, TI and NDB represented coronary bending and branching, respectively, both of which play dominant roles in coronary blow flow. The mean values of these aforementioned anatomic parameters were expressed as the average of summed value of three epicardial coronary arteries.

$$\mathrm{DR} = (\text{ostium diameter} / \text{middle diameter}) \times 100,$$

$$\mathrm{CSAR} = (\text{ostium cross-sectional area} / \text{middle cross-sectional area}) \times 100,$$

$$\mathrm{TI} = (\text{total length} / \text{shortest possible length}) \times 100.$$

As a quantitative evaluation of coronary anatomy was performed, only patients with optimal visualization of the coronary arteries were included in the present analysis. Interobserver variability was calculated as SD of the differences between two observers and expressed as a percent of the average value.

Statistical analysis

Continuous variables were expressed as mean ± SD or median (interquartile range). Categorical variables were expressed as number (percentages). Comparison of categorical and continuous variables between the two groups was performed using the χ^2-test and an independent two-sample *t*-test, respectively. Skewed data were compared using the Mann–Whitney *U*-test. The correlation between

CTFC and anatomic parameters was assessed using the Pearson correlation method. Multivariate linear regression analysis was performed to identify independent factors of CTFC by including parameters that were significantly correlated with the mean CTFC in the univariate analysis. To determine independent associates of CSFP, multiple logistic regression analysis was performed by including the parameters that were significantly different between the two groups. All statistical assessments were two-sided and evaluated at the 0.05 level of significance. Statistic analyses were performed using SPSS 15.0 (SPSS Science, Chicago, Illinois, USA).

Results

Patient characteristics

Patient demographics, clinical characteristics, laboratory parameters, and CTFC values of the CSFP and control groups are summarized in Table 1. Patients with CSFP were more likely to be men (61.9 vs. 48.9%, $P = 0.040$), and had lower platelet counts [$(199.13 \pm 44.57) \times 10^9$/l vs. $(216.14 \pm 60.46) \times 10^9$/l, $P = 0.014$] and higher serum creatinine levels [(81.55 ± 18.66) μmol/l vs. (75.9 ± 16.3) μmol/l, $P = 0.010$] than the control group. There were no significant differences between the two groups in terms of age, BMI, heart rate, mean arterial blood pressure, traditional cardiovascular risk factors, hemoglobin, lipid profiles, fasting glucose, inflammatory indicators, and ejection fraction.

The CTFC for each of the three major coronary arteries and the mean CTFC were significantly higher in the CSFP group than in the control group (all $P < 0.001$) (Table 1). Interobserver variability for the value of CTFC was 5.7%.

Table 1 Patient demographics and baseline characteristics of the coronary slow flow phenomenon and control groups

Variables	CSFP group ($n=113$)	Control group ($n=131$)	*P*-value
Age (years)	55.86 ± 8.94	56.66 ± 9.83	0.506
Male, *n* (%)	70 (61.9)	64 (48.9)	0.040
BMI (kg/m^2)	26.83 ± 3.94	26.11 ± 3.66	0.136
Heart rate (beats/min)	66.16 ± 10.79	68.46 ± 12.35	0.132
SBP (mmHg)	127.52 ± 16.94	126.20 ± 15.71	0.592
DBP (mmHg)	79.92 ± 10.87	79.12 ± 9.03	0.593
MAP (mmHg)	95.80 ± 11.86	94.77 ± 10.42	0.519
Hypertension, *n* (%)	66 (58.4)	80 (61.1)	0.672
Diabetes, *n* (%)	12 (10.6)	20 (15.3)	0.284
Smoking, *n* (%)	48 (42.5)	44 (33.6)	0.138
Hyperlipidemia, *n* (%)	9 (8.0)	18 (13.7)	0.152
Platelet counts ($\times 10^9$/l)	199.13 ± 44.57	216.14 ± 60.46	0.014
Hemoglobin (g/l)	144.60 ± 17.20	141.69 ± 15.22	0.168
Total cholesterol (mmol/l)	4.65 ± 1.40	4.54 ± 1.16	0.494
LDL cholesterol (mmol/l)	2.78 ± 0.80	2.86 ± 0.8	0.666
HDL cholesterol (mmol/l)	1.10 ± 0.3	1.13 ± 0.24	0.423
Triglyceride (mmol/l)	2.01 ± 1.89	1.68 ± 0.93	0.092
Fasting glucose (mmol/l)	5.64 ± 1.00	5.74 ± 1.47	0.544
Creatinine (μmol/l)	81.55 ± 18.66	75.70 ± 16.37	0.010
Hs-CRP (mg/l)	1.12 (0.46–2.73)	1.06 (0.41–2.13)	0.956
IL-6 (pg/ml)	4.50 (1.75–8.05)	6.90 (2.35–9.70)	0.067
TNF-α (pg/ml)	6.20 (4.25–15.40)	6.70 (3.80–13.20)	0.767
Homocysteine (μmol/l)	14.90 (12.30–19.10)	15.50 (12.00–17.85)	0.723
Ejection fraction (%)	66.60 ± 6.67	66.53 ± 6.13	0.930
TFC			
LAD	104.72 ± 38.44	33.93 ± 8.33	<0.001
LAD[a]	61.60 ± 22.61	19.96 ± 4.90	<0.001
LCX	63.96 ± 18.26	20.61 ± 5.20	<0.001
RCA	50.51 ± 17.45	19.07 ± 5.51	<0.001
Mean	58.69 ± 14.38	19.88 ± 3.66	<0.001

Data are displayed as mean ± SD, number (percentage), and median (interquartile range). *P*-values are based on independent two-sample *t*-tests, χ^2-tests, and Mann–Whitney *U*-tests, respectively.
CSFP, coronary slow flow phenomenon; DBP, diastolic blood pressure; Hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; MAP, mean arterial pressure; RCA, right coronary artery; SBP, systolic blood pressure; TFC, thrombolysis in myocardial infarction frame count; TNF-α, tumor necrosis factor-α.
[a]Corrected thrombolysis in myocardial infarction frame count (CTFC).

Anatomic properties of epicardial coronary arteries

All anatomic parameters of three coronary arteries and the mean values are presented in Table 2. Although no significant differences were observed with regard to the DR and CSAR of the LAD and LCX between the two groups, the DR of the RCA ($P = 0.027$) and the mean DR ($P = 0.004$) as well as the CSAR of RCA ($P = 0.034$) and the mean CSAR value ($P = 0.020$) were significantly

Table 2 Anatomic properties of the coronary arteries in the coronary slow flow phenomenon and control groups

Variables	CSFP group ($n=113$)	Control group ($n=131$)	*P*-value
Ostium diameter (mm)			
LAD	4.87 ± 0.88	4.46 ± 0.77	<0.001
LCX	4.49 ± 1.04	4.19 ± 1.04	0.027
RCA	4.63 ± 0.85	4.32 ± 0.81	0.004
Mean	4.67 ± 0.73	4.33 ± 0.67	<0.001
Middle diameter (mm)			
LAD	3.58 ± 0.86	3.47 ± 0.81	0.304
LCX	3.49 ± 0.96	3.41 ± 0.87	0.518
RCA	3.66 ± 0.84	3.56 ± 0.72	0.334
Mean	3.58 ± 0.64	3.48 ± 0.59	0.233
DR (%)			
LAD	140.17 ± 26.72	133.32 ± 32.25	0.075
LCX	133.85 ± 34.05	126.49 ± 31.83	0.082
RCA	130.02 ± 24.56	123.51 ± 21.23	0.027
Mean	134.68 ± 18.29	127.77 ± 18.42	0.004
CSAR (%)			
LAD	203.56 ± 81.36	188.06 ± 109.66	0.217
LCX	190.66 ± 113.21	170.05 ± 113.64	0.158
RCA	175.03 ± 70.68	157.03 ± 59.19	0.034
Mean	189.75 ± 57.36	171.71 ± 62.56	0.020
TI (%)			
LAD	126.11 ± 14.61	112.50 ± 8.05	<0.001
LCX	125.19 ± 15.09	114.16 ± 9.36	<0.001
RCA	109.50 ± 6.83	106.33 ± 4.81	<0.001
Mean	120.26 ± 9.07	111.03 ± 5.70	<0.001
NDB			
LAD	3.41 ± 1.45	2.85 ± 1.01	0.001
LCX	3.64 ± 1.60	2.80 ± 1.42	<0.001
RCA	3.35 ± 1.10	2.85 ± 1.10	<0.001

Data are displayed as mean ± SD. *P*-values are based on independent two-sample *t*-tests.
CSAR, cross-sectional area ratio of ostial segment to middle segment; CSFP, coronary slow flow phenomenon; DR, diameter ratio of ostial segment to middle segment; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; NDB, number of distal branches; RCA, right coronary artery; TI, tortuosity index.

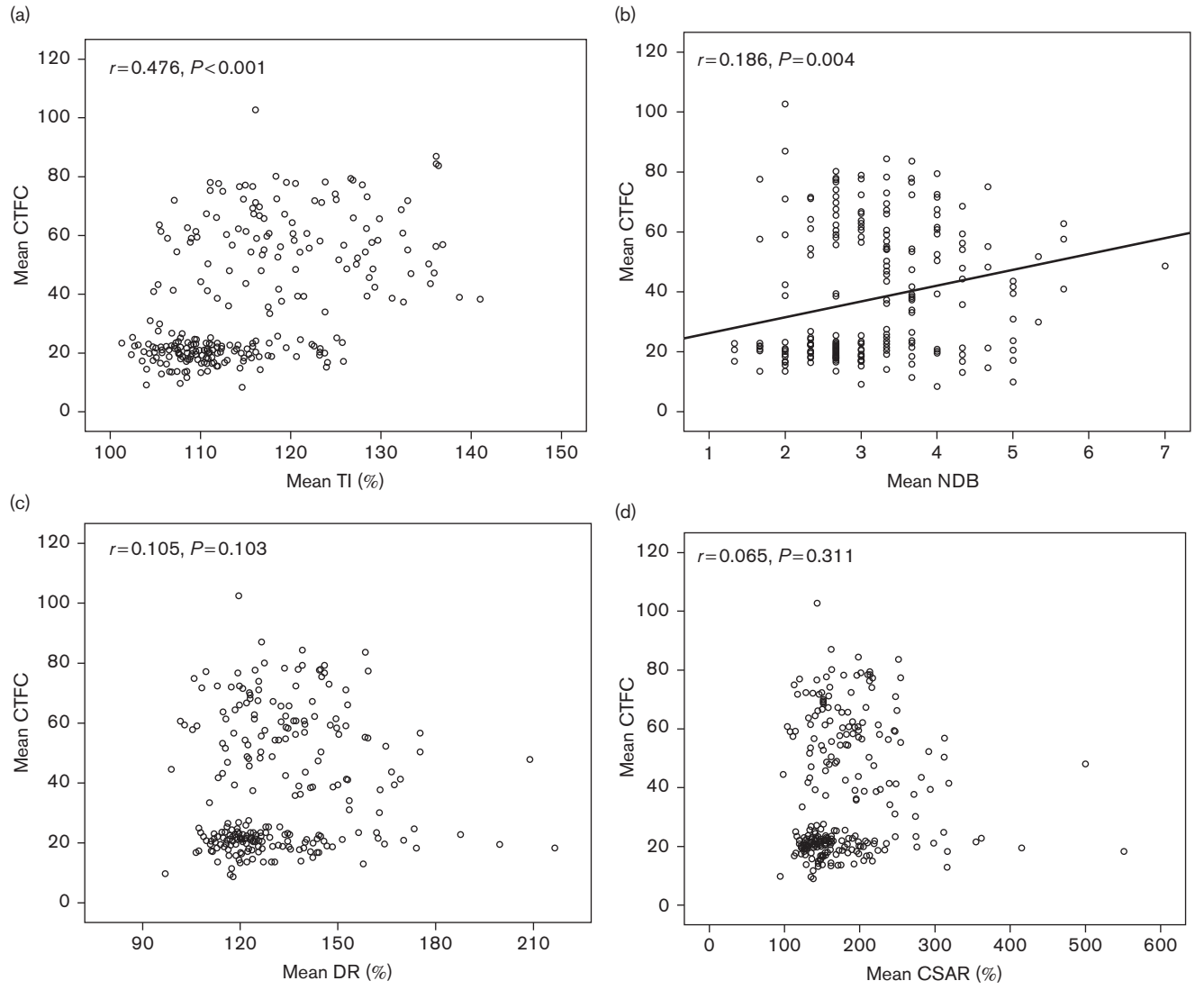
higher in CSFP patients. In addition, patients with CSFP showed higher TI and NBD in all three major coronary arteries compared with the controls (all $P < 0.05$). Interobserver variabilities for the value of DR, CSAR, TI, and NDB were 5.5, 5.2, 6.2, and 5.3%, respectively.

Correlation between anatomic properties and the mean corrected thrombolysis in myocardial infarction frame count

Linear correlation analysis was performed between the different anatomic and clinical variables and the mean CTFC. The best correlation was found for the mean TI and the mean CTFC ($r = 0.476$, $P < 0.001$) (Fig. 1). There was a weak, but significant, correlation between the mean NDB and the mean CTFC ($r = 0.186$, $P = 0.004$) (Fig. 1); however, no significantly positive correlation was found between the mean DR and the mean CTFC ($r = 0.105$, $P = 0.103$) (Fig. 1) or the mean CSAR and the mean CTFC ($r = 0.065$, $P = 0.311$) (Fig. 1). Moreover, the mean CTFC was positively correlated with male sex ($r = 0.172$, $P = 0.007$) and serum creatinine level ($r = 0.186$, $P = 0.004$), but negatively correlated with platelet counts ($r = -0.170$, $P = 0.009$).

Multivariate linear regression analysis included sex, platelet counts, serum creatinine level, mean TI, and mean NDB. The higher mean TI ($\beta = 0.424$, $P < 0.001$)

Fig. 1



Correlation between the mean corrected thrombolysis in myocardial infarction frame counts (CTFC) and (a) mean tortuosity index (TI); (b) mean number of distal branches (NDB); (c) mean diameter ratio (DR) of ostial segment to middle segment; and (d) mean cross-sectional area ratio (CSAR) of ostial segment to middle segment of the three major epicardial coronary arteries.

Table 3 Multivariate linear regression analysis for determining independent factors of corrected thrombolysis in myocardial infarction frame count

Variables	β-regression coefficient	*P*-value
Sex	−0.065	0.342
Platelet count	−0.107	0.069
Serum creatinine level	0.077	0.254
Mean TI	0.424	<0.001
Mean NDB	0.081	0.168

NDB, number of distal branches; TI, tortuosity index.

was the only independent correlate for the mean CTFC (Table 3).

Determinants of coronary slow flow phenomenon

Independent factors of CSFP were determined by multiple logistic regression analysis. The univariate logistic regression model indicated the following risk factors: sex, platelet count, creatinine, mean DR, mean TI, and mean NDB ($P < 0.05$). After multivariable adjustment for differences in baseline characteristics, the mean TI (adjusted odds ratio 1.17, 95% confidence interval 1.11–1.23, $P < 0.001$) and the mean NDB (adjusted odds ratio 2.20, 95% confidence interval 1.50–3.21, $P < 0.001$) were two strong independent factors of CSFP (Table 4).

Table 4 Univariate and multivariate logistic analysis for the occurrence of coronary slow flow phenomenon

	Univariate		Multivariate	
Variables	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)	0.99 (0.97, 1.02)	0.505	1.00 (0.96, 1.03)	0.834
Sex				
Male vs. female	1.70 (1.02, 2.84)	0.041	1.04 (0.45, 2.38)	0.930
BMI (kg/m^2)	1.06 (0.98, 1.14)	0.137	–	–
Heart rate (beats/min)	0.98 (0.96, 1.01)	0.134	–	–
MAP (mmHg)	1.01 (0.98, 1.03)	0.517	–	–
Hypertension				
Yes vs. no	0.90 (0.54, 1.50)	0.672	–	–
Diabetes				
Yes vs. no	0.66 (0.31, 1.42)	0.286	–	–
Hyperlipidemia				
Yes vs. no	0.54 (0.23, 1.26)	0.156	–	–
Smoking				
Yes vs. no	1.48 (0.88, 2.50)	0.138	–	–
Platelet counts ($\times 10^9$/l)	0.99 (0.98, 1.00)	0.017	1.00 (0.99, 1.00)	0.174
Hemoglobin (g/l)	1.01 (0.99, 1.03)	0.169	–	–
Total cholesterol (mmol/l)	1.07 (0.88, 1.31)	0.491	–	–
LDL cholesterol (mmol/l)	0.90 (0.65, 1.23)	0.493	–	–
HDL cholesterol (mmol/l)	0.68 (0.27, 1.74)	0.422	–	–
Triglyceride (mmol/l)	1.19 (0.97, 1.46)	0.096	–	–
Fasting glucose (mmol/l)	0.94 (0.77, 1.15)	0.544	–	–
Creatinine (μmol/l)	1.02 (1.00, 1.04)	0.011	1.01 (0.99, 1.04)	0.284
Hs-CRP (mg/l)	1.00 (0.92, 1.08)	0.982	–	–
IL-6 (pg/ml)	0.94 (0.88, 1.01)	0.071	–	–
TNF-α (pg/ml)	1.00 (0.98, 1.03)	0.765	–	–
Homocysteine (μmol/l)	1.01 (0.97–1.05)	0.618	–	–
Mean DR	1.02 (1.01, 1.04)	0.005	1.01 (1.00, 1.03)	0.120
Mean TI	1.18 (1.13, 1.23)	<0.001	1.17 (1.11, 1.23)	<0.001
Mean NDB	2.31 (1.66, 3.22)	<0.001	2.20 (1.50, 3.21)	<0.001

CI, confidence interval; DR, diameter ratio of ostial segment to middle segment; Hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; MAP, mean arterial blood pressure; NDB, number of distal branches; OR, odds ratio; TI, tortuosity index; TNF-α, tumor necrosis factor-α.

Discussion

The present study demonstrated that both coronary tortuosity and NBD were positively correlated with CTFC in patients with CSFP. These findings suggest that the presence of CSFP could be dependent on the local anatomic properties of coronary arteries.

Although an increasing body of hypotheses has been proposed for the pathogenesis of CSFP, there remains no clear-cut etiology to date. For example, several studies have documented abnormalities in coronary small vessels and suggested that structural defects as well as an underlying residual microvascular resistance abnormality coexisted in the coronary microcirculation [3,4]. Later, endothelial dysfunction was proposed to be responsible for CSFP [21]. Noteworthy are the recent findings showing the markers involved in endothelial dysfunction, including increased endothelin-1 release [11], reduced nitric oxide bioactivity [12], elevated plasma homocysteine levels [10], and decreased adiponectin concentrations and paraoxonase activity [8,9]. Furthermore, inflammation and diffuse atherosclerosis have also been suggested as contributors to coronary slow flow [6,7]. Hence, the intrinsic mechanism of CSFP appears to be multifactorial and remains to be elucidated.

Previous studies have focused on the histopathologic and pathophysiologic factors involved in CSFP. However, the anatomic features of the coronary arteries, which may relate to coronary slow flow, have not been well determined. Interestingly, it was recently reported that patients with CSFP exhibited smaller angulations of the main coronary arteries from the aorta, determined by multidetector CT coronary angiography. This finding implied that greater bending of the coronary arteries from their origins was associated with slowing of coronary flow [16]. In the present study, we introduced the variable called TI, representing tortuosity of the whole coronary artery, which served as a more convincing index to evaluate coronary anatomy. Our results showed that both TI of each coronary artery and the mean value were higher in the CSFP group than the control group. Also, a moderately positive correlation was noted between the mean TI and the mean CTFC. Further, the mean TI was an independent risk factor of both the mean CTFC and the presence of CSFP. At the curved sites of the artery, blood flow patterns are altered by way of flow separation and reversal [14]. It is thus plausible that an increase in TI underlies an increase in turbulent flow at vessel curves, which ultimately enhances the development of coronary slow flow.

According to basic fluid dynamics, the flow velocity of Newtonian fluids in circular-sectioned pipes changes when the pipes are suddenly enlarged or bent [22]. In parallel to this, coronary blood flow has shown to be reduced in patients with coronary ectasia using the TIMI frame count method [17,23]. Hence, we introduced DR and CSAR indicating changes in coronary diameter and cross-sectional area to explore further the impact of coronary configuration on CSFP. Only the values of RCA and the mean value were higher in patients with CSFP and no significantly positive correlation existed between DR and CSAR parameters and the mean CTFC. Therefore, in the present study, changes in vessel diameter or cross-sectional area may play a minimal role in the etiology of CSFP.

Vessel branching pattern was hypothesized to be another factor that could potentially influence coronary hemodynamics. It is well known that the majority of flow resistance resides in the arterial tree, particularly in small arterioles [24]. Hence, the arterial tree constitutes the majority of coronary circulation resistance. In the present study, patients with CSFP had increased NDB compared with controls. In addition, the mean NDB was identified as an independent risk factor for CSFP. It can be stated that coronary arteries with more distal branches generate enhanced flow resistance, which in part contributes to slowing of coronary flow.

Previous studies have shown that the heart rate had an effect on the TIMI frame count [25]. Another possible hemodynamic explanation for CSFP includes a reduced epicardial coronary perfusion pressure. In the present study, heart rate and mean arterial blood pressure were similar in CSFP patients and the controls and neither of these two variables was associated with the presence of CSFP in univariate analysis. After multivariate adjustment, the mean TI and the mean NDB were independent risk factors of CSFP, whereas the only independent associate of the mean CTFC was the mean TI. Together, these findings indicate that coronary tortuosity appeared to play a pivotal role in the pathogenesis of CSFP.

More recently, on the basis of the evidence that endothelial dysfunction appears to be a generalized process affecting both coronary and peripheral vasculature [26], our group hypothesized that CSFP was not an isolated finding, but could be part of a systemic vascular disturbance [13]. In contrast, the present study showed that the local anatomic characteristics of coronary arteries contribute to coronary slow flow. Taken together, CSFP could be caused by the interplay between both local anatomic features and systemic pathophysiologic factors.

To date, a large body of evidence supports the fact that, apart from the systemic risk factors, biomechanical parameters are also involved in the initiation and progression of coronary atherosclerosis [27–29]. Atherosclerotic lesions develop preferentially at regions of low shear stress or turbulent flow. These regions of disturbed flow are related to the geography of the vascular tree and are found in areas of branching or high vessel curvature [29]. Such coronary tortuosity may exacerbate the preexisting cyclic flexion during each cardiac contraction, leading to tissue fatigue and endothelial damage, contributing to the formation of atheromatous plagues [30]. However, it was recently proposed that CSFP may be a form of preliminary atherosclerotic disease that involves microvascular disorder, endothelial dysfunction, and inflammation [31,32]. Accordingly, it is reasonable that certain anatomic properties of coronary arteries (e.g. tortuosity, distal branching) could be factors predisposing to disturbed coronary flow and endothelial damage at the prescribed site, ultimately leading to the occurrence of CSFP.

Study limitations

Several factors, such as the naturally occurring curvatures and rotational motion of the heart, as well as the three-dimensional orientation of the coronary arteries, may influence the measurement of anatomic parameters. These effects, however, seemed to be small because the curves were relatively large compared with the tortuosity of the vessel. In addition, the anatomic properties of the coronary arteries at end-diastole were not measured. A previous study has shown differences in coronary tortuosity between end-diastole and end-systole [20]. Further detailed evaluations are needed to build upon the findings reported herein.

Conclusion

In summary, the presence of CSFP was associated with higher coronary tortuosity and an increased NBD, although detailed anatomic variables need to be verified. This study provides novel evidence that the local anatomic properties of the coronary arteries might also contribute to the development of CSFP.

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Conflicts of interest

There are no conflicts of interest.

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