Coronary Slow Flow – Prevalence and Clinical Correlations –

Beau M. Hawkins, MD; Stavros Stavrakis, MD; Talla A. Rousan, MD;
Mazen Abu-Fadel, MD; Eliot Schechter, MD

Background: Coronary slow flow phenomenon (CSFP) is defined as delayed coronary opacification in the absence of obstructive coronary artery disease. In the present study, we sought to define its prevalence and clinical features.

Methods and Results: The 1,741 consecutive patients who underwent coronary angiography (CAG) were identified. Those with normal left ventricular ejection fraction and normal coronary arteries were included in the study (n=158). TIMI frame counts were calculated, and data on demographics, comorbidities, and medication use were collected. CSFP was defined as frame count >27. Multivariate logistic regression analysis was used to identify independent predictors of CSFP. CSFP was identified in 96 (5.5%) subjects referred for CAG. Subjects with CSFP were more obese (body mass index [BMI] 33.9 vs. 29.8 kg/m², P=0.003) and had lower high-density lipoprotein levels (39.7 vs. 45.7 mg/dl, P=0.04). In the CSFP group, total cholesterol, low-density lipoprotein and frame counts increased significantly with increasing vessel involvement (1-, vs. 2-, vs. 3-vessel involvement; P<0.05 for each variable). By multivariate analysis, male sex (odds ratio 3.36, 95% confidence interval 1.17–8.61, P=0.02) and higher BMI independently predicted the presence of CSFP (odds ratio 1.09, 95% confidence interval 1.03–1.15, P=0.003).

Conclusions: CSFP is associated with male sex and obesity. Multivessel involvement may be a marker of more severe, diffuse disease. Further studies are needed to investigate this hypothesis. (*Circ J* 2012; **76**: 936–942)

Key Words: Coronary angiography; Coronary circulation; Epidemiology

Coronary angiography (CAG) is the gold standard for diagnosis of coronary artery disease (CAD). Of all patients referred for angiography, up to 20% have normal coronary arteries.^{1,2} Though noncoronary causes of chest pain may be identified in this population with normal coronaries, it has long been recognized that angina may still be present. An example of this is cardiovascular syndrome X, a condition predominantly affecting females who are found to have normal CAG following abnormal exercise stress studies.³

Editorial p 818

Another phenomenon known as the coronary slow flow phenomenon (CSFP) was first described in 1972 in 6 subjects presenting with chest pain syndromes. This syndrome is distinct from syndrome X because it is characterized by the finding of delayed coronary opacification in the absence of obstructive epicardial CAD.⁴ Since its original description, in addition to angina it has been associated with other forms of myocardial ischemia, including myocardial infarction (MI) and ventricular arrhythmias.^{5,6} The majority of patients with CSFP experience

recurrent chest pain and many are rehospitalized for chest pain syndromes following their diagnosis.⁷

Several studies have investigated the clinical features of individuals with CSFP. The 2 largest studies were conducted outside of North America and yielded conflicting results. The first study, performed by Beltrame et al,⁷ was conducted in an Australian population and identified male sex and nicotine use as significant associated conditions. Patients with CSFP were significantly younger as well. That study was limited to 45 subjects with CSFP and was a retrospective, case-control study in design. Yilmaz et al⁸ performed a similar retrospective analysis in a Turkish population and identified the features of metabolic syndrome (MetS), determined by the modified National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) criteria, as the major comorbidities associated with CSFP. Nicotine and sex were not found to be associated with this condition. The reasons for these discrepancies are unclear, but it is notable that the definition of CSFP differed between the 2 studies: Yilmaz et al included subjects with normal coronaries only,⁸ whereas the Beltrame series included subjects with "normal" or "near-normal" coronaries

Received August 29, 2011; revised manuscript received November 23, 2011; accepted December 8, 2011; released online February 1, 2012 Time for primary review: 21 days

Section of Cardiovascular Disease, Department of Internal Medicine, University of Oklahoma Health Sciences Center and Department of Veterans Affairs Medical Center, Oklahoma City, OK, USA

Mailing address: Stavros Stavrakis, MD, Williams Pavilion 3010, Section of Cardiology, Department of Internal Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA. E-mail: stavros-stavrakis@ouhsc.edu

ISSN-1346-9843 doi:10.1253/circj.CJ-11-0959

All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

Figure. Patient selection. Percentages are based on total number of subjects referred for angiography. LHC, left heart catheterization; CAD, coronary artery disease; LVEF, left ventricular ejection fraction.

defined as stenosis $<40\%$.⁷

Anecdotally, we have identified with increasing frequency the presence of slow coronary flow in subjects referred to our catheterization laboratory. Our veteran population has a high cardiovascular risk burden. Because previous reports differ on associated comorbidities specifically in relation to traditional coronary risk factors, we undertook this study to define: (1) the prevalence of CSFP in our population, (2) the pattern of coronary vessel involvement, and (3) the clinical features associated with CSFP. Determining the answers to these questions will be helpful in guiding further investigation into the prognosis and management of individuals afflicted with this condition.

Methods

Patient Selection

This study was conducted at the Oklahoma City Veterans Affairs Medical Center, which is a 192-bed tertiary care facility located in Central Oklahoma and serves the veteran population in 48 Oklahoma Counties and 2 Counties in North Central Texas. All subjects referred for CAG and left heart catheterization from August 2007 through August 2009 were retrieved from an electronic database after approval from the University of Oklahoma Health Sciences Center Institutional Review Board. Those with the following were included for further analysis: (1) normal ejection fraction (EF) and (2) normal coronaries defined as no evidence of any luminal obstruction.

Angiographic Data and Frame Counting

Left heart catheterization was performed using the standard Judkins technique. Angiographic images were obtained in standard views using right and left, and cranial and caudal angulations. All patients received nitroglycerin during angiography either in the form of sublingual tablets or intracoronary injection of 200 μg . Angiograms of all included subjects were reviewed and TIMI frame counts were determined for each

coronary vessel, by 2 trained cardiologists (BMH and SS), as described by Gibson et al.⁹ Both investigators were blinded to the clinical characteristics of the subjects. In brief, the first frame was considered to be that at which $>70\%$ lumen opacification with antegrade filling was noted. The final frames were determined when dye opacification reached a certain distal landmark in each vessel. For the left anterior descending artery (LAD), the distal bifurcation was used ("whale's tail"). The most distal bifurcation of the obtuse marginal branch furthest from the coronary ostium was used as the distal landmark for the left circumflex artery (LCX). The first branch of the posterolateral segment was used for the right coronary artery (RCA). Images were acquired at 15 frames/s and thus all values were multiplied by 2. Frame counts in the LAD were divided by a factor of 1.7 to correct for its longer length. Any frame count exceeding 27 was considered to be abnormal and indicative of slow flow based on the recommendations of Gibson et al.⁹ The intra- and interobserver coefficients of variation were 4.2% and 8.3%, respectively.

Data Extraction

Demographic variables pertaining to age, race, and sex were collected. Information on the following traditional CAD risk factors was collected: hypertension, diabetes, dyslipidemia, and nicotine use. Body mass index (BMI), blood pressure measurements, and lipid values less than 1 week preceding or at the time of CAG were recorded for all subjects. MetS was defined as presence of at least 3 of 4 of the modified ATP III criteria, excluding waist circumference, for which data were not available in our population. This definition would be expected to underestimate the prevalence of MetS. Medication use at the time of CAG was recorded with emphasis on cardioactive drugs, antiplatelet agents, and anticoagulants. Medication use during angiography was also recorded. Angiographic data relating to left ventricular EF and left ventricular end-diastolic pressure were recorded.

Table 1. Angiographic and Catheterization Data for Subjects With Slow Flow*

	Normal	Slow flow	P value
Artery involvement			
LAD (%)		67.7	0.33
LCX (%)		69.6	
RCA (%)		58.2	
Vessel involvement			
1-vessel (%)		36.7	0.42
2-vessel (%)		29.7	
3-vessel (%)		33.5	
Frame count averages			
LAD	19.4±4.9	37.3±16.9	0.0001
LCX	21.1±4.3	38.1±17.8	0.0001
RCA	18.5±5.3	34.3±15.5	0.0001
LVEDP (mmHg)	12.2±5.2	11.3±5.2	0.31

*Percentages are based on total number of subjects with slow flow. LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end-diastolic pressure.

Statistical Analysis

Subjects with slow flow were compared with those having normal flow. In addition, individuals with slow flow were stratified by vessel involvement into 1-, 2-, 3-, and multi- (2- and 3-) vessel groups. These groups were then compared with each other. For comparisons of TIMI frame counts between these 4 groups, only patients with abnormal frame counts were included. Categorical variables were analyzed using chi-square or Fisher's exact test, as applicable. Continuous variables were analyzed using unpaired t-test or 1-way analysis of variance (ANOVA), as applicable. Logistic regression analysis was used to assess predictors of slow flow. Those variables with $P < 0.1$ by univariate analysis were included in the multivariate logistic regression analysis model and the respective odds ratios (OR) with 95% confidence intervals (CI) were calculated. Continuous variables are expressed as means ± standard deviation. A 2-sided $P < 0.05$ was considered statistically significant.

Results

Slow Flow Prevalence

Figure demonstrates subject selection for this study. A total of 1,741 subjects underwent diagnostic left heart catheterization over a 2-year period and 1,583 (90.9%) of these studies had

Table 2. Demographic and Clinical Characteristics of Subjects With Slow Flow

	Normal (n=62)	Slow flow (n=96)	P value
Demographics			
Age (years)	56.4±9.3	54.5±10.0	0.23
Caucasian (%)	81.0	79.2	0.84
Male (%)	77.8	88.5	0.08
Comorbidities			
BMI (kg/m ²)	29.8±7.7	33.9±8.2	0.003
HTN (%)	76.2	80.2	0.37
DM (%)	19.1	27.1	0.25
Dyslipidemia (%)	63.5	72.9	0.21
Nicotine use (%)	33.3	30.2	0.68
Metabolic syndrome (%)	52	67	0.06
Quantitative measurements			
SBP (mmHg)	125.8±16.4	129.9±17.3	0.13
DBP (mmHg)	75.4±10.6	77.5±12.1	0.28
TC (mg/dl)	174.5±54.6	165.2±41.3	0.23
TG (mg/dl)	146.7±146.3	180.6±176.1	0.21
HDL (mg/dl)	45.7±17.7	39.7±17.4	0.04
LDL (mg/dl)	103.8±45.7	100.1±38.3	0.59
HbA _{1c} (%)	6.4±1.6	6.4±1.1	0.96
Medication usage			
Aspirin (%)	49.2	50.0	0.92
Clopidogrel (%)	15.9	16.7	0.89
Dipyridamole (%)	1.6	3.1	0.54
β-blocker (%)	49.2	53.1	0.63
CCB (%)	25.4	26.0	0.93
ACEI/ARB (%)	41.3	52.1	0.18
Nitrates (%)	20.6	20.8	0.98
Statins (%)	63.5	60.4	0.70
Other lipid medications (%)	11.1	15.6	0.42

BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA_{1c}, glycosylated hemoglobin; CCB, calcium-channel blocker; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker.

Table 3. Characteristics of Slow Flow Patients Based on the Number of Vessels Involved

	1 vessel	2 vessels	3 vessels	P value*	Multivessel	P value**
Demographics						
Age (years)	54.8±10.1	54.0±10.4	54.6±9.7	0.95	54.3±9.9	0.82
Caucasian (%)	67	70	91	0.11	82	0.57
Male (%)	83	92	91	0.45	92	0.21
Comorbidities						
BMI (kg/m ²)	33.7±8.6	34.6±8.5	36.5±19.2	0.68	35.6±15.1	0.49
HTN (%)	86	70	82	0.29	77	0.26
DM (%)	28	22	30	0.78	27	0.91
Dyslipidemia (%)	67	74	79	0.52	77	0.29
Nicotine use (%)	28	26	26	0.63	32	0.69
Metabolic syndrome (%)	66	61	65	0.97	63	0.79
Quantitative measurements						
SBP (mmHg)	130.3±18.6	131.7±18.3	128.2±15.3	0.73	129.8±16.7	0.89
DBP (mmHg)	77.3±13.9	77.9±12.5	77.3±9.7	0.97	77.6±11.0	0.90
TC (mg/dl)	148.8±28.3	180.7±44.9	171±44.9	0.02	175.3±44.8	0.002
TG (mg/dl)	146.5±96.4	177.6±133.5	184.8±189.2	0.33	197.3±203.9	0.24
HDL (mg/dl)	38.1±10.1	40.5±13.2	34.7±14.4	0.22	37.1±14.1	0.72
LDL (mg/dl)	88.8±26.3	106.9±41.7	107.3±44.6	0.08	107.1±42.9	0.02
HbA _{1c} (%)	6.2±0.9	6.2±1.1	6.6±1.3	0.55	6.4±1.2	0.56
Medication usage						
Aspirin (%)	50	59	42	0.43	50	1.00
Clopidogrel (%)	19	7	21	0.31	15	0.57
β-blocker (%)	50	44	64	0.30	55	0.63
CCB (%)	33	26	18	0.36	22	0.21
ACEI/ARB (%)	58	44	61	0.41	53	0.63
Nitrates (%)	20	22	24	0.73	23	0.44
Statins (%)	61	70	55	0.46	62	0.96
Other lipid medications (%)	11	15	18	0.71	17	0.46
Angiographic data						
LAD FC	30.3±1.9	40.9±12.3	51.3±16.1	<0.0001	46.8±15.6	0.0003
LCX FC	32.2±5.1	39.6±12.1	54.1±17.4	<0.0001	48.6±17.0	0.004
RCA FC	33.9±5.4	40.9±12.4	47.2±13.3	0.004	45.4±13.3	0.003
LVEDP (mmHg)	11.8±6.0	13.4±4.9	9.2±3.7	0.009	11.0±4.7	0.49

*1- vs. 2- vs. 3-vessel involvement. **1-vessel vs. multivessel (2- or 3-vessel) involvement. Abbreviations see in Table 2.

CAD or reduced left ventricular EF and were excluded from further analysis. Therefore, the population of interest comprised 158 subjects (133 males, 25 females; 9.1%) who had normal coronaries. Of this subgroup, 96 subjects had coronary slow flow in at least 1 coronary vessel, representing a prevalence of 5.5% of the total population.

Vessel Involvement, TIMI Frame Counts, and Other Angiographic Data

Table 1 summarizes the angiographic findings of our study population: 96 subjects had slow coronary flow in at least 1 vessel, and the LCX, LAD and RCA were involved in 69.6%, 67.7% and 58.2% of the patients, respectively, where the differences in frequencies were not statistically significant ($P=0.33$). Single-vessel involvement (36.7%) was as common as 3- (33.5%) and 2-vessel involvement (29.7%) ($P=0.42$).

TIMI frame counts were significantly higher in the slow flow group compared with the normal group in all coronary arteries (**Table 1**). Left ventricular end-diastolic pressures were similar in the 2 groups (11.9 mmHg in the slow flow group vs. 13.2 mmHg in the normal group, $P=0.06$).

Indications for Left Heart Catheterization

The majority of patients in the slow flow and normal flow groups were referred for left heart catheterization as outpatients because of angina or symptoms considered to represent anginal equivalence (68.4% vs. 68.2%, $P=0.38$, respectively). Electrocardiograms were not reviewed in the study because they would serve as an insensitive marker of ischemia in the outpatient setting. Noninvasive stress tests were abnormal, based on inducible ischemia on myocardial perfusion imaging or wall motion abnormality on stress echocardiography, in 71.2% of patients in the normal flow group compared with 69.0% of patients in the slow flow group ($P=0.68$). In the normal flow group, the indication for left heart catheterization was acute coronary syndrome (ACS) in 22 patients (5 non-ST-elevation MI, 17 unstable angina) compared with 31 patients in the slow flow group (1 ST-elevation MI, 9 non-ST-elevation MI, 21 unstable angina), a difference that was not statistically significant ($P=0.52$). We analyzed the data separately for patients with and without ACS, but found no significant differences and therefore we present only the combined data.

Table 4. Independent Predictors of Slow Flow

	OR	95%CI	P value
Male	3.36	1.17–9.61	0.02
BMI	1.09	1.03–1.15	0.003
HDL	0.99	0.96–1.01	0.22
Metabolic syndrome	0.86	0.38–1.93	0.71

OR, odds ratio; CI, confidence interval. Other abbreviations see in Table 2.

Patient Characteristics

The demographic characteristics of the slow flow and normal subjects were mostly similar. In general, both populations were predominantly Caucasian, middle-aged males (Table 2). However, the slow flow patients were significantly more obese (BMI 33.9 vs. 29.8 kg/m², $P=0.003$) and had significantly lower levels of high-density lipoprotein (HDL) compared with normal flow patients (39.7 vs. 45.7 mg/dl, $P=0.04$). No differences in other comorbidities, including hypertension, diabetes, and active nicotine use, were noted. Medication use was similar between groups. Blood pressure measurements, lipid measurements, and glycosylated hemoglobin values were all similar as well. We conducted a separate analysis of subjects with nonobstructive CAD (<50% coronary stenosis) and found similar results. Specifically, BMI remained statistically different between normal and slow flow groups, although the HDL difference was lost (data not shown).

Analysis by Vessel Involvement

Table 3 shows the results when slow flow subjects were compared with each other on the basis of the number of vessels involved. Demographic characteristics were not different between groups nor were any differences in medication use noted. Statistically significant differences were present in total cholesterol level ($P=0.02$) and left ventricular end-diastolic pressure ($P=0.009$). No difference in BMI was noted ($P=0.92$). Importantly, there was a significant association between the TIMI frame count of the involved vessels and vessel involvement. In other words, TIMI frame counts were lowest in subjects with 1-vessel involvement and increased steadily in the 2- and 3-vessel groups. This finding was consistent in each coronary artery (LAD $P<0.0001$, LCX $P<0.0001$, RCA $P=0.004$). When single-vessel involvement was compared with multivessel involvement (2- or 3-vessel), the results were essentially the same. The differences in TIMI frame count between single and multivessel disease remained statistically significant in all 3 vessels.

Independent Predictors of Slow Flow

Univariate analyses were performed for the 26 variables listed in Table 2. Male sex, high BMI, low HDL, and the presence of MetS were associated with the presence of CSFP. Multivariate analysis demonstrated male sex to be the strongest independent predictor of CSFP (OR 3.36, 95% CI 1.17–8.61, $P=0.02$). High BMI also independently predicted the presence of CSFP (OR 1.09, 95% CI 1.03–1.15, $P=0.003$) (Table 4).

Diastolic Dysfunction and Slow Flow

Echocardiographic data on diastolic dysfunction were available for 42% of patients without and 53% of patients with CSFP ($P=0.17$). Fifty two percent of the normal population had diastolic dysfunction as compared to 58% of the CSFP population ($P=0.63$). There was no difference in diastolic dysfunction in groups based on the number or type of vessels

involved (p values 0.40 and 0.89 respectively).

Discussion

To our knowledge, this is the largest study to exclusively investigate the clinical features of subjects with CSFP in a North American population. The strengths of this study lie in its relative size compared with other studies examining this condition. We also were diligent in recording medication use, associated comorbidities, and quantitative variables (ie, blood pressure) that may have affected coronary flow at the time of angiography.

Slow Flow Prevalence

Coronary slow flow was found to be a relatively common finding in subjects referred to our catheterization laboratory, occurring in 5.5% of all subjects. We did not observe any statistically significant differences in the frequencies of vessel involvement, in contrast to other reports.⁷ Moreover, single-vessel involvement was as common as 2- or 3-vessel involvement.

The prevalence of CSFP varies in the literature. Beltrame et al found that 1% of all patients referred for angiography had CSFP, using a definition of slow flow as abnormal TIMI frame count in at least 1 vessel,⁷ whereas in a subgroup the TIMI IIIA trial, approximately 5% of those subjects presenting with ACS were found to have evidence of coronary slow flow without significant CAD.¹⁰ The prevalence of CSFP in our study is higher than the previously reported estimates. It should be noted, however, that most of our total population referred for angiography had obstructive CAD. Moreover, more than one-half (60%) of our subjects with normal coronaries had slow flow in at least 1 vessel. In contrast, values between 7% and 24% have been previously reported in populations with normal coronaries only.^{11,12} The reasons for this discrepancy are not entirely clear; however, if coronary slow flow is a form of early atherosclerosis or is caused by microvascular dysfunction, as has been suggested,^{13,14} the relatively high burden of cardiovascular risk in our population may explain these findings.

Predictors of CSFP

Unfortunately, the literature to date has not consistently demonstrated the comorbidities and demographic features associated with this condition. In multivariate analyses, only male sex and BMI independently predicted the presence of CSFP, consistent with Beltrame et al (male sex)⁷ and Yilmaz et al (BMI).⁸ Other traditional cardiovascular risk factors, including hypertension, diabetes, and dyslipidemia, were not associated with CSFP in our study. The high prevalence of cardiovascular risk factors in our population, compared with previous studies, may have diluted any differences in these comorbidities. As an example, diabetes and hypertension were present in only 6% and 47%, respectively, of Beltrame et al's CSFP population,⁷ compared with 30% and 85%, respectively, in our population. An alternative explanation is that CSFP is a heterogeneous process, associated with numerous comorbidities, and that any one of a number of these combinations may lead to slow flow. Finally, it is unlikely that this result was related to lack of power to detect such differences, given the relatively large number of subjects in our population.

The largest study to date examining the clinical features of CSFP was conducted by Yilmaz et al in a Turkish population.⁸ In their study, they identified BMI, glucose levels, lipid derangements, and MetS as significantly associated with

CSFP. Although we used a similar definition of CSFP in the present study (inclusion of patients with normal coronaries only), we did not find associations with features of MetS other than obesity in the multivariate analysis. MetS, however, was associated with CSFP in the univariate analysis, despite the lack of waist circumference data in our study. Differences in ethnic background and associated comorbidities of the studied populations may account for these findings.

Importance of Vessel Involvement

The findings of our analysis based on vessel involvement are interesting. Frame counts increased as vessel involvement increased. Likewise, the lipid derangements in slow flow subjects qualitatively worsened as vessel involvement increased, though not all these changes were statistically significant. Contrary to the previously described literature, the LAD was not the predominant vessel involved in CSFP. We found that all 3 coronary vessels were equally involved. One potential explanation for this discrepancy is the much higher burden of cardiovascular risk factors in our population, conceivably leading to a more diffuse vessel involvement. These findings support the concept that multivessel involvement may represent a more severe, diffuse disease, and perhaps could portend worse prognosis. Further studies are needed to investigate this hypothesis.

Diastolic Dysfunction and CSFP

It has been hypothesized that impaired endothelial function increases microvascular resistance, reduces coronary flow reserve, and results in microvascular ischemia; which in turn may lead to diastolic dysfunction.¹⁵ Baykan et al showed that both systolic and diastolic functions are impaired in patients with CSFP by tissue Doppler imaging analysis of mitral annular velocities.¹⁶ Our study failed to show an association between slow flow and diastolic function. The differences in the studied populations may account for this discrepancy. Compared with the 2 aforementioned studies, our patients were older and had a higher prevalence of cardiovascular risk factors. However, our results should be interpreted with caution, given that only a non-random sample of the total population was examined because of missing data.

Pathophysiology

Our results are consistent with experimental and clinical studies linking CSFP with endothelial dysfunction, which is in turn associated with obesity. Although the pathophysiology of CSFP remains incompletely understood, evidence supporting endothelial dysfunction and links to atherosclerosis is accumulating. Pathologic studies have demonstrated cellular edema, microvascular thickening with luminal narrowing, myofibril disorganization, and fibromuscular hyperplasia in subjects with CSFP.^{11,17} Fractional flow reserve is abnormal in CSFP patients and intravascular ultrasound has demonstrated the presence of diffuse coronary calcification,¹³ and statin therapy has been shown to improve coronary flow in CSFP subjects.^{18,19} Moreover, endothelial function appears to be abnormal in patients with CSFP.²⁰ Importantly, indirect evidence suggests that obesity may be causally linked to endothelial dysfunction, and thus may be related to CSFP. A large, population-based study examining nearly 4,000 elderly men identified a strong association between BMI and markers of endothelial dysfunction. In addition to having increased interleukin-6 activity, more obese subjects were found to have elevated levels of von Willebrand factor, tissue plasminogen activator, and plasma viscosity.²¹ Moreover, a study by Ponti-

rolì et al showed that reduction in BMI after gastric banding procedures was associated with improvement in markers of endothelial dysfunction.²² Nitric oxide bioavailability has been implicated in the pathophysiology of endothelial dysfunction, which can lead to stiffening of the arteries both structurally and functionally. This in turn leads to a decrease in the amount of blood stored in the large arteries during systole, which may result in impaired coronary blood flow.²³

Other biochemical markers have been linked to CSFP. A study by Xia et al, which included 47 patients with CSFP, showed that elevated serum uric acid, platelet count, 2-h postprandial glucose, and high-sensitivity C-reactive protein level are independent predictors for CSFP.²⁴ The accumulated evidence suggests that CSFP is a form of endothelial dysfunction and likely not a benign condition.⁷ Studies better defining the prognosis of these patients and identifying effective management strategies are needed. A recent study by Selcuk et al found that patients with chronic obstructive pulmonary disease had a significantly higher incidence of coronary slow flow, which was thought to result from chronic inflammation, as they had elevated levels of high-sensitivity C-reactive protein.²⁵

Study Limitations

The limitations of this study relate primarily to its observational design. We used multivariate regression analysis to adjust for known confounders and identify independent predictors of CSFP. However, in such studies it is not possible to control for unknown confounders. Angiographic examinations were performed by different clinicians and it is likely that studies were performed with different sized catheters and angiographic projections. However, these factors are unlikely to significantly influence our results. Given that veterans are predominantly male and likely not representative of the general population, caution is advised when extrapolating our results to the general population. We did not include patients with nonobstructive CAD (<50% coronary stenosis) in our primary analysis. Importantly, a universal definition of CSFP is lacking.^{6,7} In order to facilitate comparisons with future studies, we would recommend that a consensus definition for CSFP be formulated specifically with regards to the inclusion or exclusion of subjects with nonobstructive CAD. Finally, this study lacks intracoronary Doppler or combined pressure and flow examinations, as well as an evaluation of coronary endothelial function using acetylcholine. Lee et al. showed that coronary flow reserve is low in patients presenting with angina and with normal coronary arteries, and is an indicator of cardiovascular risk factors.²⁶ Future studies should explore the intracoronary indices and classify patients accordingly.

Conclusions

CSFP was a prevalent condition in this veteran population. Male sex and obesity were independent predictors of CSFP. Further studies are needed to define the mechanisms of these relationships, and to determine if therapy directed at coronary slow flow improves outcomes.

Disclosures

The authors have no relevant financial disclosures.

References

1. Dart AM, Davies HA, Dalal J, Ruttlely M, Henderson AH. 'Angina' and normal coronary arteriograms: A follow-up study. *Eur Heart J* 1980; 1: 97–100.

2. Kemp HG, Kronmal RA, Vlietstra RE, Frye RL. Seven year survival of patients with normal or near normal coronary arteriograms: A CASS registry study. *J Am Coll Cardiol* 1986; **7**: 479–483.
3. Kemp HG, Elliott WC, Gorlin R. The anginal syndrome with normal coronary arteriography. *Trans Assoc Am Physicians* 1967; **80**: 59–70.
4. Tambe AA, Demany MA, Zimmerman HA, Mascarenhas E. Angina pectoris and slow flow velocity of dye in coronary arteries: A new angiographic finding. *Am Heart J* 1972; **84**: 66–71.
5. Przybojewski JZ, Becker PH. Angina pectoris and acute myocardial infarction due to “slow-flow phenomenon” in nonatherosclerotic coronary arteries: A case report. *Angiology* 1986; **37**: 751–761.
6. Saya S, Hennebry TA, Lozano P, Lazzara R, Schechter E. Coronary slow flow phenomenon and risk for sudden cardiac death due to ventricular arrhythmias: A case report and review of literature. *Clin Cardiol* 2008; **31**: 352–355.
7. Beltrame JF, Limaye SB, Horowitz JD. The coronary slow flow phenomenon: A new coronary microvascular disorder. *Cardiology* 2002; **97**: 197–202.
8. Yilmaz H, Demir I, Uyar Z. Clinical and coronary angiographic characteristics of patients with coronary slow flow. *Acta Cardiol* 2008; **63**: 579–584.
9. Gibson CM, Cannon CP, Daley WL, Dodge JT Jr, Alexander B Jr, Marble SJ, et al. TIMI frame count: A quantitative method of assessing coronary artery flow. *Circulation* 1996; **93**: 879–888.
10. Diver DJ, Bier JD, Ferreira PE, Sharaf BL, McCabe C, Thompson B, et al. Clinical and arteriographic characterization of patients with unstable angina without critical coronary arterial narrowing (from the TIMI-III Trial). *Am J Cardiol* 1994; **74**: 531–537.
11. Mangieri E, Macchiarelli G, Ciavolella M, Barilla F, Avella A, Martinotti A, et al. Slow coronary flow: Clinical and histopathological features in patients with otherwise normal epicardial coronary arteries. *Cathet Cardiovasc Diagn* 1996; **37**: 375–381.
12. Goel PK, Gupta SK, Agarwal A, Kapoor A. Slow coronary flow: A distinct angiographic subgroup in syndrome X. *Angiology* 2001; **52**: 507–514.
13. Pekdemir H, Cin VG, Cicek D, Camsari A, Akkus N, Doven O, et al. Slow coronary flow may be a sign of diffuse atherosclerosis: Contribution of FFR and IVUS. *Acta Cardiol* 2004; **59**: 127–133.
14. Beltrame JF, Limaye SB, Wuttke RD, Horowitz JD. Coronary hemodynamic and metabolic studies of the coronary slow flow phenomenon. *Am Heart J* 2003; **146**: 84–90.
15. Sezgin AT, Topal E, Barutcu I, Ozdemir R, Gullu H, Bariskaner E, et al. Impaired left ventricle filling in slow coronary flow phenomenon: An echo-Doppler study. *Angiology* 2005; **56**: 397–401.
16. Baykan M, Baykan EC, Turan S, Gedikli O, Kaplan S, Kiris A, et al. Assessment of left ventricular function and Tei index by tissue Doppler imaging in patients with slow coronary flow. *Echocardiography* 2009; **26**: 1167–1172.
17. Mosseri M, Yarom R, Gotsman MS, Hasin Y. Histologic evidence for small-vessel coronary artery disease in patients with angina pectoris and patent large coronary arteries. *Circulation* 1986; **74**: 964–972.
18. Cakmak M, Tanriverdi H, Cakmak N, Evrenkul H, Cetemen S, Kuru O. Simvastatin may improve myocardial perfusion abnormality in slow coronary flow. *Cardiology* 2008; **110**: 39–44.
19. Caliskan M, Erdogan D, Gullu H, Topcu S, Ciftci O, Yildirim A, et al. Effects of atorvastatin on coronary flow reserve in patients with slow coronary flow. *Clin Cardiol* 2007; **30**: 475–479.
20. Camsari A, Pekdemir H, Cicek D, Polat G, Akkus MN, Doven O, et al. Endothelin-1 and nitric oxide concentrations and their response to exercise in patients with slow coronary flow. *Circ J* 2003; **67**: 1022–1028.
21. Wannamethee SG, Whincup PH, Rumley A, Lowe GD. Interrelationships of interleukin-6, cardiovascular risk factors and the metabolic syndrome among older men. *J Thromb Haemost* 2007; **5**: 1637–1643.
22. Pontiroli AE, Pizzocri P, Paroni R, Folli F. Sympathetic overactivity, endothelial dysfunction, inflammation, and metabolic abnormalities cluster in grade III (World Health Organization) obesity: Reversal through sustained weight loss obtained with laparoscopic adjustable gastric banding. *Diabetes Care* 2006; **29**: 2735–2738.
23. Tomiyama H, Yamashina A. Non-invasive vascular function tests: Their pathophysiological background and clinical application. *Circ J* 2010; **74**: 24–33.
24. Xia S, Deng SB, Wang Y, Xiao J, Du JL, Zhang Y, et al. Clinical analysis of the risk factors of slow coronary flow. *Heart Vessels* 2011; **26**: 480–486.
25. Selcuk H, Maden O, Selcuk MT, Celenk MK, Geyik B, Tufekcioglu O. Documentation of impaired coronary blood flow in chronic obstructive pulmonary disease patients. *Circ J* 2010; **74**: 346–352.
26. Lee DH, Youn HJ, Choi YS, Park CS, Park JH, Jeon HK, et al. Coronary flow reserve is a comprehensive indicator of cardiovascular risk factors in subjects with chest pain and normal coronary angiogram. *Circ J* 2010; **74**: 1405–1414.