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ORIGINAL ARTICLE

CARDIAC SYNDROME Y: RETROSPECTIVE CLINICAL AND ANGIOGRAPHIC STUDY

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ABSTRACT

Background: Cardiac syndrome Y, coronary slow flow phenomenon (CSFP) or primary coronary slow flow was defined as delayed distal opacification of coronary arteries without significant narrowing with incidence of 1 to 7 % and coronary angiography (CA) as diagnostic gold standard. We aimed to evaluate patients with CSFP regarding prevalence, clinical presentation, risk profile, predictors, and angiographic findings. **Methods:** A single center retrospective study screening all patients who underwent CA in Cath. Lab. in the period from January 2016 to June 2020. Out of 9351 cases screened, 162 patients who had CSFP were selected as the patients' group, and 3 other age and sex matched control groups were selected (normal CA, isolated coronary artery ectasia and significant atherosclerotic disease). **Results:** The prevalence of CSFP in our study was 1.73 %. CSFP group included 107 (66 %) males and 55 (34 %) females with mean age of 55.07 ± 9.57 years. Chronic coronary syndrome (CCS) was the most common presentation of CSFP patients (73.5 %). Left anterior descending artery was the most affected coronary by CSFP (93.8 %). Smoking, hypertension, positive family history of atherosclerosis, abnormal ECG and CHA2DS2-VASc-HSF score are independent predictors of CSFP in comparison to patients with normal CA. **Conclusions:** CSFP is an important angiographic finding that should be suspected in middle-aged male patients with CCS and abnormal ECG. CHA2DS2-VASc-HSF score is a simple and clinical predictor of CSFP that can be easily calculated. Larger-scale studies are recommended to better characterize this entity.

Key words: Cardiac syndrome Y, coronary slow flow phenomenon, coronary angiography.

INTRODUCTION

Cardiac syndrome Y, coronary slow flow phenomenon (CSFP) or primary coronary slow flow was defined by **Tambe et al.** [1] as delayed distal opacification of coronary arteries without significant narrowing. **Fineschi and Gori** [2] suggested the name syndrome Y due to the suspected role of Neuropeptide Y in CSFP pathogenesis. Some conditions must be excluded before the diagnosis of CSFP as slow flow of contrast during coronary angioplasty or secondary causes of CSFP as coronary artery ectasia (CAE), coronary artery spasm, or valvular heart disease. The specific pathophysiologic mechanisms of CSFP are not clear [3]. **Beltrame et al.** [4] suggested multiple mechanisms for CSFP involving the microcirculation, inflammation, subclinical atherosclerosis, and endothelial dysfunction [5].

The incidence of CSFP ranges from 1 to 7 % in patients undergoing coronary angiography (CA) with chest pain as the most common presentation in 80% of cases, other presentations include myocardial infarction, non-sustained and sustained ventricular tachycardia, and ventricular fibrillation [6]. By using corrected thrombolysis in myocardial infarction frame count (CTFC) as a quantitative index of coronary flow, CA is the diagnostic gold standard of CSFP [7]. CSFP may be a diffuse, non-obstructive disease involving both small and epicardial coronary arteries [5]. Few studies have evaluated the pathogenesis and predisposing factors of CSFP [8]. In clinical practice, the clinical significance of CSFP is commonly underestimated because of unclear

pathophysiology and relatively low frequency [7]. The CHA2DS2-VASc-HSF score (CS) can be used to predict severe CAD and to assess the need for referral to CA [9].

Due to the presence of significant differences in the clinical features and angiographic characteristics among different studies, further research is needed for more assessment of CSFP. We aimed to evaluate the risk profile, clinical presentations, predictors, and angiographic features of CSFP patients and compare them to three age and sex-matched control groups (normal CA, isolated CAE, and significant atherosclerotic CAD).

METHODS

This is a single center retrospective study screening all patients who underwent CA for chest pain or CAD evaluation in Cath. Lab. in Mansoura Medical Specialized Hospital, Mansoura University, in the period from January 2016 to June 2020 using Philips angiographic machine. All patients who had isolated primary CSFP were selected as the patients' group. Three age and sex matched control groups were selected (normal CA, isolated CAE, and significant atherosclerotic CAD). Patients with an ejection fraction < 50 %, cardiomyopathies (dilated, restrictive, and hypertrophic), and more than mild valvular heart disease were excluded from the study. Data were collected from the CA reports and films, including CV risk factors, clinical presentation of the patients either by chronic coronary syndrome (CCS), unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) or ST segment elevation myocardial infarction (STEMI), ECG presentation by a normal ECG or an abnormal ECG defined as the presence of STT changes, ST depression, Q waves and left bundle branch block. The CHA2DS2-VASc-HSF score was calculated from the following items: congestive cardiac failure (C), Hypertension (H), Age ≥ 75 years (A), Diabetes Mellitus (D), Stroke (S), vascular diseases (V), Age between 65–74 years (A), Sex Category (Sc), Hyperlipidemia (H), Smoking (S) and Family history of CAD (F). 2 points are given for stroke or transient ischemic attacks and age ≥ 75 years. 1 point is given for other elements and 1 point is given for male sex. CA of patients was revised, and different angiographic patterns were defined. Normal CA was defined as normal coronary filling and emptying with a smooth outline of coronary arteries. Obstructive CAD was defined as > 70 % stenosis in the epicardial coronary arteries and/or > 50 % stenosis in the left main coronary artery (LMCA). CAE is defined as lumen ≥ 1.5 folds wider than normal coronary segments. CTFC was calculated according to **Gibson et al.** [10]. The first frame is identified by antegrade opacification of more than 70 % of coronary lumen. The last frame is identified by a distal landmark for each coronary artery; The left anterior descending artery (LAD) by the most distal bifurcation, the left circumflex artery (LCX) by the most distal bifurcation of the obtuse marginal branch, and the right coronary artery (RCA) by the first branch of the posterolateral branch. Images were acquired at 15 frames per second, and values were multiplied by 2. Frame counts in the LAD were divided by a factor of 1.7 to correct for its length. CSFP was defined as CTFC of more than 27 frames in one or more of the coronary arteries without CAE or luminal irregularities [10].

STATISTICAL ANALYSIS

Data were analyzed using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 21). The normality of the data was first tested with one-sample Kolmogorov-Smirnov test. Qualitative data were presented as number and percent and analyzed by Chi-square test. Continuous variables were presented as mean ± SD (standard deviation) and compared by student t- test for parametric data and presented as median (min-max) and compared by Mann whitney test for non-parametric data. Significant variables entered into Logistic regression model using enter statistical technique to predict the most significant determinants and to control for possible interactions and confounding effects. The significance threshold was fixed at 5% level. The results were considered significant if $p \leq 0.05$. The smaller the p-value, the more significant the results.

The study protocol was approved by Institutional Research Board of Mansoura Faculty of Medicine (the proposal code is R.20.10.5 - 2020/10/15). Confidentiality and personal privacy were maintained for all participants. The data will not be utilized for other purpose. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

RESULTS

9351 patients underwent CA for CAD evaluation in Cath. Lab. in the period from January 2016 to June 2020. 162 patients with CSFP were found with a prevalence of 1.73 % and enrolled as

the patients' group. They were 107 (66 %) males and 55 (34 %) females with mean age of 55.07 ± 9.57 years. Three age and sex matched control groups (normal CA, isolated CAE and significant atherosclerotic CAD) were selected.

Table 1 shows that CSFP patients had significantly higher smoking and hypertension than normal and CAE groups, family history of CAD and abnormal ECG than normal group and significantly lower diabetes, dyslipidemia, hepatitis C virus positivity and UA than atherosclerotic group. CCS was the most common presentation of CSFP patients (73.5 %) and was significantly lower than normal group and significantly higher than atherosclerotic group. NSTEMI, STEMI and CS were significantly lower in CSFP group than atherosclerotic group and significantly higher than normal group.

Table 2 shows that CTFC was significantly higher in CSFP group than CAE group in all coronary arteries affected.

Table 3 shows that smoking and CS were significantly higher in male than female patients with CSFP, but there was no significant difference as regard other CV risk factors, clinical presentation, abnormal ECG, ejection fraction or coronary arteries affection.

Table 4 and figure 1 shows patterns of coronary affection in patients with CSFP. LAD was the most affected by CSFP (93.8 % of cases), and this was significantly higher than CAE group. LAD was affected alone in 38 cases (23.4 %). Single vessel affection was significantly lower in CSFP group than atherosclerotic group. Multivessel affection defined as more than 2 vessels affection was significantly higher in CSFP group than atherosclerotic group and significantly lower than CAE group.

Table 5 shows logistic regression analysis of independent predictors of CSFP. Using normal CA as a reference group, independent predictors of CSFP included smoking, hypertension, positive family history of atherosclerosis, abnormal ECG and CS. Using CAE as a reference group, independent predictors of CSFP included smoking and hypertension. Using atherosclerosis as a reference group, independent predictors of CSFP included clinical presentation by CCS and lower prevalence of diabetes.

Table 1: Demographic data, risk factors and clinical data of all groups:

	CSFP group (no = 162)	Normal group (no = 162)	CAE group (no = 162)	Atherosclerosis group (no = 162)	P1 value	P2 value	P3 value
Age (years)	55.07 ± 9.57	54.17 ± 7.66	55.15 ± 9.70	56.76 ± 9.18	0.354	0.940	0.106
Male sex	107 (66.0 %)	103 (63.6 %)	103 (63.6 %)	110 (67.9 %)	0.642	0.642	0.723
Smoking	73 (45.1 %)	34 (21.0 %)	44 (27.2 %)	74 (45.7 %)	≤ 0.001*	0.001*	0.911
Diabetes	39 (24.1 %)	35 (21.6 %)	33 (20.4 %)	76 (46.9 %)	0.597	0.423	≤ 0.001*
Hypertension	91 (56.2 %)	63 (38.9 %)	71 (43.8 %)	88 (54.3 %)	0.002*	0.026*	0.737
Dyslipidemia	59 (36.4 %)	48 (29.6 %)	56 (34.6 %)	77 (47.5 %)	0.194	0.728	0.043*
Family history	34 (21.0 %)	20 (12.3 %)	30 (18.5 %)	39 (24.1 %)	0.037*	0.577	0.506
HCV	43 (26.5 %)	34 (21.0 %)	50 (30.9 %)	60 (37.0 %)	0.240	0.390	0.043*
CS (median)	3 (0 – 7)	2 (0 – 5)	3 (0 – 8)	4 (0 – 7)	≤ 0.001*	0.096	≤ 0.001*
CCS	119 (73.5 %)	148 (91.4 %)	107 (66.0 %)	59 (36.4 %)	≤ 0.001*	0.147	≤ 0.001*
Unstable angina	16 (9.9 %)	14 (8.6 %)	15 (9.3 %)	36 (22.2 %)	0.701	0.850	0.002*
NSTEMI	21 (13.0 %)	0	30 (18.5 %)	40 (24.7 %)	≤ 0.001*	0.170	0.007*
STEMI	6 (3.7 %)	0	10 (6.2 %)	27 (16.7 %)	0.03*	0.305	≤ 0.001*
Abnormal ECG	136 (84 %)	105 (64.8 %)	125 (77.2 %)	134 (82.7 %)	≤ 0.001*	0.123	0.766
Ejection fraction	62.29 ± 3.77	63.06 ± 4.16	61.68 ± 4.86	60.16 ± 4.97	0.082	0.212	0.063

CSFP = coronary slow flow phenomenon, CAE = coronary artery ectasia, HCV = hepatitis C viral positivity, CS = CHA2DS2-VASc-HSF score, CCS = chronic coronary syndrome, STEMI = ST segment elevation myocardial infarction, NSTEMI = non-ST segment elevation myocardial infarction, ECG = electrocardiogram, P1: CSFP versus normal groups, P2: CSFP versus CAE groups, P3: CSFP versus atherosclerosis groups.

Table 2: CTFC in CSFP and CAE groups:

	CSFP group (no = 162)	CAE group (no = 162)	P value
CTFC LAD	59.19 ± 18.33	39.83 ± 11.75	≤ 0.001*
CTFC LCX	40.13 ± 10.42	32.21 ± 4.84	≤ 0.001*
CTFC RCA	57.26 ± 15.86	41.62 ± 10.33	≤ 0.001*

CSFP = coronary slow flow phenomenon, CAE = coronary artery ectasia, CTFC = corrected thrombolysis in myocardial infarction frame count, LAD = left anterior descending artery, LCX = left circumflex artery, RCA = right coronary artery.

Table 3: Comparison between male and female patients with CSFP:

		Male (no = 107)	Female (no = 55)	P value
Age (years)		54.66 ± 10.73	55.87 ± 6.80	0.448
Smoking		65 (60.7 %)	8 (14.5 %)	≤ 0.001*
Diabetes		25 (23.4 %)	14 (25.5 %)	0.768
Hypertension		56 (52.3 %)	35 (63.6 %)	0.170
Dyslipidemia		37 (34.6 %)	22 (40.0 %)	0.497
Family history		22 (20.6 %)	12 (21.8 %)	0.852
Hepatitis C positivity		29 (27.1 %)	14 (25.5 %)	0.822
CS [Median (min - max)]		3 (1-7)	2 (0-7)	≤ 0.001*
Clinical presentation	**CCS** **Unstable angina** **NSTEMI** **STEMI**	81 (75.7 %) 9 (8.4 %) 12 (11.2 %) 5 (4.7 %)	38 (69.1 %) 7 (12.7 %) 9 (16.4 %) 1 (1.8 %)	0.367 0.383 0.356 0.362
Abnormal ECG		91 (85.0 %)	45 (81.8 %)	0.596
Number of vessels affected	**Single vessel**	29 (27.1 %)	`19 (34.5 %)	0.326
	2 vessels	37 (34.6 %)	15 (27.3 %)	0.346
	3 vessels	41 (38.3 %)	21 (38.2 %)	0.987
LAD		100 (93.5 %)	52 (94.5 %)	0.785
LCX		62 (57.9 %)	31 (56.4 %)	0.847
RCA		63 (58.9 %)	29 (52.7 %)	0.454
Ejection fraction		62.21 ± 3.87	62.43 ± 3.61	0.725

CSFP = coronary slow flow phenomenon, CS = CHA2DS2-VASc-HSF score, CCS = chronic coronary syndrome, STEMI = ST segment elevation myocardial infarction, NSTEMI = non-ST segment elevation myocardial infarction, LAD = left anterior descending artery, LCX = left circumflex artery, RCA = right coronary artery.

Table 4: Patterns of coronary affection in CSFP, CAE and atherosclerotic groups:

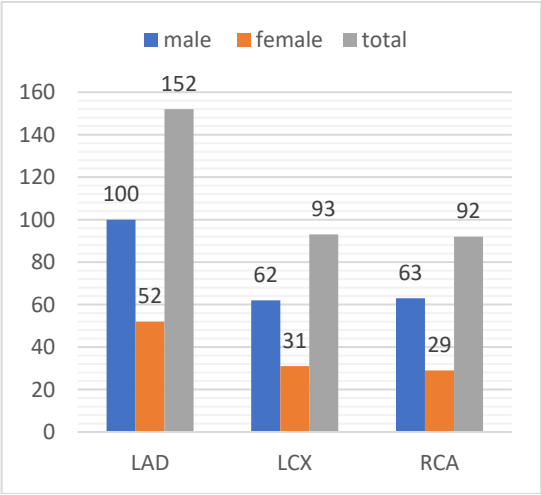
	CSFP group (no = 162)	CAE group (no = 162)	Atherosclerosis group (no = 162)	P1 value	P2 value
Single vessel affection	48 (29.6 %)	46 (28.4 %)	76 (46.9 %)	0.807	0.001*
2 vessels affection	52 (32.1 %)	34 (21.0 %)	48 (29.6 %)	0.024*	0.630
3 vessels affection	62 (38.3 %)	82 (50.6 %)	38 (23.5 %)	0.025*	0.004*
LAD affection	152 (93.8 %)	133 (82.1 %)	145 (89.5 %)	0.001*	0.159
LCX affection	93 (57.4 %)	115 (71.0 %)	75 (46.3 %)	0.011*	0.045*
RCA affection	92 (56.8 %)	112 (69.1 %)	68 (42.0 %)	0.021*	0.008*

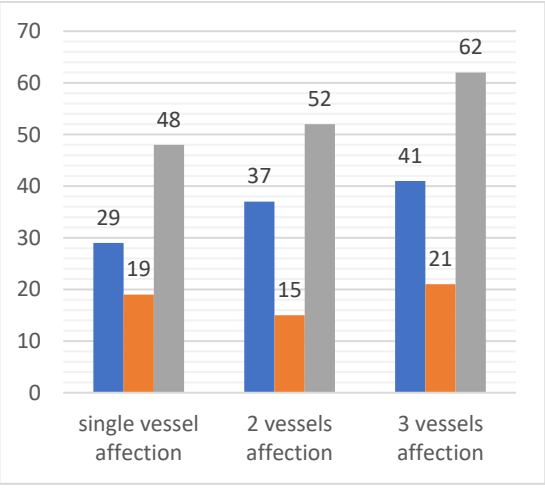
CSFP = coronary slow flow phenomenon, CAE = coronary artery ectasia, LAD = left anterior descending artery, LCX = left circumflex artery, RCA = right coronary artery, P1: CSFP versus CAE groups, P2: CSFP versus atherosclerosis groups.

Table 5: Logistic regression analysis for independent predictors of CSFP group:

Reference group	Predictors	Beta	Standard error	Odds ratio	95% CI	P value
Normal group	**Smoking**	-1.191	0.257	3.290	1.999 - 5.442	≤ 0.001*
	Hypertension	0.772	0.734	2.164	1.358 - 3.447	≤ 0.001*
	Family history	0.790	0.323	2.202	1.170 - 4.147	0.014*
	CS	-0.434	0.086	0.479	0.548 - 0.767	≤ 0.001*
	Abnormal ECG	-0.923	0.278	0.304	0.231 - 0.685	≤ 0.001*
CAE group	**Smoking**	0.922	0.246	2.1	1.552 - 4.070	≤ 0.001*
	Hypertension	0.671	0.240	1.8	1.222 - 3.131	0.005*
Atherosclerosis group	**Diabetes**	-1.045	0.288	0.352	0.200 - 0.619	≤ 0.001
	CCS	-1.888	0.538	0.151	0.053 - 0.434	≤ 0.001

CSFP = coronary slow flow phenomenon, CS = CHA2DS2-VASc-HSF score, CAE = coronary artery ectasia, ECG = electrocardiogram, CCS = chronic coronary syndrome, CI = confidence interval.





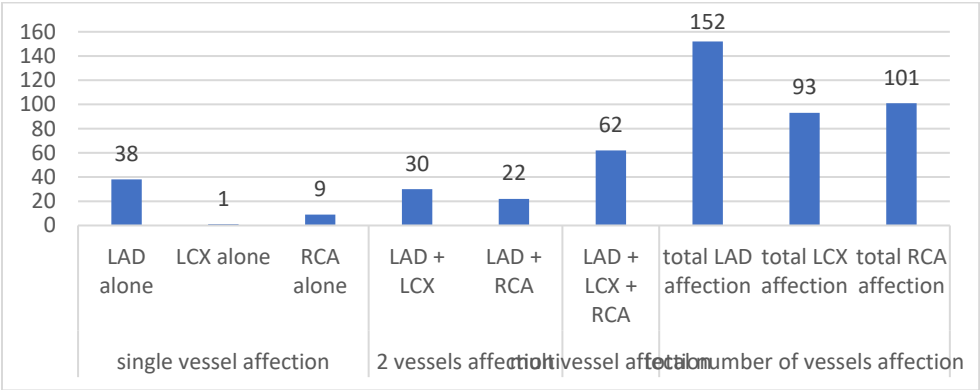


Figure 1: Coronary affection patterns in coronary slow flow group.
LAD = left anterior descending artery, LCX = left circumflex artery, RCA = right coronary artery.

DISCUSSION

The clinical course, prognosis, and management of CSFP may be challenging with recurrent chest pain and hospital admissions [6]. We aimed to evaluate different clinical and angiographic features of CSFP patients and compare them to three age and sex matched control groups (normal CA, isolated CAE and significant atherosclerotic CAD). The prevalence of CSFP in our study was 1.73 %. This was higher than some studies as 0.8 % by **Mukhopadhyay et al.** [11], 1 % by **Baltrame et al.** [4] and **Mangieri et al.** [12] and comparable to some studies as 2 % by **Sanati et al.** [13] and lower than some studies as 5.5 % by **Hawkins et al.** [9] and 5 % of ACS patients **by Diver et al.** [14]. The variation in the prevalence of CSFP among studies may be due to different patients' population regarding different races or risk factors profile or technical errors in the estimation of CTFC or underestimation of CSFP by different operators. Also, we included only patients with normal coronary arteries, some studies used the same definition [15] whereas other studies included subjects with "normal" or "near-normal" coronaries defined as stenosis < 40% [6].

The present study shows that CSFP was more reported among men (66 %) and the mean age was 55.07 ± 9.57 years with 62 % of patients between 40 to 60 years. In CSFP group, comparing male and female patients showed that smoking and CS were significantly higher in males, but there was no significant difference as regard other CV risk factors, clinical presentation, ECG or coronary arteries affection. Previous studies suggested male sex as an independent predictor of CSFP [6, 9, 16, 17]. The age prevalence in our study was comparable to most studies [8, 13, 18, 19, 20].

In our study, CCS was the most common presentation and affected 119 patients (73.5 %), 16 patients (9.9 %) had UA, 21 patients (13.0 %) had NSTEMI, 6 patients (3.7 %) had STEMI, 4 anterior and 2 inferior STEMI. Our results were in accordance with most studies that showed that CCS was the most common presentation of CSFP (56 % by Rao and Garre [18], 50 % by Mukhopadhyay et al. [11] and 80 % by Arbel et al. [16]. Lanza and Crea [21] showed that 5–10 % of patients had myocardial infarction. Results of our study disagree with Sanghvi et al. [3] and Beltrame et al. [6] who showed that acute coronary syndrome was the most common clinical presentation in 75 % of patients with CSFP. In the present study, abnormal ECG was present in 136 patients (84 %) which is higher than other studies as 31 % by Zhu et al. [22] and 33 % by Baltrame et al. [23].

Our results showed that multivessel, 2 vessels and single vessel affection occurred in 38.3 %, 32.1 % and 29.6 % respectively. Previous studies showed comparable results [8, 20, 24]. In our study, LAD was the most affected by CSFP (93.8 % of cases). Our results are in accordance with most studies that showed LAD affection in about 90 % of CSFP cases [3, 11, 13, 23]. Hawkins et al. [9] on the contrary, found that the LAD was not the predominant vessel involved in CSFP, but all 3 coronary vessels were equally involved. In our study, CSFP patients had significantly lower single vessel and higher multivessel affection than atherosclerotic group and significantly lower multivessel affection than CAE group. No previous studies compared vessel affection in CSFP to CAE or atherosclerotic patients. The causes of these variations in the vascular distribution of CSFP among studies are

unclear but may be due to variation in the inclusion criteria of CSFP or technical errors.

In our study, logistic regression analysis showed that the independent predictors of CSFP included smoking, hypertension, family history of atherosclerosis, abnormal ECG and CS in comparison to normal CA, smoking and hypertension in comparison to CAE and clinical presentation by CCS and lower prevalence of diabetes in comparison to significant atherosclerotic disease. In most studies, logistic regression analysis for predictors of CSFP compared it to normal CA and showed similar independent predictors as smoking [6, 16] and hypertension [13, 25]. Other studies found different independent predictors of CSFP as diabetes [25, 26] and dyslipidemia [15, 17]. Contrary to our results, Hawkins et al. [8] concluded that hypertension, diabetes, and dyslipidemia, were not associated with CSFP. No previous studies evaluated CS as a predictor of PCSF.

CONCLUSIONS

In conclusion, CSFP is a relatively frequent finding among patients scheduled for CA for CAD evaluation with a prevalence of 1.73 %. CSFP is seen more frequently in male patients (66 %) and the mean age is 55.07 ± 9.57 years. CCS was the most common presentation of CSFP patients (73.5 %). LAD was the most affected coronary by CSFP (93.8 % of cases). Single vessel affection was significantly lower in CSFP group than atherosclerotic group. Multivessel affection was significantly higher in CSFP group than atherosclerotic group and significantly lower than CAE group. Smoking, hypertension, positive family history of atherosclerosis, abnormal ECG and CS are independent predictors of CSFP in comparison to patients with normal CA, smoking and hypertension in comparison to CAE group and clinical presentation by CCS and lower prevalence of diabetes in comparison to atherosclerotic group.

RECOMMENDATIONS

CSFP is an important angiographic finding that should be a distinct clinical entity to be considered in middle-aged male patients presented with CCS and abnormal ECG. CS is a simple and clinical predictor of CSFP that can be easily calculated. CSFP is not uncommon and sometimes underdiagnosed and physicians should be aware of the clinical importance of CSFP and its links to acute and chronic coronary syndromes. Larger clinical trials are recommended to better characterize this phenomenon.

Limitation of the study:

The design as a single center retrospective study.

Conflict of interest: None

Financial disclosures: None

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