RESEARCH ARTICLE

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Serum Osmolality as a Predictor of Coronary Slow Flow Phenomenon

Ramy Raymond Elias, Michael Medhat Naguib Aziz, Inas Ibrahim Eweda, Mina Magued Abdalla Iskandar

Department of Cardiology, Ain Shams University Hospital, Cairo, Egypt

Abstract

Background and Aim: Coronary slow flow (CSF) phenomenon is defined as a delay in the filling of epicardial coronary arteries in the absence of obstructive disease. Primary CSF phenomenon (PCSFP) is a noteworthy angiographic observation that should be regarded as a distinct clinical condition, although its precise pathophysiology is not yet fully understood. This study aims to investigate the correlation between serum osmolality and PCSFP in patients subjected to coronary angiography.

Materials and Methods: This is a case-control study that included one hundred and twenty patients who presented to Ain Shams University. They were divided into two equal groups. Group A: patients who had PCSFP and Group B: patients with normal coronary flow.

Results: Among PCSFP patients, the mean age was recorded as 54.53±11.6 years. Male sex was significantly associated with PCSFP, with an [odds ratio (95% confidence interval) of 2.582 (1.16-5.75)] and a *P*-value of 0.019. Among the traditional risk factors, smoking was markedly higher, contributing to 66.7% of the slow flow group of patients compared to 40% of the control group, with *P*-value = 0.003. PCSFP patients had increased hemoglobin and triglyceride levels, and both were strongly associated with PCSFP following multivariate analysis. A significant increase in serum osmolality was observed in PCSFP patients in comparison to control subjects. The calculated serum osmolality values were 295.08±6.77 mOsmol/kg in the PCSF group and 284.64±4.74 mOsmol/kg in the control group (*P*-value ≤ 0.001).

Conclusion: PCSFP predominantly affects males with a history of smoking. Furthermore, hypertriglyceridemia, higher hemoglobin levels, and greater serum osmolality have been identified as independent predictors of its development.

Keywords: Osmolality, primary coronary slow flow, thrombolysis in myocardial infarction frame count

INTRODUCTION

Coronary slow flow (CSF) phenomenon refers to an angiographically observed delay in the advancement of injected contrast within the coronary arteries, resulting in prolonged opacification of the epicardial vessels despite no evident obstructive coronary pathology.[1]

It is a frequently unrecognized risk factor in patients experiencing chest pain and abnormal non-invasive ischemia, despite having non-obstructive coronary arteries.[2] This condition has been documented in 1% to 7% of cases among patients subjected to coronary angiography due to clinical suspicion of coronary artery disease (CAD).[3]

Primary CSF phenomenon (PCSFP) is a noteworthy angiographic finding commonly identified in patients presenting with acute coronary syndrome (ACS), particularly those with unstable angina. It warrants recognition as a distinct clinical entity characterized by unique pathophysiological attributes, well-

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Address for Correspondence: Michael Medhat Naguib Aziz, Department of Cardiology, Ain Shams University Hospital, Cairo, Egypt
E-mail: michaelaziz@med.asu.edu.eg
ORCID ID: orcid.org/0000-0001-7526-800X

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defined diagnostic parameters, and specific underlying mechanisms.[4]

The precise pathophysiology of the CSF phenomenon is not fully understood. Multiple mechanisms have been proposed in the pathophysiology of this condition, encompassing endothelial dysfunction, microvascular disturbances, undetected atherosclerosis, and inflammatory cascades.[5]

This phenomenon must be clearly differentiated from the contrast delay seen in coronary reperfusion strategies, including percutaneous interventions for acute myocardial infarction, as well as from secondary causes such as coronary stenosis, arterial ectasia, or transient vasospasm.[6]

Serum osmolality, a key indicator of solute particle concentration within bodily fluids, is determined by the levels of several biochemical markers, including sodium (Na), blood urea nitrogen (BUN), chloride, proteins, and glucose. The normal range for serum osmolality is typically between 275 and 295 mOsmol/kg.[7]

Serum osmolality estimates the body's hydration balance, so we thought of correlating it with this phenomenon of dehydration, as dehydration has been linked previously to PCSFP.[8]

Multiple formulas have been devised for the estimation of serum osmolality. In 1976, Smithline and Gardner proposed a widely recognized equation, expressed as [2(Na) + glucose/18 + BUN/2.8], to facilitate this calculation.[9] Worthley et al.[10] highlighted the Smithline-Gardner formula as the superior method for serum osmolality estimation, citing its precision and reliability.

Previous studies have investigated the association of PCSF with different clinical risk factors such as diabetes, dyslipidemia, and smoking, and various hematological and biochemical parameters such as hematocrit, platelet count, uric acid, glycosylated hemoglobin A1c (HbA1c), and serum triglycerides.[3,4,6]

This study to assess the potential correlation between serum osmolality and the development of PCSFP.

METHODS

In the period between January and July 2024, 120 patients presenting to the Cardiology Department at Ain Shams University were recruited for this case-control study. This time frame was selected to ensure alignment with our institutional review board (IRB) and the availability of clinical and research staff during this period. Our study employed a matched case-control design. Matching was performed on a 1:1 ratio based on key demographic and clinical characteristics, including age, sex, and the presence of major comorbidities. The participants were allocated to two groups: 60 patients with PCSFP confirmed by coronary angiography and 60 individuals in the control group with normal coronary flow.

The inclusion criteria were: patients above 18 years of age presenting either by ST segment elevation myocardial infarction (STEMI), non-ST ACS or chronic coronary syndrome (CCS), the exclusion criteria included the presence of CAD (including plaque, spasm, ectasia, or obstructive lesion), presence of a myocardial bridge, patients who underwent previous percutaneous coronary intervention in the vessel showing slow flow, and patients with history of coronary artery bypass grafting.

Prior to participation, all patients were given a detailed explanation of the procedure, and written informed consent was duly acquired. The study adhered to the ethical principles outlined by the IRB, Ain Shams University Faculty of Medicine Research Ethics Committee (approval number: FWA000017585, date: 14.02.2024).

Participants Were Subjected to

History and clinical examination

- A full history was taken from all patients regarding age, gender, detailed risk profile including smoking status, hypertension, history of CAD, drug history, previous coronary intervention, family history of premature ischemic heart disease (IHD) and dyslipidemia. The examination included vital data, and a full cardiac examination.

- A standard 12-lead surface electrocardiogram (ECG) was done for all participants.

- In line with the American Society of Echocardiography guidelines, a complete transthoracic echocardiographic evaluation was conducted for each patient using the General Electric (GE) Vivid E95 cardiac ultrasound device with a 3.5 MHz transducer.

- Laboratory investigations: Blood samples were collected from all the participants, including: complete blood picture, random blood sugar, kidney function tests, serum electrolytes, lipid profile, and HbA1C. Smithline and Gardner formulae were used to calculate serum osmolality: Serum Osmolality = 2(Na+) + glucose/18 + BUN/2.8.

- Coronary angiography: the procedure was performed by expert interventional cardiologists. All patients underwent coronary angiography using cine angiographic equipment, Philips Allura Xper Flat Detector 10 and GE Innova 2100 Angio Systems, with cineframes at 15 fps. A scaling factor of 2 was implemented to convert frame rate values from 15 frames per second to match the 30 frames per second acquisition speed

used in the initial cine angiographic studies. Sterilization and local infiltration with 2% lidocaine, followed by femoral or radial artery puncture, were performed using the Seldinger technique. To visualize coronary arteries, selective angiography was performed with multi-angulated projections-including right, left, cranial, and caudal views-utilizing 6Fr Judkins catheters and Iohexol (Omnipaque 350 mg/mL) as the contrast medium.

Angiographic interpretation was performed by experienced clinicians who were blinded to the clinical characteristics and outcomes of the patients. To minimize potential diagnostic bias and ensure an objective evaluation of coronary flow, with normal coronary flow is defined as the absence of any significant obstruction or irregularity in the coronary vessels, achieving thrombolysis in myocardial infarction (TIMI) III flow. The definition of normal flow was further corroborated by consensus between two independent reviewers to ensure consistency in the assessment.

As per the description by Gibson et al.[11], PCSFP was diagnosed through the TIMI frame count technique. This technique quantifies the number of cine frames required for contrast dye to reach specific distal landmarks within the coronary arteries. Using the cine viewer frame counter, we recorded number of frames needed for contrast to reach standard distal reference points in the left circumflex (LCX) artery, left anterior descending (LAD) artery, and right coronary artery (RCA). The initial frame corresponded to the instant when contrast fully occupied the artery, with the dye reaching both sides at its origin and progressing antegradely. The last frame was noted at the moment the contrast medium arrived at key distal reference points: the "whale's tail" structure at the LAD apex, the bifurcation of the primary obtuse marginal branch for the LCX, and the initial branch extending from the posterior lateral RCA beyond the posterior descending artery's origin.

To obtain the corrected TIMI frame count (CTFC), the final TIMI frame count for the LAD artery was adjusted by dividing the count by 1.7.

CSF was defined as a CTFC greater than 27, a threshold exceeding the normal reference range of 21±3 by more than two standard deviations.[11]

Statistical Analysis

The dataset was collected, meticulously reviewed, systematically coded, and subsequently entered into IBM SPSS 23 for analysis. Categorical variables were represented as frequencies and corresponding percentages, whereas continuous data were summarized using means with standard deviation and ranges for normally distributed variables and medians with interquartile ranges (IQR) for those following a non-parametric distribution after applying the Kolmogorov-Smirnov test for normality.

To assess disparities in categorical data between groups, the chi-square test was employed. For non-parametric distributions, the Mann-Whitney U tests was conducted, while an independent t-test was used to assess parametric quantitative data. The receiver operating characteristic curve was used to assess the best cut-off point for serum osmolality to differentiate between patients with and without slow flow with its sensitivity, specificity, positive, negative predictive values, and area under the curve. Univariate and multivariate logistic regression analysis (Backward-Wald model), assess the most important factors associated with slow flow among the studied patients. Also, variance inflation factors were used to assess the multicollinearity, and we used the Hosmer-Lemeshow test to assess the fit of the logistic regression model. A 95% confidence interval was applied with a 5% margin of error, and a statistical significance level was set at $P < 0.05$.

RESULTS

Throughout this study, the mean age of patients affected by PCSFP was 54.53±11.6 years. Males constituted a notably greater percentage of the slow flow group (78.3%) than control group (58.3%), with a *P*-value of 0.019.

As presented in Table 1, smoking emerged as a notable traditional risk factor, accounting for 66.7% of patients in slow-flow group compared to 40% in control group ($P = 0.003$).

The most common presentation of the slow flow group was unstable angina followed by non-STEMI (NSTEMI). Figure 1 demonstrates the clinical presentation of the two groups.

Table 2 shows that hemoglobin level was significantly higher, with a mean value of 14±1.92 in the study group, compared to 13.17±1.78 in the control group, with a *P*-value of *P*-value = 0.015. Also, serum creatinine was found significantly higher, at a mean value, of 1.02± 0.42 in the CSF group compared to 0.88±0.28 in the control group with *P*-value = 0.044. In addition, serum triglycerides (TGs) were found greater in the CSF group with a median (IQR) of 142.5 (103.5-200) as compared to 112 (85-155) in the control group, with *P*-value = 0.016. A notable increase in serum osmolality and its determinants (BUN, Na, and glucose) was observed in CSF patients. The mean serum osmolality was 295.08±6.77 mOsmol/kg in the slow flow group, compared to 284.64±4.74 mOsmol/kg in the control group ($P<$ 0.001).

The receiver operating characteristic curve, illustrated in Figure 2, identified >290.28 mOsmol/kg as the optimal cut-off value for serum osmolality in distinguishing patients with and without CSF. The established threshold attained a sensitivity of 91.67%, a specificity of 88.33%, and an area under the curve of 0.953, denoting superior diagnostic precision.

Table 1: Comparison between both groups regarding demographic data and risk factors

		Slow flow group	Control group	Test value	*P*-value	Sig.
		No:60	No:60			
Age (years)	Mean ± SD	54.53±11.6	54.48±12.39	0.023•	0.982	NS
	Range	21-76	27-78	0.023•	0.982	NS
Gender	Female	13 (21.7%)	25 (41.7%)	5.546*	0.019	S
	Male	47 (78.3%)	35 (58.3%)	5.546*	0.019	S
Smoking		40 (66.7%)	24 (40.0%)	8.571*	0.003	HS
Hypertension		24 (40.0%)	33 (55.0%)	2.707*	0.100	NS
Diabetes mellitus		19 (31.7%)	15 (25.0%)	0.657*	0.418	NS
Dyslipidemia		17 (28.3%)	14 (23.3%)	0.391*	0.532	NS
Ischemic heart disease		6 (10.0%)	1 (1.7%)	3.793*	0.051	NS
Chronic kidney disease		3 (5.0%)	1 (1.7%)	1.034*	0.309	NS
Atrial fibrillation		2 (3.3%)	3 (5.0%)	0.209*	0.647	NS
Hypothyroidism		1 (1.7%)	4 (6.7%)	1.878*	0.170	NS

P-value < 0.05: Significant; •: Independent t-test, *: Chi-square test, SD: Standard deviation, Sig.: Significance, No: Number, NS: Not significant, HS: Highly significant

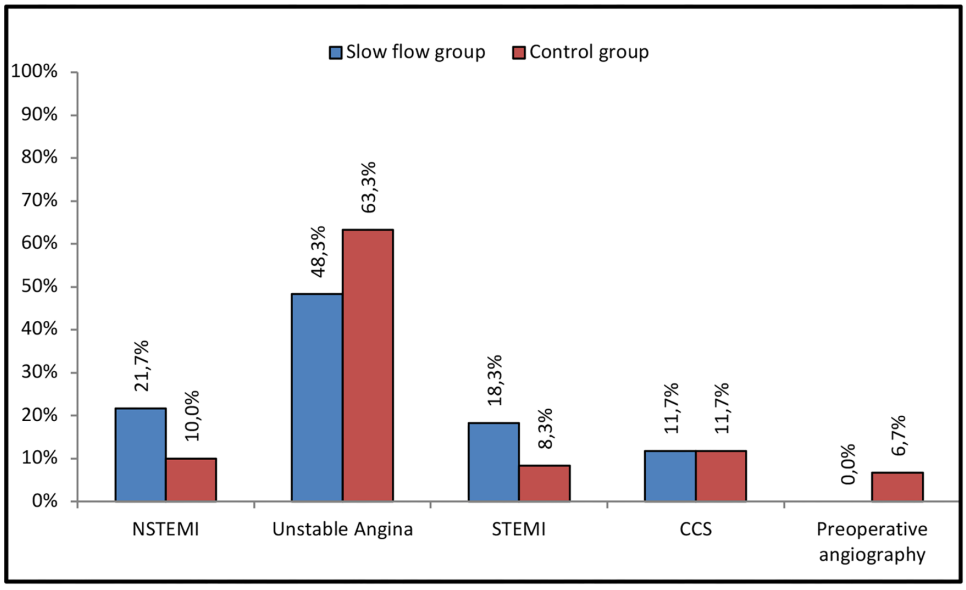


Figure 1: Comparison between patients with slow flow and control group regarding clinical presentation. The most common presentation of the slow flow group was an unstable angina followed by NSTEMI, and the patients undergoing preoperative coronary angiography were more prevalent in the control group

NSTEMI: Non-ST segment elevation myocardial infarction, STEMI: ST segment elevation myocardial infarction, CCS: Chronic coronary syndrome

As shown in Table 3, univariate logistic regression analysis revealed a significant association between all assessed parameters and CSF phenomenon. Furthermore, multivariate logistic regression identified serum osmolality > 290.26 mOsm/kg as the strongest predictor, with an [odds ratio (OR) (95% confidence interval (CI)] of 83.119 (4.488-1539.245) and a *P*-value of 0.003. This was followed by serum glucose > 127 mg/dL (OR = 20.291, 95% CI: 2.611–157.687, *P* = 0.004), smoking (OR = 15.366, 95% CI: 1.458–161.956, *P* = 0.023), BUN > 14 mg/dL (OR = 12.057, 95% CI: 1.827–79.566, *P* = 0.010), and TGs > 127 mg/dL (OR = 7.729, 95% CI: 1.251–47.738, *P* = 0.028).

DISCUSSION

We aimed to investigate in our study the correlation of serum osmolality with the PCSFP among Egyptian people. To assess

Table 2: Comparison between the two groups regarding laboratory parameters

		Slow flow group No: 60	Control group No: 60	Test value	*P*-value	Sig.	Cohen's d
Hemoglobin (g/dL)	Mean ± SD	14±1.92	13.17±1.78	2.465•	0.015	S	0.45
	Range	9.4-19.8	9-17				
Total leukocyte count (x10^3/uL)	Mean ± SD	8.86±3.48	8.84±2.98	0.025•	0.980	NS	0.006
	Range	2.8-19.8	3.3-19.4				
Platelets (x10^3/uL)	Mean ± SD	260.67±81.02	260.62±81.74	0.003•	0.997	NS	0.0006
	Range	84-557	121-532				
Creatinine (mg/dL)	Mean ± SD	1.02±0.42	0.88±0.28	2.033•	0.044	S	0.39
	Range	0.5-2.88	0.33-2.08				
Potassium (mmol/L)	Mean ± SD	4.17±0.43	4.1±0.46	0.901•	0.369	NS	0.16
	Range	3.4-5	2.5-5				
HbA1c (%)	Mean ± SD	6.33±1.34	6.02±1.11	1.371•	0.173	NS	0.25
	Range	4.9-10.3	4.8-9.8				
Total cholesterol (mg/dL)	Mean ± SD	170.48±47.92	183.48±53.91	-1.396•	0.165	NS	0.25
	Range	76-312	83-300				
Triglycerides (mg/dL)	Median (IQR)	142.5(103.5-200)	112(85-155)	-2.412≠	0.016	S	0.45
	Range	49-474	47-397				
Low density lipoprotein (mg/dL)	Mean ± SD	102.23±39.51	113.32±44.04	-1.451•	0.149	NS	0.27
	Range	12-194	38-230				
High density lipoprotein (mg/dL)	Mean ± SD	38.77±13.18	41.78±11.96	-1.313•	0.192	NS	0.24
	Range	14-108	25-75				
Sodium (mmol/L)	Mean ± SD	139.28±2.71	136.3±2.79	5.941•	0.000	HS	1.08
	Range	132-149	127-142				
Random blood glucose (mg/dL)	Mean ± SD	165.87±56.28	125.43±50.09	4.157•	0.000	HS	0.76
	Range	90-370	81-400				
Blood Urea Nitrogen (mg/dL)	Median (IQR)	18(15 – 20)	14(11 – 16)	-4.944≠	0.000	HS	1.01
	Range	9 – 107	6 – 27				
Serum Osmolality (mOsm/kg)	Mean ± SD	295.08 ± 6.77	284.64 ± 4.74	9.790•	0.000	HS	1.79
	Range	284.64 – 330.49	267.15 – 293.13				

P-value < 0.05: Significant, •: Independent t-test; ≠: Mann-Whitney test, IQR: Inter quantile range, SD: Standard deviation, Sig.: Significance, No: Number, NS: Not significant, HS: Highly significant

Cohen's d Interpretation: Neglected: < 0.2, Small: > 0.2, Medium: > 0.5, Large: ≥0.8

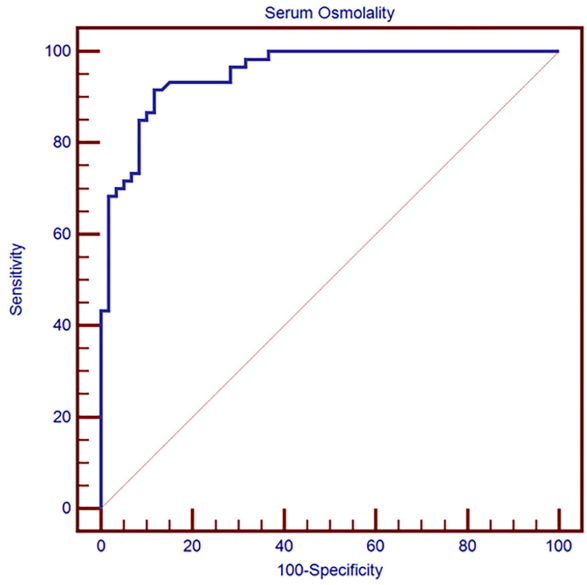
coronary flow, the TIMI frame counting method was used as it is a quantitative and relatively objective method.[11]

In our study, the mean age was 54.53±11.6 years. This is consistent with previous studies that found individuals with PCSFP are generally younger compared to those with obstructive CAD.[4]

In a cohort study involving 213 patients with CSF, Mikaeilvand et al.[12] reported a mean patient age of 53.81±11.91 years.

Seventy-eight-point three percent of PCSFP patients were males, indicating that PCSFP is more often encountered in males. Male gender was statistically significant in PCSFP with OR (95% CI) of 2.582 (1.16-5.75) and with *P*-value = 0.02. Male sex was independently associated with PCSFP in multivariable regression analysis. This finding may be explained by the greater incidence of smoking in men and the cardioprotective influence of female hormones against atherosclerosis.[13] This is consistent with other studies as Hawkins et al.[14] and Sanghvi et al.[15] where they found that male sex was significant in PCSFP than in normal coronary flow. Hawkins et al.'s [14] study revealed that male sex independently predicted the presence of CSFP with OR (95% CI) of 3.36 (1.17-8.61) and a *P*-value = 0.02.

Smoking was notably associated with PCSFP in our study, with 66.7% of patients in the PCSFP group being smokers. A notable variation was observed, and multivariate regression analysis confirmed smoking as an independent predictor of PCSFP (OR = 15.366, 95% CI: 1.458-161.956, *P* = 0.023).



Cut-off point	AUC 95% (CI)	Cross validated AUC (CI)	Sensitivity 95% (CI)	Specificity 95% (CI)	PPV 95% (CI)	NPV 95% (CI)
> 290.28	0.953 (0.898-0.983)	0.870 (0.79–0.95)	91.67 (77.4 - 95.2)	88.33 (81.6 - 97.2)	88.7 (81.0 - 97.1)	91.4 (78.1- 95.3)

Figure 2: ROC curve for serum osmolality level to differentiate between patients with and without slow flow

ROC: Receiver operating characteristic, AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value

Table 3: Univariate and Multivariate logistic regression analysis for predictors of slow flow group

	Univariate				Multivariate			
	P-value	OR	95% CI for OR		*P*-value	OR	95% CI for OR	
			Lower	Upper			Lower	Upper
Male gender	0.020	2.582	1.160	5.750	0.796	1.348	0.140	12.967
Smoking	0.004	3.000	1.424	6.319	0.023	15.366	1.458	161.956
Dilated LA	0.034	0.381	0.156	0.930	0.411	0.388	0.041	3.700
Hemoglobin	0.034	2.347	1.067	5.162	0.905	1.131	0.149	8.576
Creatinine	0.026	2.366	1.111	5.040	0.337	2.261	0.428	11.952
Triglycerides	0.011	2.600	1.243	5.439	0.028	7.729	1.251	47.738
Sodium	0.000	10.789	4.520	25.753	0.570	2.272	0.134	38.627
Serum glucose	0.000	12.000	5.072	28.391	0.004	20.291	2.611	157.687
Blood urea nitrogen	0.000	7.410	3.094	17.748	0.010	12.057	1.827	79.566
Serum osmolality	0.000	68.143	21.482	216.157	0.003	83.119	4.488	1539.245

OR: Odds ratio, CI: Confidence interval

This might be attributed to the injurious effect of smoking on vascular endothelium and its contribution to subclinical atherosclerosis. Also, smokers generally have higher hemoglobin and hematocrit levels, which have been linked to the pathogenesis of this phenomenon.[16] These results harmonize with the evidence presented by Kalayci et al.[17] and disagree with Güneş et al.[18], in which smokers represented only 30% of the cases; this might be due to their small study population, which was only 30 patients.

Our study did not establish a meaningful association between PCSFP and either diabetes mellitus or hypertension. Our results concur with those reported by Sanghvi et al.[15] ; however, they diverge from the study by Sanati et al.[19] on an Iranian population, which demonstrated a substantial prevalence of

hypertension in the CSF group than in the control group (52% vs. 31%, $P = 0.008$).

According to the clinical presentation, the PCSFP presentation varied from STEMI, NSTEMI, unstable angina, and CCS. In our study, unstable angina was the most common mode of presentation (48.3%). This disagrees with the study by Kumar and Garre[20] where the common clinical presentation was CCS (56%).

Regarding the ECG, Mohammad Muthiullah's prospective cross-sectional study stated that 67% of patients with PCSFP had an abnormal resting ECG[21]; this matches the results of our study as most patients in our study presented with an abnormal resting ECG (56.7%).

All the echocardiographic parameters were statistically non-significant between the 2 study groups except dilated left atrium and presence of significant valvular lesions which were more found in the control group. This is due to higher representation of patients undergoing preoperative coronary angiography for valvular heart disease in the control group.

Based on the vessel affected in PCSFP, slow flow affecting the three vessels was the most common angiographic finding (60%). This supports the theory that the phenomenon is a systemic condition.

LAD was the most common artery involved. LAD, LCX, and RCA were involved in 88.3%, 81.7%, and 73.3% of cases, respectively. Our results resonate with those of Sanghvi et al.[15], who documented the highest incidence of involvement in the LAD artery (82.5%), followed by the LCX artery (67.5%) and the RCA (60%).

As part of the investigation into PCSFP, commonly available laboratory markers, including platelet count, hemoglobin levels, and white blood cells (WBCs) count, were assessed. Our findings revealed no correlation between PCSFP and WBCs or platelet counts, and no notable difference was detected between the PCSFP and control groups. This is consistent with the study by Ghaffari et al.[22], which found no link between PCSFP and WBCs, unlike platelet count, which was elevated in PCSFP relative to normal coronary flow in their study.

The hemoglobin level of patients in the PCSFP group was higher than in the control group, demonstrating a substantial variation between groups, with a mean value of 14 ± 1.92 in the study group relative to 13.17 ± 1.78 in the control group, with a P-value = 0.015. In addition, a strong association between hemoglobin level and PCSFP was found following multivariate analysis. It can be hypothesized that a rise in erythrocyte concentration could lead to a reduction in coronary blood flow by increasing blood viscosity.[23] This agrees with Ghaffari et al.[22] and with Nough et al.[24], who found that the hemoglobin level of patients in the PCSFP group was higher than in the normal coronary flow group.

Regarding lipid profile, there was a statistically significant variation in the TGs level between both groups. TAG level was elevated in the PCSFP group, relative to the control group, with median (IQR) of 142.5 (103.5-200) and 112 (85-155), respectively. TAG levels were determined to be independent predictors of PCSFP through multivariable analysis, yielding an OR (95% CI) of 7.729 (1.251-47.738) with a P-value of 0.028. In contrast, no notable variations were detected in total cholesterol, low-density lipoprotein (LDL), or high-density lipoprotein levels between the groups. This is in agreement with Kalayci et al.[17] regarding TAG level, it disagrees regarding the rest of the lipid profile, where there was a notable correlation between the PCSFP phenomenon and higher TAG, cholesterol, and LDL levels. Reflecting our results, Sezgin et al.[25] also reported that high TAG levels might cause endothelial dysfunction in PCSFP patients.

According to HbA1c levels, the two groups did not differ substantially the two groups. This is consistent with the study by Kalayci et al.[17]

PCSFP patients were found to have markedly greater serum osmolality levels than the control group, as demonstrated in this study. Calculated serum osmolality values were 295.08 ± 6.77 mOsmol/kg in the PCSF group and 284.64 ± 4.74 mOsmol/kg in the control group (P-value ≤ 0.001).

Also, the multivariate logistic regression analysis showed that serum osmolality was a strong predictor of CSF phenomenon, with serum osmolality > 290.26 mOsm/kg, OR of 83.119 (95% CI, 4.488-1539.245) and P-value = 0.003.

This observation corresponds with the study by Kargin et al.[8], which found that dehydration was significantly more pronounced in CSFP patients than in the control group.

Serum osmolality and Na act as essential biomarkers for assessing the body's hydration balance.[26] The pathophysiological link between hyperosmolality and CSF may involve increased blood viscosity and resultant endothelial dysfunction. Elevated osmolality can promote hemoconcentration and oxidative stress, both of which have been implicated in microvascular dysfunction. Moreover, hyperosmolar conditions may impair nitric oxide availability and contribute to inflammatory responses, affecting the vascular endothelial factors known to underlie PCSFP.[27]

Furthermore, as serum osmolality reflects hydration status and given that hydration was not directly measured in our study, the potential influence of dehydration on osmolality,

and indirectly on coronary flow, cannot be excluded. Previous studies have emphasized that markers like Na and osmolality may partly reflect intravascular volume depletion, especially in the absence of direct fluid status monitoring.[26,27]

Study Limitation

Certain limitations should be considered in this study. First, the single-center nature of the study may limit the generalizability of our findings. Additionally, the observational and cross-sectional design raises the concern of reverse causation, as PCSFP, could potentially lead to elevated serum osmolality through a stress response (e.g., catecholamine release). Also, the relatively small sample size due to the rarity of the disease may limit the statistical power. The lack of extended follow-up in our study population also prevents us from assessing long-term outcomes and the temporal stability of the observed associations. Finally, while we adjusted for several key confounders, residual confounding from unmeasured factors such as hydration status, subclinical inflammation, or neurohormonal activation remains a possibility.

CONCLUSION

Primary coronary phenomenon is more common in males. Smoking, hypertriglyceridemia, elevated hemoglobin levels, and serum osmolality can be considered independent predictors of this phenomenon.

Thus, while our findings support a strong association between hyperosmolality and PCSFP, further studies are warranted to clarify the causal relationship and elucidate whether correcting hydration imbalances could modify the risk or severity of PCSFP.

Ethics

Ethics Committee Approval: This study was approved by the Ain Shams University Faculty of Medicine Research Ethics Committee (approval number: FWA000017585, date: 14.02.2024).

Informed Consent: Prior to participation, all patients were given a detailed explanation of the procedure, and written informed consent was duly acquired.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.R.E., M.M.A.I., Concept: R.R.E., I.I.E., Design: R.R.E., M.M.N.A., Data Collection or Processing: R.R.E., M.M.N.A., I.I.E., M.M.A.I., Analysis or Interpretation: M.M.N.A., I.I.E., M.M.A.I., Literature Search: R.R.E., M.M.A.I., Writing: R.R.E., M.M.A.I.

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