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Original Article

Long-Term Prognosis in Patients with Coronary Slow Flow

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Abstract

Background: *Coronary slow flow (CSF) is defined as decreased coronary blood circulation velocity and delayed opacification of contrast media during angiography. Evidence is insufficient regarding the course and prognosis of CSF patients. Long-term follow-up can help better understand the physiopathology and outcome of CSF. Accordingly, we assessed the long-term outcomes of CSF patients in this study.*

Methods: *This retrospective cohort study was carried out on 213 CSF patients consecutively admitted to a tertiary health care center from April 2012 through March 2021. After data collection from the patients' files, follow-up was done via telephone call invitations and assessments of existing data in the outpatient cardiology clinic. The comparative analysis was conducted using a logistic regression test.*

Results: *The mean follow-up length was 66.26±15.32 months, 105 patients (52.2%) were male, and the mean age of the patients was 53.81±11.91 years. The left anterior descending was the main affected artery (42.8%). At long-term follow-up, 19 patients (9.5%) required repeated angiography. Three patients (1.5%) had a myocardial infarction and 5 (2.5%) died from cardiovascular etiologies. Three patients (1.5%) underwent percutaneous coronary intervention. No patient required coronary artery bypass grafting. The need for a second angiography had no association with sex, symptoms, and echocardiographic findings.*

Conclusion: *The long-term outcome of CSF patients is good, but their follow-up is necessary for the early diagnosis of cardiovascular-related adverse events.*

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Introduction

Coronary slow flow (CSF) is defined as decreased coronary blood circulation velocity, leading to the delayed opacification of contrast media during angiography.[1] The increased resistance of small blood vessels is the cornerstone of the disease, and no significant coronary artery stenosis is usually seen in angiography.[1] The syndrome was initially

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introduced by Tambe et al[2] in 1972. CSF is not secondary to procedures such as angioplasty and stent insertion.[3] It is seen in 1% to 5% of diagnostic coronary angiograms and is typically accompanied by recurrent chest pain, especially in young male smokers.[4] The left descending anterior coronary artery (LAD) is affected in 50% to 90% of patients, followed by the right coronary and left circumflex arteries.[5] The pathogenesis of the disease is not completely understood, and genetic and metabolic disorders, microvascular and endothelial dysfunction, atherosclerosis, and inflammatory processes are suggested as possible etiological factors.[6,7] Nonspecific incidental findings in CSF include long P waves, increased QT intervals, ST-segment changes, recurrent paroxysmal atrial fibrillations, and positive exercise tests.[8] Recurrent chest pain and syncope due to arrhythmias result in hospital admission in 20% of patients. Some studies have shown the relationship between CSF and sudden cardiac death, life-threatening cardiac arrhythmias, and recurrent acute coronary syndromes.[9] Nonetheless, other studies have suggested a benign course without significant morbidity and mortality.[10] There are controversies surrounding the course and prognosis of CSF patients.[11-14] Long-term cohorts can help better understand the physiopathology and outcome of this group of patients. We, therefore, conducted the present study to assess the long-term outcome of patients with CSF.

Methods

This retrospective cohort study, conducted from April 2012 through March 2021 in a tertiary health care center, enrolled 213 consecutively admitted CSF patients. The inclusion criterion was CSF established by angiography, and the exclusion criteria consisted of patient inaccessibility, lack of appropriate angiography recordings, and patient non-collaboration for follow-up. All coronary angiograms were taken using 6F diagnostic catheters from femoral access. Thrombolysis in myocardial infarction (TIMI) flow grade II was used to define CSF. The opacity of the distal branches of a coronary artery in at least 3 beats was drawn upon to establish CSF.[5]

The study protocol was approved by the Ethics Committee of Urmia University of Medical Sciences. After the completion of the early phase by data collection from medical records (by a medical student of Urmia University of Medical Sciences who was a member of our research team), the second phase was done using semi-interviews with the patients or their relatives via phone call invitations and assessments of existing data in the outpatient cardiology clinic (by a team headed by 2 cardiologists). All angiography films were reported by 2 cardiologists who were experts in reporting angiograms. Patients with stenotic coronary lesions, severe left ventricular dysfunction (left ventricular ejection fraction <40%), hypotension during angiography, vasovagal reactions during angiography, and coronary artery ectasia were excluded from the study.

Nine patients were also excluded: in 6 patients follow-up was not possible because of missing contact data, in 3 patients both cardiologists did not agree on CSF criteria after angiography reviews, and 3 patients did not agree to be a part of this research. Consequently, 201 out of the 213 enrolled patients were included in the final analysis (Figure 1).

Data analysis was done using the Statistical Package for Social Sciences (SPSS), version 20.0. The mean and the standard deviation (SD) were reported for continuous data, and frequencies and percentages were determined for categorical data. The comparative analysis was done using a logistic regression test. A P value under 0.05 was considered statistically significant.

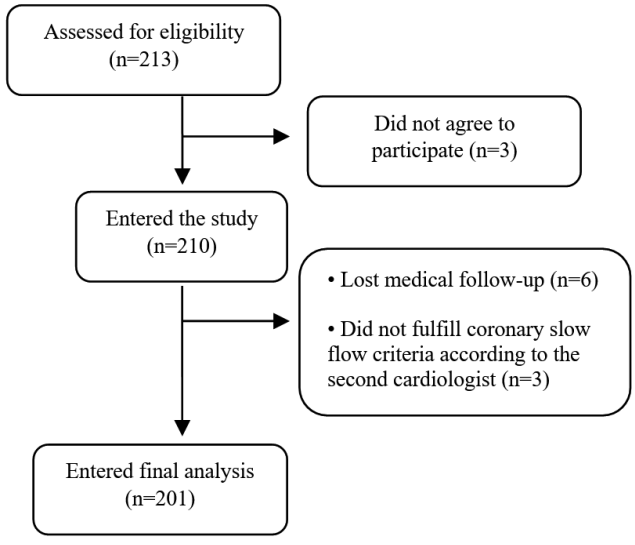

Figure 1. The image illustrates the process of patient enrollment and follow-up

Results

In the current study, the mean follow-up length was 66.26±15.32 months, ranging from 42 to 101 months. Male patients accounted for 52.2% (n=105) of the study population. The mean age of the patients was 53.81±11.91 years, ranging from 22 to 89 years.

Table 1 presents the demographic characteristics and laboratory data of the studied patients.

According to admission echocardiography, the mean ejection fraction was 50.8±7.32%, ranging from 20% to 60%, and it was under 40% in 9 patients (4.5%). Valvular disorders were present in 60 patients (29.9%): mitral regurgitation (MR) in 54 (26.9%), aortic insufficiency (AI) in 22 (10.9%), and simultaneous AI and MR in 16 (8%). None of the patients had stenosis in the aortic or mitral valve. The severity degrees of MR and AI are presented in Table 2.

The reasons for angiography were unstable angina in 125 patients (62.2%), positive exercise tests in 36 (17.9%), electrocardiographic alterations including arrhythmias in 10 (5.0%), MI in 3 (1.5%), positive nuclear scans in 2 (1.0%), unstable angina plus positive exercise tests in 19 (9.5%), positive exercise tests plus positive nuclear scans in 4 (2.0%), congestive heart failure in 1 (1.0%), and sick sinus syndrome in 1 (1.0%). LAD was the main diseased artery as CSF in angiography (Table 3).

Totally, 98 patients (48.8%) required admission to the cardiac care unit, with a mean length of stay of 2.69±1.03 days (range =1–6 d). The total length of hospital stay was 4.19±2.11 days, ranging from 1 to 14 days. Only 1 patient required cardiopulmonary resuscitation.

At long-term follow-up, 19 patients (9.5%) required repeat angiography, which was performed more than once in 3 patients, with a mean time interval to repeat angiography of 3.6±1.40 years (range =2–6 y). MI was reported in 3 patients (1.5%): 1 female and 2 males. The affected CSF was LAD plus the right coronary artery in 2 patients and LAD alone in 1 patient. Two out of the 3 subjects with MI expired. Totally, 5 patients (2.5%) died from cardiovascular etiologies: 1 female and 4 male. The causes of death were MI and heart failure in 3 patients and sudden cardiac death in 2. Three noncardiac deaths were reported: 1 due to cerebral stroke, 1 caused by a car accident, and 1 because of thrombocytopenia. Percutaneous coronary intervention (PCI) was done in 3 patients (1.5%): 2 female and 1 male. All these patients had CSF in LAD. Coronary artery bypass grafting (CABG) was not carried out in the studied patients. The median of readmission times was 2, and the maximal admission time was 16. The mean length of hospital stay in readmission was 13.1±15.72 days, with a maximal stay of 100 days.

Table 4 depicts the association between different variables

Table 1. Demographic and laboratory data of the study population

Variables	Values (n=201)
Age	53.81±11.91
Sex (Male) n(%)	
Hypertension n (%)	67 (33.3)
Diabetes mellitus n (%)	25 (12.4)
Hyperlipidemia n (%)	38 (18.9)
Smoking n (%)	63 (31.3)
Blood sugar	130.62±49.52
Triglycerides	207.00±162.89
Cholesterol	256.32±165.12

Table 2. Severity of valvular disorders in admission echocardiography

Severity	Mitral Regurgitation	Aortic Insufficiency
Mild	45 (83.3%)	17 (77.3%)
Moderate	8 (14.8%)	4 (18.2%)
Severe	1 (1.9%)	1 (4.5%)
Total	54 (100%)	22 (100%)

Table 3. Diseased vessels by coronary slow flow in angiography

Vessels	n (%)
Left anterior descending	86 (42.8)
Right coronary artery	4 (2.0)
Left circumflex artery	2 (1.0)
Left anterior descending + Right coronary artery	14 (7.0)
Left anterior descending + Left circumflex artery	32 (15.9)
Left anterior descending + Left circumflex artery + Right coronary artery	62 (30.8)
Left main	1 (0.5)
Total	201 (100)

Table 4. Logistic regression analysis for the need to repeat angiography

Variables	Odds ratio	Lower limit	Upper limit	P
Sex (Male)	1.088	0.402	2.939	0.868
LVEF=40-50%	0.961	0.097	9.541	0.973
Having exertional chest pain	0.719	0.220	2.355	0.568
≥ moderate AI or MR	1.238	0.394	3.888	0.715

LVEF, Left ventricular ejection fraction; AI, Aortic regurgitation; MR, Mitral regurgitation

and repeat angiography. Our results revealed the need for a second angiography had no association with sex, symptoms, and echocardiographic findings.

Discussion

CSF is a generally neglected entity in the cardiovascular era, and its long-term prognosis is not yet recognized in affected patients. The current cohort of CSF patients evaluated the long-term prognosis (the mean follow-up length >3 y) and revealed that 9.5%, 1.5%, 2.5%, and 1.5% of the studied patients had cardiovascular mortality, repeat angiography, MI, and PCI, respectively. CSF investigations have reported diverse findings.[15] Sadr-Ameli et al,[12] similar to our study, followed up on their cases for 5 to 7 years. In our investigations, male patients comprised approximately 52% of the study population. Icli et al[18] reported a 68% rate of male patients, and Hawkins et al[28] also reported a higher chance for men to develop CSF. All these findings are in line with the results of our study. The mean age of our study population was approximately 54 years.

In our study, the left ventricular ejection fraction was above 40% in 192 patients, and the mean value was 51%. Sadr-Ameli et al[12] reported a mean value of 48%.

MR was seen in approximately 27% of our studied patients, similar to the figure reported by Li et al.[16] In our study, nearly 11% of the subjects had AI, which is comparable with some other studies.[17,18] The main affected coronary artery in our study was LAD. In contrast, Amirzadegan et al[14] reported the right coronary artery as the main involved vessel. It should be noted that we could not determine a higher probability for LAD to develop CSF. In our study, approximately 62% of angiography procedures were performed for unstable angina. Likewise, Zhu et al[19] found that the principal reasons for angiography in their CSF patients were clinical symptoms and unstable angina.

Repeat angiography was required in 9.5% of our patients, with a mean interval length of 3.6 years. Sadamatsu et al[10] assessed only 11 CSF patients, but none suffered major adverse cardiac events or required repeat angiography. Sadr-Ameli et al[12] reported repeat angiography in 36 out of 217 patients within 5 to 7 years of follow-up. Amirzadegan et al[14] reported that 3 out of their 81 CSF patients needed repeat angiography during a follow-up period of 2 to 4 years.

In our study, MI was seen in 1.5% of CSF patients (including 2 male subjects) at long-term follow-up. Zhu et al[19] found a rate of 0.7% for MI. Other investigations have also reported low rates.[18,32] Yetkin et al[20] reported angina pectoris in 80% of their CSF patients and deterioration of conditions in one-third of their subjects; nevertheless, they mentioned that MI was not common in their study population. They also found a higher CSF rate in patients with previous MI, which is also reported in other studies.[21,22] Sadamatsu et al[10] detected no major adverse cardiac events; however, it is worthy of note that their sample size was small. CSF may have a potential association with MI.[23] These comparisons reveal that although MI in CSF patients has a low incidence rate, it should be considered a potential adverse event.

In our study, 2.5% of the patients expired due to cardiovascular causes. Zhu et al[19] and Voelker et al[11] reported cardiovascular mortality in 1.2% and 3.4% of their study populations, respectively, indicating a relatively low incidence rate of cardiovascular deaths in CSF patients. According to our findings, 1.5% of the CSF patients, including 2 females, needed PCI. In contrast, none of the patients evaluated by Zhu et al[19] required PCI. Still, concordant with the study by Zhu et al,[19] none of our patients underwent CABG at long-term follow-up. Almost 30% of our CSF patients required readmission, with a median rate of 2 times. Voelker et al[11] reported a readmission rate of 21.5%, and Li et al[16] revealed that one-third of their CSF patients with chest pain had readmissions. Another study revealed a higher readmission rate in CSF patients due to chest pain,[7] in concordance with our study. Our logistic regression analysis yielded no predictive factors for repeat angiography.

Choi et al[24] reported MI, cardiovascular death, PCI/CABG, stroke, and chest pain in 0.4%, 0.1%, 0.3%, 0.6%, and 8.1% of their CSF patients, respectively. Lichtlen et al[15] reported a cardiovascular mortality rate of 1.1% in subjects with CSF.

Follow-up programming can lessen frequent hospital admissions and angiography procedures and, thus, lower economic burdens and hospital costs for patients and health settings. It is also essential to consider various medications that can decrease the readmission rate in patients with CSF as a permanent but not transient cardiovascular entity.[10,13]

This was a retrospective cohort study, rendering loss to follow-up inevitable. We missed 6 patients because they either failed to reply to our phone calls or changed their phone numbers. Moreover, there are some reports that the CSF phenomenon may be affected by changing seasons, which could affect patients' outcomes.

Conclusion

The present long-term study on 201 CSF patients demonstrated higher rates of MI, cardiovascular death, and the need for PCI/CABG procedures than other studies. Higher readmission rates and more repeat angiographies associated with CSF suggest that this syndrome may be deemed a potential cardiovascular risk factor that should not be considered completely non-hazardous. Accordingly, routine outpatient monitoring and therapeutic modalities for CSF patients can decrease hospital admissions and lengths of stay and prevent adverse events. Still, further studies with larger sample populations and multicenter sampling, besides

the enrollment of other possible contributing factors for the long-term outcome, can contribute to higher quality of care for CSF patients.

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References

1. Kopetz V, Kennedy J, Heresztyn T, Stafford I, Willoughby SR, Beltrame JF. Endothelial function, oxidative stress and inflammatory studies in chronic coronary slow flow phenomenon patients. Cardiology 2012;121:197-203.
2. 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.
3. Wang X, Nie SP. The coronary slow flow phenomenon: characteristics, mechanisms and implications. Cardiovasc Diagn Ther 2011;1:37-43.
4. Fineschi M, Gori T. Coronary slow-flow phenomenon or syndrome Y: a microvascular angina awaiting recognition. J Am Coll Cardiol 2010;56:239-240.
5. Alvarez C, Siu H. Coronary Slow-Flow Phenomenon as an Underrecognized and Treatable Source of Chest Pain: Case Series and Literature Review. J Investig Med High Impact Case Rep 2018;6:2324709618789194.
6. Tanriverdi H, Evrengul H, Mergen H, Acar C, Seleci D, Kuru O, Tanriverdi S, Kaftan A. Early sign of atherosclerosis in slow coronary flow and relationship with angiotensin-converting enzyme I/D polymorphism. Heart Vessels 2007;22:1-8.
7. Yilmaz H, Demir I, Uyar Z. Clinical and coronary angiographic characteristics of patients with coronary slow flow. Acta Cardiol 2008;63:579-584.
8. Wozakowska-Kapłon B, Niedziela J, Krzyzak P, Stec S. Clinical manifestations of slow coronary flow from acute coronary syndrome to serious arrhythmias. Cardiol J 2009;16:462-468.
9. 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.
10. Sadamatsu K, Koga Y, Tashiro H. Long-Term Follow-up of Patients with Coronary Slow Flow Phenomenon. Am J Cardiovasc Drugs 2018;18:73-74.
11. Voelker W, Euchner U, Dittmann H, Karsch KR. Long-term clinical course of patients with angina and angiographically normal coronary arteries. Clin Cardiol 1991;14:307-311.
12. Sadr-Ameli MA, Saedi S, Saedi T, Madani M, Esmaeili M, Ghardoost B. Coronary slow flow: Benign or ominous? Anatol J Cardiol 2015;15:531-535.
13. Erdogan D, Caliskan M, Gullu H, Sezgin AT, Yildirir A, Muderrisoglu H. Coronary flow reserve is impaired in patients with slow coronary flow. Atherosclerosis 2007;191:168-174.
14. Amirzadegan A, Motamed A, Davarpasand T, Shahrzad M, Lotfi-Tokaldany M. Clinical characteristics and mid-term outcome of patients with slow coronary flow. Acta Cardiol 2012;67:583-587.
15. Lichtlen PR, Bargheer K, Wenzlaff P. Long-term prognosis of patients with anginalike chest pain and normal coronary angiographic findings. J Am Coll Cardiol 1995;25:1013-1018.
16. Li N, Tian L, Ren J, Li Y, Liu Y. Evaluation of homocysteine in the diagnosis and prognosis of coronary slow flow syndrome. Biomark Med 2019;13:1439-1446.
17. Icli A, Mutlu H, Karabag T, Kahraman H. Decreased coronary blood flow velocity in patients with aortic insufficiency but normal coronary arteries: the use of TIMI frame count in aortic insufficiency cases. Int J Clin Exp Med 2015;8:16358-16363.
18. Chen Z, Chen X, Li S, Huo X, Fu X, Dong X. Nicorandil improves myocardial function by regulating plasma nitric oxide and endothelin-1 in coronary slow flow. Coron Artery Dis 2015;26:114-120.
19. Zhu X, Shen H, Gao F, Wu S, Ma Q, Jia S, Zhao Z, Tong S, Zhang Z, Zhou Y. Clinical Profile and Outcome in Patients with Coronary Slow Flow Phenomenon. Cardiol Res Pract 2019;2019:9168153.
20. Yetkin E, Turhan H, Erbay AR, Aksoy Y, Senen K. Increased thrombolysis in myocardial infarction frame count in patients with myocardial infarction and normal coronary arteriogram: a possible link between slow coronary flow and myocardial infarction. Atherosclerosis 2005;181:193-199.
21. Sen T. Coronary Slow Flow Phenomenon Leads to ST Elevation Myocardial Infarction. Korean Circ J 2013;43:196-168.
22. Wang Y, Liu MJ, Yang HM, Ma CY, Jia PY, Jia DL, Hou AJ. Association between increased serum alkaline phosphatase and the coronary slow flow phenomenon. BMC Cardiovasc Disord 2018;18:138.
23. Aksakal E, Yapici O, Yazici M, Yilmaz O, Sahin M. Apical hypertrophic cardiomyopathy: a case of slow flow in lad and malign ventricular arrhythmia. Int J Cardiovasc Imaging 2005;21:185-188.
24. Choi BG, Rha SW, Yoon SG, Choi CU, Lee MW, Kim SW. Association of Major Adverse Cardiac Events up to 5 Years in Patients With Chest Pain Without Significant Coronary Artery Disease in the Korean Population. J Am Heart Assoc 2019;8:e010541.