Addiction & Health

https://ahj.kmu.ac.ir
10.34172/ahj.2022.1211
Vol. 14, No. 3, 2022, 224-228

Original Article

Factors Determining Primary Coronary Slow Flow Phenomenon among Opium Users and Non-users: A Case Control Study in Northern Iran

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Abstract

Background: Coronary slow flow phenomenon (CSFP) represents a clinical entity with recurrent chest pain leading to living impairment. The present study aimed to investigate whether opium use correlates with primary CSFP.

Methods: This study included Iranian patients with suspected coronary artery disease who underwent myocardial perfusion imaging. Coronary blood flow was measured quantitatively using the thrombolysis in myocardial infarction (TIMI) frame count and slow flow was defined as TIMI grade 2 standard deviations. Age and clinical conditions including diabetes mellitus (DM), hypertension (HTN), hyperlipidemia (HLP), history of chest pain, and opium use were recorded. First, the characteristics of the two groups were compared and then the main analyses were conducted to examine the relationship between CSFP and opium use. Data were analyzed using *t* test and chi-square test via SPSS 25.0. The significance level was set at $P<0.05$.

Findings: This study was conducted on 44 male patients with documented CSFP who had no stenotic lesions and 134 control group male patients who had normal coronary arteries with normal flow. The mean age was similar in the two groups (54.25 vs.52.69, $P=0.474$). Two groups were significantly different in terms of history of chest pain ($P=0.003$), but there was no significant difference in HTN ($P=0.084$), DM ($P=0.284$), HLP ($P=0.183$), smoking ($P=0.696$), and opium use ($P=0.107$).

Conclusion: This study indicated that opium use is not associated with primary CSFP.

Keywords: Angiography, Chest pain, Coronary artery disease, Opium, Slow flow phenomenon

Citation: Javadi HR, Mirakbari SM, Allami A, Salavati E. Factors determining primary coronary slow flow phenomenon among opium users and non-users: a case control study in northern iran. *Addict Health*. 2022;14(3):224-228. doi:10.34172/ahj.2022.1211

Received: December 26, 2020, **Accepted**: December 19, 2021, **ePublished**: July 29, 2022

Introduction

Opium and opiates have been used for centuries as sedative and pain relief drugs.[1] In addition, they have had great influence on human mood and behavior and have resulted in widespread abuse and addiction despite the awareness about their adverse effects on health.[1-3] Opium has been the first narcotic choice among Iranians for medicinal and recreational purposes.[4] Opium addiction is more common in Middle Eastern countries particularly Afghanistan, Pakistan, and Iran.[5] Qazvin is among the first six provinces of Iran in terms of high prevalence of drug addict arrests following Gilan and Hormozgan provinces. Decrease in the age of addicts (from 25 years in 2011 to 15 years in 2015), increase in drug use among women (from 5% in 2011 to 10% in 2015), increase in drug use among educated people, and increase in synthetic addictive drugs have been observed.[6]

There are traditional positive beliefs about opium particularly in the elderly and patients suffering from chronic illness such as cardiovascular diseases.[7,8] As deducted from some old resources, there is a popular assumption that opium acts as a complementary treatment for coronary diseases, hypertension (HTN), and diabetes mellitus (DM).[9] Coronary slow flow phenomenon (CSFP) is an underrecognized risk factor for patients with chest pain and abnormal noninvasive ischemia with non-obstructive coronary arteries.[10] The CSFP is an important angiographic entity characterized by delayed progression of the injected contrast medium through the coronary tree. It is a frequently encountered finding, typically observed in patients with acute coronary syndromes. Although it is well known to cardiologists over many decades of time, the mechanisms resulting in this phenomenon are still unclear.[11]

Although many previous studies available in the literature on Iranians have questioned the beneficial and protective properties of opium in cardiovascular risk factors,[12,13] little has been documented about the correlation of opium use with CSFP. Therefore, this study aimed to investigate whether opium use correlates with

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primary CSFP.

Methods

Study design and data sources

This cross-sectional case control study was conducted at the cardiology department of Bu Ali hospital, an inner-city tertiary care hospital affiliated to Qazvin University of Medical sciences (QUMS), from august 2016 to august 2017. All patients admitted to the hospital with chest pain underwent thorough medical examination and cardiac tests. Predefined exclusion criteria were implemented to enroll study participants (Figure 1). The participants were informed of the purpose of the study and the interviews were conducted by a cardiology resident. Each participant signed an informed consent and self-reported opium use. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. This study was approved by the institutional review board and strictly followed the institution's ethical guidelines.

Clinical data

Previous medical history of patients was obtained and all clinical entities that could mimic or contribute to the CSFP and the secondary CSFP were excluded. To minimize diagnostic bias, some clinical conditions were defined with identical interpretation standards including myocardial infarction with elevated troponin I level and serial electrocardiogram, chronic kidney disease with glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2, chronic obstructive pulmonary disease with abnormal spirometry, and anemia with hemoglobin concentration less than 13 mg/dL in adult males. For all troponin tests,

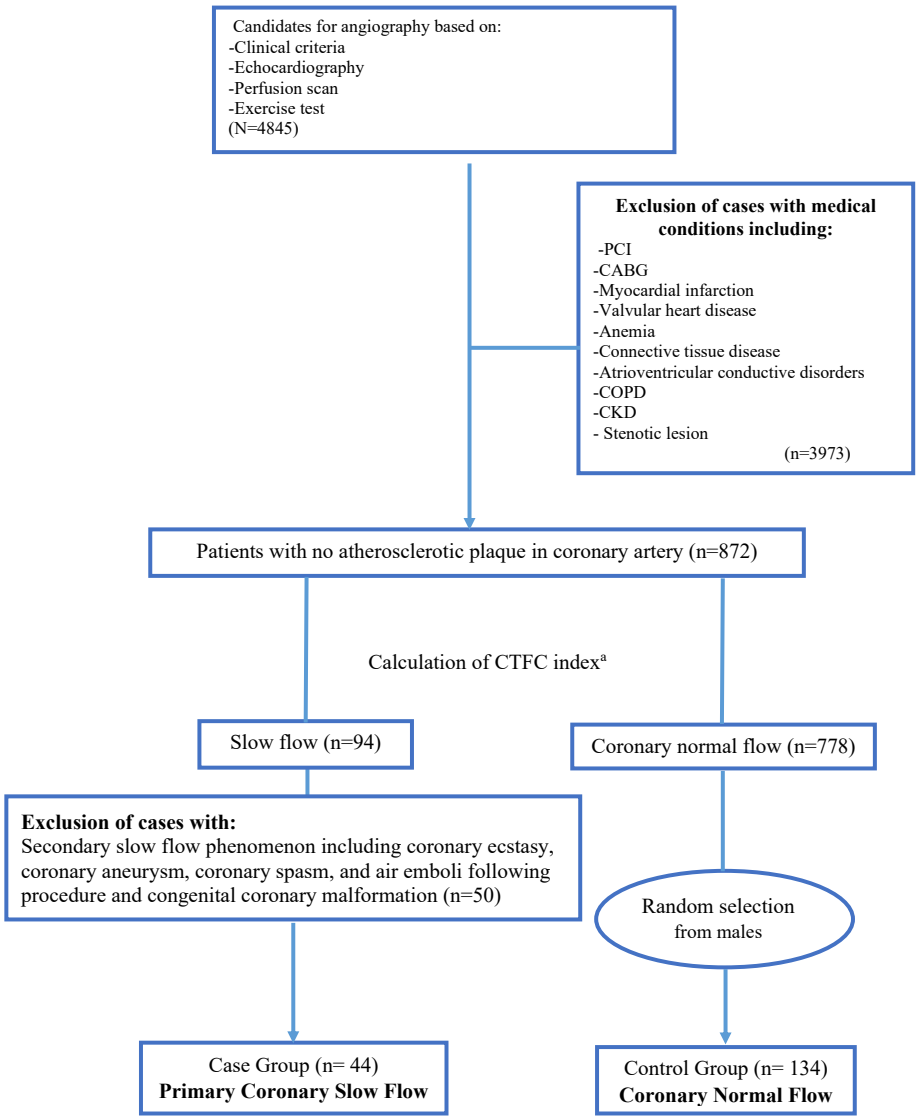

Figure 1. Flow diagram of various stages of selecting patients for the case-control study (N = 178). Abbreviations: PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CKD, Chronic Kidney Disease. [a] Corrected thrombolysis in myocardial infarction (TIMI) frame count.

the cut-off values recommended by the manufacturers of tests were considered in their own population of patients. The blood samples for cardiac troponin I (cTnI) concentrations were measured using ARCH STAT Troponin-I, Abbott Diagnostics (cut-off value: 0.009 ng/mL, 99th percentile: 0.012, 10% coefficient of variation: 0.032, ROC curve: 0.3). An internist was consulted when needed. History of chest pain was defined as prior experience of clinical presentations consistent with myocardial ischemia in patients without significant coronary occlusion in angiography.

Definition of exposures and outcomes

A quantitative index of coronary flow, corrected thrombolysis in myocardial infarction (TIMI) frame count (CTFC), that represents the number of cine-frames required for contrast to first reach standardized distal coronary landmarks was implemented for flow assessment, and slow flow was defined as TIMI grade 2 standard deviations (SD) from normal published range.[14-16] Figure 1 illustrates the research design and various stages of including and excluding the cases.

In accordance with the predefined exclusion criteria, all patients in the primary slow flow group were male. Thus, the control group included randomly selected males with coronary normal flow (CNF) and females were excluded to reduce the confounding bias in adjustment analysis. Frequency of opium users in case group was compared with that of the control group. Opium users were included in the study if they were opium-dependent and smoked or orally consumed opium regularly at least 5 days a week for at least one year and were labeled as opium users. Those who had quitted opium consumption were classified as former users (past history of opium use), hence excluded from the study.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (IBM SPSS) version 25. Descriptive statistical analysis was used to calculate absolute frequency and percentage for qualitative data and mean ± standard deviation (SD) for quantitative data. T-test was used to compare continuous variables in case of normal distribution of variance and nonparametric tests were used in case of non-normal distribution of variables. Chi-square test and Fisher exact test were used to determine the frequency distribution in the agreement tables. Pearson's and spearman's correlation tests were utilized to determine unadjusted bivariate correlation between two variables. The *P* value less than 0.05 was considered significant.

Results

Patient characteristics

A total of 4845 cases underwent angiography during the study period. After excluding the cases based on the predefined exclusion criteria and randomly selecting CNF to match case group, 178 male cases were enrolled in the study. A total of 44 cases with primary slow flow phenomenon were assigned to the case group and 134 cases with normal coronary flow were allocated to the control group. The mean age of patients with CSFP was 54 ± 13 years (range 35 to 81 years). The most prevalent risk factor for coronary disease in CSFP patients was HTN (43.2%). Two study groups were further compared with respect to the defined demographic and clinical characteristics (Table 1).

Primary outcome analysis

According to chi-square analysis, there was no significant difference between CNF and CSFP groups regarding opium use ($P = 0.107$). Moreover, there were no significant difference between these groups regarding age ($P = 0.474$), cigarette smoking ($P = 0.696$), ejection fraction ($P = 0.207$), DM ($p = 0.284$), HTN ($P = 0.084$), and HLP ($P = 0.183$). History of chest pain was significantly higher in case group in comparison with the control group ($P = 0.003$) (Table 1).

The results of univariate analysis showed that the number of slow flow vessels in angiography was closely related to chest pain history ($r = 0.250$, $p = 0.001$), but not to other variables (Table 2).

Discussion

Findings/meaning

There are limited specific data on predisposing factors for CSFP in the medical literature. The results of this study indicated that opium use is not associated with higher CSFP in adult males. Previous studies on different ethnic groups have found different risk factors to be associated with CSFP.[15]

Comparison with related studies

In a study on Australian participants, the male sex and smoking were found to be independent risk factors,[17] while a study on Chinese participants reported DM as an independent risk factor associated with CSFP.[18] Two studies in Iran, both conducted in Kerman province addressed the correlation of opium use with CSFP.[19,20] Moazenzadeh et al concluded that opium addiction was more frequent in those with CSFP than with CNF.[19] It was also demonstrated that opium addiction, DM, and HTN are the main independent predictors of CSFP. Esmaeili Nadimi et al showed opium addiction could be considered a risk factor for microvascular coronary dysfunction, a term used instead of CSFP.[20] Both studies included males and females but the present study investigated only males. Regardless of gender differences, some methodological differences and inherent confounders usually observed in consequences of opium use including cardiovascular

Table 1. Characteristics of study participants (N = 178)

	Total (n = 178)	CNF Group (n = 134)	CSF Group (n = 44)	*P*
Age, year	53.08 ± 12.45	52.69 ± 12.31	54.25 ± 12.93	0.474
EF (%)	55.17 ± 4.48	54.93 ± 4.59	55.91 ± 4.07	0.207
History of chest pain, No. (%)	8 (4.5)	2 (1.5)	6 (13.6)	0.003*
HLP, No. (%)	29 (16.3)	19 (14.2)	10 (22.7)	0.183
Smoking History, No. (%)	27 (15.2)	17 (12.7)	10 (22.7)	0.696
Opium use (with DM and/or HTN), No. (%)	29 (16.3)	21 (15.7)	8 (18.2)	0.107
Opium use only (excluding DM and HTN)	116 (65.2)	92 (68.7)	24 (54.5)	
DM or HTN	35 (19.7)	24 (17.9)	11 (25.0)	0.103
DM + HTN	27 (15.2)	18 (13.4)	9 (20.5)	
Number of slow flow vessels				
One vessel	16 (36.4)	-	16 (36.4)	
Two vessels	12 (27.3)	-	12 (27.3)	-
Three vessels	16 (36.4)	-	16 (36.4)	

Abbreviations: CNF, coronary normal flow; CSF, coronary slow flow; EF, ejection fraction; DM, diabetes mellitus; HTN, hypertension; HLP, hyperlipidemia. Data are presented as mean or number (%) of patients. * Significant, All P-values are statistically significant at $P < 0.05$. T-test or Chi-square tests.

Table 2. Parametric and nonparametric correlations between number of slow flow vessels and study variables

Number of slow flow vessels (0 to 3)	Age	EF	Smoking history	Opium consumption history	DM	HTN	Chest pain history	HLP
Correlation coefficient	0.087	0.053	0.018	0.119	0.101	0.128	0.250	0.110
P value	0.248	0.486	0.811	0.113	0.181	0.089	0.001*	0.145

Abbreviations: EF, ejection fraction; DM, diabetes mellitus; HTN, hypertension; HLP, hyperlipidemia.
Pearson for Age and EF, and Spearman's rho for others variables, 0: Normal flow, 3: slow blood flow in all three vessels.

problems may have contributed to different study results.[21]

In the present study, the prevalence of opium use in those with CSFP was estimated as 18.2% that was lower than the rate reported by Moazenzadeh et al (43.5% in CSF group and 29.0% overall).[19] The prevalence of substance abuse is different among various regions of Iran. In 2013, the Iranian National Network Scale Up survey was designed to estimate the prevalence of opium consumption and accordingly stratify the country into low, intermediate, and high-risk zones. Kerman and Qazvin were classified as high and low risk regions, respectively.[22] In fact, the southeast of Iran is well known for high prevalence of opium consumption. The self-reported life time prevalence of opium use in Iran (12.9%, 95% CI: 6.8-19.0) is higher than the current consumption rate estimated as 5.4%. Lifetime prevalence of opium use is significantly higher in men than women (21.5% versus 4.0%).[2,23]

In this study, the history of chest pain was significantly higher in CSFP group than in the control group. Similar results were reported by other studies.[10,11,16,19,20] Clinically, this phenomenon occurs most commonly in men admitted with acute coronary syndrome. The clinical implications of CSFP are significant as over 80% of CSFP experience recurrent chest pain, resulting in considerable impairment in quality of life, most occurring at rest, which necessitates readmission to the coronary care unit in almost 20% of affected patients.[24]

Finally, the current study demonstrated that male gender and history of chest pain are associated with CSFP, whereas, there are no significant differences between the two groups with and without this phenomenon in terms of HTN, HLP, and cigarette smoking.

Study limitations

The limitations of this study are similar to those of any other study that attempts to measure the effects of opium use on health or disease risk factors. Obtaining validated data from opium users is difficult as using opium is still formally forbidden in Iran.[25] Opium is a mixture of different substances, about 70-80 substances mostly alkaloids, with different effects.[5] Furthermore, drug impurity caused by various adulterants differs in various sources in different time periods and may lead to different results. Besides, large-scale clinical studies are warranted to better characterize this phenomenon, and most importantly, explore its potential relationship with opium consumption. Considering that opium dependent patients with CSFP have a history of chest pain, one may ask whether opium use was primary or secondary to the chest pain. It should be noted that this was a cross-sectional study in which the precedence or recency of opium use could not be assessed. Meanwhile, this study aimed to investigate the association between primary CSFP and opium use rather than the causal relationship.

Conclusion

This study indicated that opium use is not correlated with high primary CSFP. The study of the impact of opium use on cardiac function has inherent limitations that may render different results in different regions.

Acknowledgments

The authors would like to thank the technical assistance of the staff of the catheterization laboratory at Bu Ali Hospital. This research was conducted with administrative support from Qazvin University of Medical Sciences, Iran.

Authors' Contribution

HRJ, AA, and SMM designed the research study. ES collected data. AA and SMM Mirakbari analyzed the data. SMM wrote the paper.

Conflict of Interests

This study received no financial support or grant such as funds, fees, or holding stocks and shares in an organization that may profit or lose through publication of this paper. The authors have no conflict of interest to declare.

Ethics Approval

The ethics committee of Qazvin University of Medical Sciences approved the study with the code IR.QUMS.REC.1396.13.

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