

## EVALUATION OF REPOLARIZATION DISORDERS (RDS) IN ELECTROCARDIOGRAPHY (ECG) OF PATIENTS WITH CORONARY SLOW FLOW (CSF) HOSPITALIZED WITH ACUTE CORONARY SYNDROME (ACS) DIAGNOSIS

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### ARTICLE INFO

**Received:**

03<sup>th</sup> Jun 2017

**Accepted:**

29<sup>th</sup> Nov 2017

**Available online:**

14<sup>th</sup> Dec 2017

**Keywords:** RDS, ACS, CSF.

### ABSTRACT

**Introduction:** CSF is an angiographic finding characterized by delayed filling of the distal vessels with no visible stenosis in epicardial coronary arteries. The aim of this study was to specify repolarization changes in the ECG of patients with CSF hospitalized with patients ACS diagnosis.

**Method:** In this cross-sectional study, 37 patients hospitalized with ACS diagnosis undergoing angiography and having CSF evidence according to TIMI flow rate entered the study. The files of 37 subjects with normal coronary were studied as the control group. The patients were analyzed using the changes in ST-T segment, as well as QT, QTc and TPe values with the results analyzed using SPSS21.

**Results:** According to the multivariate logistic regression model, two factors of male sex (OR = 14.324, P = 0.001) and history of diabetes mellitus (OR = 6.265, P = 0.029) were the predictors of incidence of CSF. Nevertheless, none of QT, QTc, TPe factors, or the ratio of TPe to QT was associated with the occurrence of CSF.

**Conclusion:** The predictive and related factors to CSF incidence were male gender and history of diabetes mellitus. Accordingly, the incidence of CSF is not associated with the increase in electrocardiographic variations such as ST-T changes, T inversion, left ventricular hypertrophy (LVH) as well as changes in QT, QTc, and TPe criteria. In other words, the occurrence of electrocardiographic changes is not associated with the existence of CSF.

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**To Cite This Article:** Reza Faramrza Zadeh, Venus Shahabi Rabori, Mojgan Haj Ahmadi, Shahin Mirza Mohammadi, (2017), "Evaluation of repolarization disorders (RDs) in electrocardiography (ECG) of patients with coronary slow flow (CSF) hospitalized with acute coronary syndrome (ACS) diagnosis", *Pharmacophore*, **8(6S)**, e-1173573.

### Introduction

CSF is an angiographic finding characterized by a delay in the filling of the distal arteries in the absence of visible stenosis in the epicardial coronary arteries. Although this phenomenon has well been recognized by cardiologists over the past 40 years, the pathologic mechanism of the disease has not been fully understood yet. Besides identification of the various aspects of this phenomenon, the clinical relevance of this phenomenon to myocardial ischemia, the incidence of life-threatening arrhythmias, sudden cardiac death, and ACS have been identified in clinical studies (1-6). Although different clinical definitions of CSF are presented, the main feature of CSF is the delay in the progression of intra-arterial contrast agent to coronary artery during

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angiography. This might be seen in one or more coronary arteries, first elaborated on in 1972 (7-8). Thus, this is also known with other names such as CSF syndromes, Y syndrome, or early slow coronary flow (9-11). The important point is that this phenomenon should be distinguished from other cases leading to CSF as a secondary coronary flow. Thus, cases such as coronary artery anomalies, coronary spasm, heart valve disease, or connective tissue disease should be distinguished from CSF (13-12). CSF findings are common laboratory findings with an incidence of 1 to 7% in patients undergoing diagnostic angiography (9,14). This phenomenon is far more prevalent in younger men, in smokers as well as in patients admitted with ACS (15). In more than 80% of cases, patients with CSF suffer complications such as recurrent chest pain mostly at rest, leading to admission to ICUs in 20% of cases (16). More importantly, CSF becomes connected with some life-threatening arrhythmias and sudden cardiac death, based on which evidence of increased QTc dispersion is evident in most patients (17). In some studies, it has been shown that patients with CSF as opposed to the control group have higher prevalence of metabolic syndrome in the presence of higher serum total cholesterol, fasting blood glucose and glucose resistance (18). Furthermore, cases of insulin resistance have been seen in relation to CSF (18, 19). Therefore, the main pathophysiology of CSF and metabolic syndrome looks to be commonly connected with endothelial dysfunction (19). The first evidence of coronary flow or delayed flow was obtained quantitatively by calculation of the TIMI score gained from observations (20). Later on, the use of quantitative TIMI or CTFC framing method led to standardization of TIMI grading (21). Based on the use of the CTFC index, CSF evaluation became possible with path ease. Nevertheless, overall in spite of the invasive nature of angiographic evaluation, it is not possible to evaluate long-term clinical patients by this method. Recent progress in the use of Doppler echocardiography has made possible the non-invasive evaluation of coronary flow patterns, especially in LAD artery (24-22). Accordingly, the possibility of distal LAD evaluation was easily obtained with a diagnostic accuracy of 92.3% using Doppler echocardiography. Thus, patients with CSF are associated with a reduction in velocity flow in the LAD coronary distal, allowing a long-term assessment of the event.

Some studies have been shown that most patients with CSF have transient changes in ST-T completely overlapping with myocardial ischemia during the onset of ACS (1). In addition, in several studies, QT and QTc have been examined as markers of incongruent dispersion of Ventricular transmural repolarization in patients with CSF (16). Since QT and QTc increase is often associated with an increased risk of ventricular arrhythmias and mortality. The present study was aimed to assess the specific changes of ST-T in CSF patients and to compare them with data from normal coronary subjects, in order to assess the hypothesis that these marker changes are from microvascular dysfunction. In addition, QT and QTc are evaluated in coronary patients of coronary artery disease diagnosed with ACS to evaluate the effect of microvascular disorder on ventricular repolarization and arrhythmic risk.

The purpose of this project was to determine repolarization changes in ECG of patients with CSF hospitalized with ACS diagnosis.

### Methodology:

In this cross-sectional study, 37 patients hospitalized with ACS diagnosis undergoing angiography and having CSF evidence according to TIMI flow rate entered the study. Moreover, 37 subjects with normal coronary flow were included as the control group. All patients underwent 24-hour ECG monitoring and changes in ST-T segment of the patients were assessed. In this study, ST-T changes were defined in the form of a change in the level of the ST-T segment of more than 1 mm in more than two continuous ECG lines and recorded as cases of T inversion as well. Moreover, ST-T fluctuation value was measured in patients.

**Exit criteria:** The existence of electrolyte disorders, thyroid problems, pacemaker insertion history, conduction disorders in ECG, ventricular fibrillation rhythm, patients whose medications may prolong QT (antiarrhythmias, antihistamines, triangular antidepressants, anti-psychotics).

LVH was evaluated as a confounding factor in patients and its relationship with target variables was evaluated and analyzed through statistical analysis.

After collecting the data, SPSS 21 was used to analyze the data.

### Results

Overall, 74 patients were evaluated, 37 of whom were in CSF group and 37 as the control in the normal coronary group. The mean age of patients in the two groups was  $51.05 \pm 10.98$  years and  $49.51 \pm 9.65$  years, respectively, with no difference between the two groups ( $P = 0.523$ ). In terms of gender, in CSF group, 59.5% were men and 40.5% women, which was 18.9% and 81.1% in the control group, and the frequency of men in CSF group was significantly higher ( $P=0.001$ ). Concerning risk factors, in both groups - with and without CSF - the prevalence of hypertension was respectively 40.5% and 32.4% ( $P=0.469$ ). The frequency of incidence of previous history of ischemic heart disease was respectively 8.1% and 10.8%, ( $P=0.691$ ), the frequency of diabetes mellitus was 21.6% and 10.8%, respectively ( $P=0.207$ ), hyperlipidemia was 8.1% and 8.1% ( $P=0.999$ ), and the frequency of smoking was 18.9% and 8.1% ( $P=0.174$ ), which showed no difference between the two groups in terms of the prevalence of cardiac risk factors.

In terms of electrocardiographic criteria, evidence of left ventricular hypertrophy was seen in 13.5% and 21.6% of patients with and without CSF, respectively, with no difference between the two groups ( $P=0.359$ ). Moreover, in both groups with and

without CSF, ST-T changes were 35.1% and 27%, respectively, and 16.1% and 18.9%, respectively ( $P = 0.451$ ) and reverse T occurrence was 16.2% and 18.9%, respectively ( $P = 0.76$ ). There was no difference between the two groups in terms of ST-T variations and reverse T.

In both groups with and without CSF, mean QT index was  $0.39 \pm 0.03$  and  $0.39 \pm 0.03$  respectively, which did not differ between the two groups ( $P= 0.672$ ). The mean QTc index in the two groups was  $0.43 \pm 0.03$  and  $0.42 \pm 0.04$ , respectively, with no difference between the two groups ( $P=0.692$ ). In terms of TPe index, the mean of this index in the two groups with and without CSF was  $0.07 \pm 0.02$  and  $0.07 \pm 0.02$ , which did not differ between the two groups ( $P=0.335$ ). The mean ratio of TPe to QT in the two groups with and without CSF was  $0.19 \pm 0.06$  and  $0.18 \pm 0.06$ , respectively, which did not differ between the two groups ( $P=0.364$ ). Moreover, mean TPe to QTc ratio between the two groups was  $0.17 \pm 0.06$  and  $0.18 \pm 0.16$ , respectively, which did not differ between the two groups ( $p=0.708$ ). Based on the multivariate logistic regression model, male sex ( $OR=14.324$ ,  $P = 0.001$ ) and a history of diabetes mellitus ( $OR=6.265$ ,  $P=0.029$ ) were the predictors of CSF incidence. However, none of QT, QTc, TPe factors, or the ratio of TPe to QT was connected with the incidence of CSF (Table 1)

**Table 1: Factors related to incidence of CSF in the multivariate regression model**

Item	P-value	OR	95.0% CI for OR	
			Lower	Upper
Male sex	0.001	14.324	3.183	64.469
Age	0.400	0.975	0.920	1.034
HTN	0.076	3.546	0.877	14.346
IHD	0.351	2.562	0.354	18.526
DM	0.029	6.265	1.206	32.558
HL	0.543	1.912	0.237	15.417
CS	0.430	2.136	0.324	14.094
Constant	0.272	0.100		

### Discussion and conclusion

Different factors are connected with the incidence of CSF, some of which are ischemic or non-ischemic, some are local, and some related to systemic factors. Accordingly, given the association of some pathophysiologic cardiovascular factors such as endothelial dysfunction and inflammatory processes, it appears that electrocardiographic changes, especially ST-T changes, as well as changes that can occur in QT and TPe intervals can be connected with occurrence of CSF. Thus, the present study aimed to compare the relationship between the occurrence of electrocardiographic changes between the two groups with and without CSF. In terms of comparing the primary indices of patients including demographic characteristics and risk factors for heart disease between the two groups with CSF and normal coronary flow, we concluded that the incidence of CSF in men was significantly higher than that of women, which was proven in the multivariate logistic regression model, so that the risk of CSF in men was about 14 times that of women. Thus, male gender will be as a potential factor contributing to the occurrence of CSF in our population. However, the age of patients was not specified as a factor connected with the occurrence of CSF. In terms of CSF risk factors, the only factor associated with CSF, obtained in multivariate regression models, was the history of diabetes mellitus in patients, so that the risk of CSF occurring in diabetic patients compared to non-diabetic patients was 6 times. Other risk factors were not considered as factors associated with the occurrence of CSF. Thus, it seems that the greatest risk of CSF and possibly its adverse clinical outcomes is to men, especially those with diabetes mellitus. Overall, more CSF in men compared to women was due to a higher prevalence of cardiac pathophysiological disorders in men and the pre-emptive effects of female hormones in women. On the other hand, the cause of higher incidence of CSF in diabetics is likely to be due to the high prevalence of endothelial disorders as well as active inflammatory processes in diabetics compared to non-diabetics.

In contrast to the first hypothesis stated connected to the relationship between ECG and CSF occurrence indices, none of the observed factors in ECG was connected with the incidence of CSF. In other words, it seems that the occurrence of CSF has not been significantly correlated with RCG criteria in our study. This lack of relationship can be related to a plethora of reasons. First, according to the results of our study, there might be no pathophysiological relationship between CSF and ECG criteria. Secondly, our study might have been affected by some confounding factors, such as the small sample size, errors and mistakes in the interpretation of ECG strip by the assistants or the lack of recognition of CSF in some patients. This issue is considered important in our study when some patients in the group without CSF with normal coronary flow, have a history of ischemic heart disease and some changes such as ST-T changes, as well as left ventricular hypertrophy, so our control group does not appear to be isolated.

Comparing our study with previous studies indicates some significant differences between studies, though studies in this area are very limited. In the study by Cutri et al., the results indicated that among patients with CSF, 20% had ST-T

changes. Contrary to that, none of the subjects in the control group had ST-T changes. Moreover, T wave changes occurred in 85% and 5% of subjects in both groups, respectively. Furthermore, quantitative ECG analysis in two groups based on the fluctuation index in ST-T segment indicated this fluctuation value of  $160 \pm 45$  Mv in CSF group and  $49 \pm 21$  mV in the control group, which was completely a significant difference (25). In another study by Cutri et al., it was shown that T wave changes occurred in 37% of patients, which was independent of the gender and age of the patients. These changes in T wave occurred mostly in the left-to-left position (86%) and then in the left-to-right position (29%). Changes in the T wave were mainly related to V2 (100%), then V3 (57%) and V1 (14%). Variations in ST-T segment in these individuals did not occur in various situations (25).

Overall, based on the results of this study, the predictive factors associated with CSF were male sex and a history of diabetes mellitus. In this regard, the occurrence of CSF was not coincided with an increase in electrocardiographic changes such as ST-T changes, inversion of T, left ventricular hypertrophy and changes in QT, QTc, and TPe criteria. In other words, the occurrence of electrocardiographic changes in repolarization phase is not related to CSF.

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