

Comparison between the ventricular function in patients affected by primary Slow Coronary Flow and Normal Coronary Flow

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Abstract

Aims: The Coronary Slow Flow Phenomenon (CSFP) is a syndrome which according to normal or near normal angiography findings is characterized by delayed progression of the injected contrast medium through the coronary vessels. The causes of this disease are unknown. Therefore, the identification of the disease's pathogen, an effective cure and the long-term prognosis of these patients is still in need of more research. This research attempts to analyze and compare the systolic and diastolic function of the left and right ventricle in people affected by primary Slow Coronary Flow and Normal Coronary Flow. **Methods and Results:** This case-control study was conducted with the participation of 44 patients undergoing coronary angiography in Qazvin's Bu Ali Sina Hospital in 2017. The patients were divided in two groups of primary Slow Coronary Flow (33 people) and Normal Coronary Flow (11 people) and the systolic and diastolic function of the left ventricle and the systolic function of the right ventricle was analyzed and compared between the two groups. The frequency of left ventricular systolic and diastolic dysfunction and right ventricular systolic dysfunction was similar and no significant statistical difference was seen between the two groups. **Conclusion:** In this research the frequency of left ventricular systolic and diastolic dysfunction and right ventricular systolic dysfunction was similar and no significant statistical difference was seen between the two primary Slow Coronary Flow and Normal Coronary Flow groups. **Keywords:** left ventricular systolic function, left ventricular diastolic function, right ventricular systolic function, Coronary Slow Flow

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Introduction: The Coronary Slow Flow Phenomenon (CSFP) is a syndrome which according to normal or near normal angiography findings is characterized by delayed progression of the injected contrast medium through the coronary vessels. The causes of this disease are unknown. Therefore, the identification of the disease's pathogen, an effective cure and the long-term prognosis of these patients is still in need of more research. This research attempts to analyze and compare the systolic and diastolic function of the left and right ventricle in people affected by primary Slow Coronary Flow and Normal Coronary Flow.

Methods and Results: This case-control study was conducted with the participation of 44 patients undergoing coronary angiography in Qazvin's Bu Ali Sina Hospital in 2017. The patients were divided in two groups of primary Slow Coronary Flow (33 people) and Normal Coronary Flow (11 people) and the systolic and diastolic function of the left ventricle and the systolic function of the right ventricle was analyzed and compared between the two groups.

Diastolic function of the left ventricle in control group 82.0% of patients had a normal function and 18% have mild dysfunction. Among the cases, 72.7% had a normal function and 8 people (24.2%) mild dysfunction

(3.1%) had moderate dysfunction; whereas the frequency distribution of the diastolic dysfunction of the left ventricle in the two study groups was similar ($P>0.05$). The analysis of the echocardiographic indices shows that the frequency distribution of the left ventricular systolic dysfunction is similar in the two groups.

Conclusion: In this research the frequency of left ventricular systolic and diastolic dysfunction and right ventricular systolic dysfunction was similar and no significant statistical difference was seen between the two primary Slow Coronary Flow and Normal Coronary Flow groups.

Keywords: left ventricular systolic function, left ventricular diastolic function, right ventricular systolic function, Coronary Slow Flow

INTRODUCTION

The Coronary Slow Flow Phenomenon (CSFP) or the Y syndrome was first introduced by Tambe (Tambe et al, 1978) [1]. The CSFP is a Phenomenon which is characterized by delayed distal vessel opacification of contrast, in the absence of significant epicardial coronary stenosis. This condition can exist in one or all coronary arteries of a heart. Anatomic factors such as the angle of differentiation of the left main coronary artery from the aorta has been mentioned in the etiology of this disease. Some anatomical dysfunctions could through the malfunction in the coronary blood flow resulting in the endothelial dysfunction and ultimately lead to CSFP [2,3]. Histological studies shows the myofibers hypertrophy, the thickening of elastic muscular fibers of the small arteries along with the inflammation of endothelial cells and dissection and narrowing of the arteries lumen among these patient [4]. Pathophysiology of CSFP is still not well-known. In these patients an increase in the resistance of coronary arteries during rest periods has been seen. The evaluation of microvascular dysfunction was first mentioned by Mangieri (Mangieri et al, 1996) after the improvement of the coronary arteries blood flow following the injection of dipyridamole and a nonresponse to nitroglycerin [5].

The frequency of CSFP has been reported in different studies ranging from a rare finding to a rather prevalent which could be due to difference among existing definitions in this regard [5] [1]. According to different studies, the incidence of CFSP between 1 to 7 percent among patients undergoing coronary angiography has been reported and is more prevalent among young male smokers. The presentations of syndrome cover a wide variety, from stable to unstable angina, myocardial infarction with and without ST segment elevation, ventricular Tachycardia and sudden death [6]. Approximately 85 percent of these patients experience recurrent chest pain throughout their life span and 15 percent of them need to be hospitalized and a second angiography. The data shows that electrocardiography at rest in CSFP patients represent the T wave and ST segment changes. In other studies, episodes of non-sustain ventricular Tachycardia and an increase in QT dispersion have been reported [6]. In addition when the patient was experiencing chest pain, electrocardiographic change and sign of ischemia could be seen in 25 percent of them [1].

Even though in some studies left ventricular systolic and diastolic dysfunction among CSFP patients has been reported [7–15] but in others no meaningful relationship has been reported between CSFP and left ventricular dysfunction [16]. This functional disorder can have clinical implications on patients' functional capacity [12]. Also, in CSFP patients, life-threatening arrhythmias and sudden cardiac death can take place but the pathologic mechanism and its effect on the left ventricle is still not clear [9]. Being male and a high body mass index (BMI) are two independent factors predicting CSFP but further research has been recommended in this regard [7]. In some studies the outbreak of metabolic disorders in CSFP patients has been more than the control group [16,17]. According to different reports about the characteristics of CSFP patients and the effect of the disease on the function of the left and right ventricle, we compared the relationship between systolic and diastolic left ventricular function and the systolic right ventricular function in patients affected by primary Slow Coronary Flow and others who have Normal Coronary Flow.

METHODS

The study population: patients referred to Bu Ali Sina Hospital who had been subject to coronary artery angiography due to chest pain from April 2017 to March 2018.

Study Design

From the 4845 patients who underwent coronary angiography in 2017 at Buali Sina University Hospital in Qazvin-Iran, 33 patients who had the diagnostic criteria of "primary slow flow, coronary syndrome" according to the inclusion criteria and method for diagnosis of slow flow in angiography of coronary arteries selected as the case group. From 837 patients with normal angiography findings and normal coronary flow, 11 patients were evaluated as the control group. The samples were chosen to use the nonrandomized convenient sampling method. The results were recorded after completion of angiography. Echocardiography was then conducted to analyze the systolic and diastolic left and right ventricular function. The data were entered into a pre-designed checklist and then analyzed.

Inclusion criteria

Patients who were expected to undergo angiography due to their clinical symptoms, electrocardiography and echocardiography variations, perfusion myocardial scan or other reasons excluding ischemia and myocardial infarction (such as arrhythmias or conduction disorders and...) were included in the study.

Exclusion criteria

Patients with history of congestive heart failure (CHF), Percutaneous coronary intervention (PCI) and Stenting, coronary artery bypass graft (CABG) and myocardial infarction, coronary artery disease, chronic obstructive pulmonary disease (COPD), more than mild valvular dysfunctions, connective tissue diseases and atrioventricular conduction disorder were excluded from the study. In addition, patients with anemia and chronic kidney disease, electrolyte disturbance, coronary artery ectasia and aneurysm, coronary artery spasm, iatrogenic air embolism during procedure and congenital coronary artery anomalies which could lead to the slow flow of blood in the coronary arteries, were excluded from the study. The cases and controls were matched according to age, BMI and risk factors.

The criteria and method for diagnosis of slow blood flow in angiography of coronary arteries

The diagnosis of CSFP was conducted through coronary angiography and based on quantitative and qualitative Thrombolysis in myocardial infarction (TIMI) method[4]. Siemens Artis zee C-arm angiography system was used. Coronary angiography was performed via the Judkins standard method and through the femoral artery using the necessary standard 4F catheters. Coronary arteries were analyzed from right and left cranial and caudal angulations. Manual contrast injection was done for all patients using Vizipaque with medium osmolality. The coronary flow of all patients was measured and registered using TIMI frame count (TFC). The patients' coronary arteries TFC was determined through the Gibson method (Gibson, et al, 1996) [18]. All angiography projections were evaluated and reported by a cardiologist with adequate skill and knowledge who was unaware of the patients' prior clinical information.

In this method, first the number of consecutive frames with the speed of 30 frames per second are recorded and then counted. The number of frames needed for the injected contrast medium to reach standard signs at the distal of the coronary artery, at the left anterior descending artery (LAD), left circumflex artery (LCX) and the right coronary artery (RCA) are counted. The predefined points include the distal LAD bifurcation, the distal bifurcation in the longest segment of LCx and the first branch of the posterior LV (PLV) branch for the RCA. The standard average for the natural formation of coronary arteries is 36.2 ± 2.6 frames for LAD, 22.2 ± 4.1 frames for LCX and 20.4 ± 3 frames for RCA. Since the LAD artery is bigger than other coronary arteries, the counted TIMI is normally overestimated, therefore, to obtain a modified TIMI frame for LAD, the obtained values are divided by 1.7. The corrected standard TIMI frame count for LAD is 21.1 ± 1.5 . CSF is considered if the corrected TIMI frame counts exceeds two standard deviations from the standard value [19]. In order to determine the average number of TIMI frames per person, the total number of LAD, LCX and RCA corrected frames is divided into three.

Echocardiography

Echocardiography was performed 72 hours after coronary artery angiography using a VIVID S5-(GE) Di-

mension Ultrasound with a 2-4 megahertz probe. During the echocardiography the patients lay on their left side and breath normally. The images and parameters of the systolic and diastolic function of the left and right ventricle were evaluated according to the recommended standards of the American Society of Echocardiography (ASE) Executive Committee by an echocardiography specialist who was unaware of the patients' clinical information [20]. The data of at least three consecutive heart cycles were recorded.

The Simpson method was used in order to evaluate the left ventricular systolic function. Based on this method ejection fraction (EF) values of less than 52% for men and less than 54% for women were considered as a systolic dysfunction.

The evaluation of the left ventricular diastolic function was done by Tissue Doppler (TDI) with the evaluation of the Mitral Inflow Pattern and the Pulmonary venous Doppler Flow pattern using Doppler echocardiography and then the results were divided into 3 categories of mild, moderate and severe dysfunctions based on Fig.1 [19].

In order to evaluate the right ventricular systolic function, the Fractional Area Change (FAC) value was calculated using the RVAd-RVAs/RVA method. The Tricuspid Annular Plane Systolic Excursion (TAPSE) using the M-mode and Tissue derived Doppler tricuspid lateral annular systolic velocity methods were measured. Values of under 35% for RVFAC, under 17 millimeters for TAPSE and less than 9.5 Centimeters/Second for Tissue derived Doppler tricuspid lateral annular systolic velocity were considered as right ventricular systolic dysfunction [21].

Statistical analysis

The data was analyzed using the SPSS software version 16. Quantitative variables were described as numerical indices (Mean \pm SD) and qualitative variants were described as frequencies and percentages. The normalization of quantitative data was evaluated using Shapiro-Wilk test. The t-Student test was used in order to compare the quantitative variables and in order to analyze the relationship between qualitative variants chi-square test and Fisher's exact test were used. A P value <0.05 was considered statistically significant.

Ethical considerations

In this study ethical considerations in medical research were considered according to the Helsinki Statement and the National Research Ethics in Medical Studies. Informed consent was obtained from all patients before entering the study and all their information was kept confidential. This research has the confirmation number (IR.QUMS.REC.1396.33) from the Medical Research Ethics Committee of Qazvin University of Medical Sciences.

RESULTS

This study was conducted on 33 patients with Coronary Slow Flow and 11 patients with Normal Coronary Flow in order to compare their systolic and diastolic left ventricular function and right ventricular systolic function. The findings indicate that there is a no statistical significant difference in the age, gender, smoking, mean systolic and diastolic pressure and heart rate characteristics between the two study groups (Table 1).

The findings demonstrate that there is no statistical significant difference between the two groups concerning the indication for coronary angiography (Table 2) (P=0.731).

The frequency of the arteries with coronary slow flow (CSF) among the study population is shown in table 3. There was no left or right ventricular systolic dysfunction among any of the patients with RCA involvement. Left ventricular diastolic dysfunction was only seen in one of the patients with RCA and LCX involvements. Among 10 patients who had one vessel involvement, 6 individuals (20.2%) had LAD and 4 patients (10.1%) had LCX involvement.

In analyzing the echocardiographic criteria, only the values of Peak velocity flow in early diastole (E wave) as well as Late diastolic velocities measured at a lateral site of the mitral annulus (A 'lateral) had mea-

ningful significance (P values= 0.022 and 0.033, respectively), even though A' (lateral) does not have a role in analyzing the systolic and diastolic function of the left and right ventricles (Table 4). An evaluation of echocardiographic criteria shows that the normal ratios of the right ventricle including the FAC, TAPSE and RVS' of the two groups are the same ($P>0.05$) (Table 5).

Among the left ventricle's echocardiographic parameters, in 8 people in the control group (72.7%) systolic (S) and diastolic phase (D) waves were seen in the form of S more than D and in 3 people (27.3%) systolic-(S) and diastolic-phase (D) waves were seen in the form of D more than S. In the cases, 31 people (93.9%) had systolic-(S) and diastolic-phase (D) waves in the form of S more than D and in 2 people (6.1%) systolic and diastolic phase (D) waves were such that D was more than S. Thus, the distribution of systolic (S) and diastolic phase (D) waves in the two groups is similar ($P>0.05$). Also, in the control group 3 people (27.3 %) had an E/A wave ratio of less than 0.75 and the other 8 people (72.7%) had an E/A ratio between 0.75 and 1.5. Among the cases, the results showed that 9 people (27.3 %) had an E/A wave ratio of less than 0.75 and 24 people (72.7%) had an E/A ratio between 0.75 and 1.5. In conclusion, altogether the frequency distribution of the E/A Wave ratio in the two groups was similar ($P>0.05$).

In the control group the Early mitral inflow velocity/mitral annular early diastolic velocity ratio (E/e') among all eleven people was less than 10, whereas 30 patients (90.9%) among the cases had ratio of less than 10 and 3 patients (9.1%) had this ratio of more than or equal to 10; thereby the frequency distribution of Early mitral inflow velocity/mitral annular early diastolic velocity (E/e') ratio between the two groups was similar ($P>0.05$). In the control group 3 people (27.3%) had mild reduction of EF and 8 people (72.7%) had normal EF. Among the cases 9 people (27.3%) had mild reduction of EF and 24 people (72.7%) had normal EF. The frequency distribution of this criteria was therefore similar in the two study groups ($P>0.05$).

In the Simpson method of measuring LVEF, 2 people in the control group (18.2%) had a mild dysfunction and 9 people (81.8%) had normal EF. Among the cases the numbers were 7 people (21.2%) and 26 people (78.8%), respectively. Therefore, the frequency distribution of the ejection fraction or in other words the left ventricular systolic function was similar in the two study groups ($P>0.05$). In analyzing the diastolic function of the left ventricle in the control group, 9 people (82.0%) had a normal function and 2 people (18%) have mild dysfunction. Among the cases, 24 people (72.7%) had a normal function and 8 people (24.2%) mild dysfunction and 1 person (3.1%) had moderate dysfunction; whereas the frequency distribution of the diastolic dysfunction of the left ventricle in the two study groups was similar ($P>0.05$). (Table 6)

The analysis of the echocardiographic indices shows that the frequency distribution of the left ventricular systolic dysfunction is similar in the two groups (Table 6).

DISCUSSION

Considering different reports concerning Coronary Slow Flow (CSF) patients and its effect on the cardiac function, in this study we have compared the systolic and diastolic function of the left and the systolic function of the right ventricle in patients with primary CSF and CNF. The frequency of left ventricular systolic and diastolic dysfunction and the right ventricular systolic dysfunction was similar in the two groups and no statistical significance was seen between the primary CSF and the CNF group.

There are different reports regarding the impact of CSF on the function of the left ventricle. In the study of Fineschi, M. et al. coronary flow reserve (CFR) has been reported to be normal in CSF patients [22]. On the other study, Erdogan, D. et al. has reported the coronary flow reserve (CFR) to be impaired in CSF patients [23]. In the study of Barutcu, A. et al. the LV-twist of the left ventricle was impaired in CSF patients and the severity of impairment had a direct correlation with the TIMI frame count (TFC) [1]. In the study of Beau, et al. there was no relationship between CSF and the left ventricular diastolic function [3] which is similar to the results of this research. In the research of Zencir et al. a comparison between left ventricular systolic and diastolic function did not reveal any statistically significant difference among CSF patients and the control group [15] which is also in line with the results of our research. In the study of Baykan et al. left ventricular systolic and diastolic function was reported as being impaired among CSF patients [7]. However, in our study this impairment was not different from the control group. In the study of Y. Li et al. the global

and regional left ventricular diastolic function was reported as being impaired in CSF patients and moreover the number of affected coronary arteries, determined the severity of the left ventricular dysfunction more than the coronary artery TFC [8]. Such a correlation, however, was not witnessed in this research.

In the research of Balci et al. despite the left ventricular dysfunction, the right ventricular systolic and diastolic functions were normal among CSF patients and further study has been suggested in order to determine the mechanism of these findings [9] which evermore highlights the importance of studies such as this research. It has been stated in the research of Altunkas et al. that despite the normal right ventricular function, CSF can lead to echocardiographic changes and a degree of reduced left ventricular function [10]. Although such a reduction was not statistically significant in this study. In the study of Elsherbiny left systolic and diastolic ventricular dysfunction in CSF patients has been reported to have clinical implications on these patients' functional capacity and close follow up of these patients in order to categorize risk levels has been reiterated [11]. We have however, like most other researches not seen any statistical significance in our research.

In the study of Nurkalem et al, despite maintaining ejection fraction, the regional and global strain in CSF patients has been reduced and the longitudinal left ventricular systolic function in these patients was impaired [13] which is not in line with the findings of this research. Sezgin et al., also reported diastolic dysfunction in CSF patients [14]. The patients' diastolic dysfunction in this study was similar to that of the control group. In the study of Aksal et al. an increase in the time to peak systolic strain in CSF patients has been reported and stated that the degree of this increase can be used to predict the worsening of the regional myocardial contractility among these patients [18] This timeframe was similar between the two groups in our study.

CONCLUSIONS

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DISCLOSURES

The authors have declared that no competing interests exist.

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**Table No 1-
Comparison of
baseline
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Variables	Normal (N=11)	CSF (N=33)	P-Value
Age (Year)	55.9±11.8	53.3±12.2	0.541
Gender			
Male	7 (63.6%)	23 (69.7%)	0.709
Female	4 (36.4%)	10 (30.3%)	
Smoking			
Yes	2 (18.2%)	1 (3.0%)	0.107
No	9 (81.8%)	28 (84.8%)	
Cessation of smoking	0 (0.0%)	4 (12.1%)	
Hypertension			
Positive	4 (36.4%)	12 (36.4%)	1.0
Negative	7 (63.6%)	21 (63.6%)	
Systolic Blood Pressure (mmHg)	124.1±9.4	121.21±13.7	0.520
Diastolic blood pressure (mmHg)	75.2±5.1	72.88±8.1	0.379
Heart rate (Beat per minute)	73.7±5.6	75.36±5.8	0.412
Values are presented as mean ± SD or frequency (percent). Abbreviations: SD, standard deviation.	Values are presented as mean ± SD or frequency (percent). Abbreviations: SD, standard deviation.	Values are presented as mean ± SD or frequency (percent). Abbreviations: SD, standard deviation.	Values are presented as mean ± SD or frequency (percent). Abbreviations: SD, standard deviation.

Table 2- the distribution of angiography reasons among the case and the control groups

Coronary angiography reasons	Normal (N=11)	CSF (N=33)	Total
Typical chest pain (TCP)	6 (54.5%)	20 (60.6%)	26 (59.1%)
Positive exercise tolerance test (ETT)	2 (18.2%)	6 (18.2%)	8 (18.2%)
Myocardial perfusion imaging defect (MPI)	3 (27.3%)	5 (15.2%)	8 (18.2%)
Total	11	33	44
P-Value=0.731			

Table 3-The distribution of affected arteries in slow coronary flow patients

Number of vessels involved	Location	Frequency (%)
1	LAD	6 (18.18%)
	LCX	4 (12.12%)
2	LAD, LCX	5 (15.15%)
	LAD, RCA	2 (6.06%)
	LCX, RCA	2 (6.06%)
3	LAD, LCX, RCA	14 (42.4%)

Table 4- the echocardiographic criteria of the ventricular function in the case and the control

groups

Variables (unit)

LV end-diastolic diameter (mm)
 LV end-systolic diameter (mm)
 Interventricular septum (mm)
 LV Posterior wall (mm)
 LV end-diastolic volume (ml)
 LV end-systolic volume (ml)
 LV ejection fraction (%) Simpson method
 LV Ejection fraction (%) visual method
 Mitral deceleration time (ms)
 Mitral e' (cm/s)
 Mitral E/e' Ratio
 Septal E' (cm/s)
 Lateral E' (cm/s)
 Septal A' (cm/s)
 Lateral A' (cm/s)
 Systolic-phase (S wave) cm/s
 Diastolic-phase (D wave) cm/s
 Peak – mitral E wave (m/s)
 Peak – mitral A wave (m/s)
 Peak mitral E/A wave Ratio
 RV end-diastolic area (cm²)
 RV end-systolic area (cm²)
 TAPSE (mm)
 Right ventricle pulse Doppler S wave (RVS')
 Right ventricular fractional area change (%)
A: Late diastolic flow velocity; **A':** Late diastolic (mitral) annular velocity; **E:** Early diastolic flow velocity; **E':** Early diastolic

Table 5- Comparison of the echocardiographic indices of the normal and abnormal right ventricular systolic function in the case and the control groups

	Normal (N=11)	CSF (N=33)	P-Value
Right ventricular fractional Area Change (%)			
Abnormal	0 (0.0%)	1 (3.0%)	1.000
Normal	11 (100%)	32 (97.0%)	
Tricuspid annular plane systolic excursion (mm)			
Abnormal	0 (0.0%)	0 (0.0%)	1.000
Normal	11 (100%)	33 (100%)	
Right ventricle pulsed Doppler S wave (cm/s)			
Abnormal	0 (0.0%)	3 (9.1%)	0.562
Normal	11 (100%)	30 (90.9%)	

Table 6-Comparison of the echocardiographic indices for the left ventricular systolic and diastolic function in the case and control groups

	Normal (N=11)	CSF (N=33)	P-value
Peak velocity flow in early diastole (E wave) /peak mitral inflow velocity at atrial contraction (A wave)			
< 0.75	3 (27.3%)	9 (27.3%)	1.000
0.75<E/A<1.5	8 (72.7%)	24 (72.7%)	
Early mitral inflow velocity / mitral annular early diastolic velocity (E/e')			
<10	11 (100%)	30 (90.9%)	0.562
[?]10	0 (0.0%)	3 (9.1%)	
Ejection fraction			
Mild dysfunction	3 (27.3%)	9 (27.3%)	1.000
Normal	8 (72.7%)	24 (72.7%)	
LV-EF (Simpson)			
Mild dysfunction	2 (18.2%)	7 (21.2%)	1.000
Normal	9 (81.8%)	26 (78.8%)	
Systolic (S) and diastolic phase (D) waves			
S>D	8 (72.7%)	31 (93.9%)	0.091
D>S	3 (27.3%)	2 (6.1%)	
Diastolic function			
Normal	9(82.0%)	24 (72.7%)	0.705 F
Mild dysfunction	2 (18.0%)	8 (24.2%)	
Moderate dysfunction	0 (0.0%)	1 (3.1%)	

Figure 1- Doppler criteria for the categorization of the left ventricular diastolic function. (M. M. Redfield, S. J. Jacobsen, J. John C. Burnett, D. W. Mahoney, K. R. Bailey, and R. J. Rodeheffer, “Burden of Systolic and Diastolic Ventricular Dysfunction in the Community: Appreciating the Scope of the Heart Failure Epidemic,” *JAMA* , vol. 289, no. 2, pp. 194–202, Jan. 2003, doi: 10.1001/jama.289.2.194.)

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