Tropical Journal of Pharmaceutical Research November 2021; 20 (11): 2443-2449
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v20i11.29

Original Research Article

Safety of low-dose dobutamine stress test in coronary slow flow phenomenon

Jian Wu[1], Rongchong Huang[2], Shuang Meng[3], Yanzong Yang[1]*
[1]Department of Cardiology, The First Affiliated Hospital of Dalian Medical University, Dalian City, 116011, [2]Cardiac Center/Department of Cardiology, Beijing Friendship Hospital, Capital Medical University, Beijing City 100053, [3]Department of Ultrasound, The First Affiliated Hospital of Dalian Medical University, Dalian City 116011, China

For correspondence: **Email: yangyanzong1608@sina.com; **Tel/Fax:** 0086-411-83635963*

Sent for review: 22 April 2021 *Revised accepted: 30 September 2021*

Abstract

Purpose: *To investigate the feasibility and safety of a low-dose dobutamine stress test in coronary slow flow phenomenon (CSFP) patients.*
Methods: *One hundred and forty-two CSFP patients, and forty-four patients without CSFP or significant epicardial coronary stenosis who served as the control group, were retrospectively reviewed. All patients were infused intravenously with dobutamine at an initial infusion rate of 5 μg/kg/min which was then increased at 8-min intervals to 10, 15, and 20 μg/kg/min. Symptoms and echocardiography were monitored simultaneously.*
Results: *Patient tolerance decreased as the doses of dobutamine increased. No termination of the test occurred without dobutamine or at the infusion rate of 5 μg/kg/min. Nonetheless, when the infusion rates were adjusted to 15 and 20 μg/kg/min, the incident of side effects reached up to 30.9 %, and a few patients experienced ST-segment depression in precordial electrocardiographic leads. There were no induced arrhythmias without dobutamine, while the incidence of arrhythmias was highest at the infusion rate of 20 μg/kg/min. Malignant arrhythmias such as ventricular fibrillation and sustained ventricular tachycardia, were not detected. No significant differences were showed in echocardiogram result for left ventricular ejection fraction (LVEF) between CSFP and control group (63.7±7.9 in the CSFP group, versus 64.3±7.2 in the control group; p = 0.63).*
Conclusion: *A low-dose dobutamine stress test is safe and feasible in CSFP patients.*

Keywords: *Coronary slow flow phenomenon, Dobutamine stress test, Echocardiography, Tachycardia, Malignant arrhythmia, Ventricular fibrillation*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Coronary slow flow phenomenon (CSFP), a type of coronary heart disease (CHD), was first reported in 1972 by Tambe *et al* [1,2]. Ever since, CSFP has been considered as a distinct clinical syndrome. The incidence of CSFP is about 1-7 % in queried cardiovascular patients under coronary angiographic observation [3]. It has been demonstrated that CSFP is a microcirculation disorder caused by dysfunction in microvascular resistance [4].

It was once universally acknowledged that CSFP

patients had good overall prognoses. However, recent investigations indicated that more than 80 % of CSFP patients would suffer from recurrent chest pain attacks, while nearly 30 % of CSFP patients would be repeatedly hospitalized owing to acute aggravation of angina pectoris [5]. In addition, several CSFP patients have been reported to suffer from acute cardiovascular events, including malignant arrhythmia and myocardial infarction (MI) [6]. Moreover, 30 – 75% of CSFP patients exhibit myocardial under-perfusion, and CSFP is linked to high prevalence of cardiac diastolic dysfunction.

Echocardiography is widely employed to for investigating cardiac function in CSFP patients, although its use is limited by the lack of consistency [7]. A major reason for the inconsistency is that echocardiography presents have low sensitivity to minor changes in heart function at rest. Precise evaluation of heart function in CSFP patients is a prerequisite for estimating how CSFP patients will fare in the long run. Therefore, it is crucial to develop a more suitable diagnostic method for studying how the heart works under stress.

Dobutamine stress echocardiography (DSE) has been widely used to assess heart function and structure [8,9]. Unfortunately, large doses of dobutamine evidently increase myocardial oxygen consumption and may even induce cardiac ischemia and/or arrhythmias. To the best of our knowledge, there are limited studies on the safety or feasibility of DSE in CSFP patients. In the present study, 12-lead and cardiac echocardiograms were recorded simultaneously to investigate the possibility of carrying out a low-dose dobutamine stress test in CSFP patients.

EXPERIMENTAL

Study population

This was a single-center study carried out in the Department of Cardiology, The First Affiliated Hospital of Dalian Medical University. A total of 191 patients underwent coronary angiography between September 2015 and September 2018, and it was found that they were had normal coronaries. Out of the 191 subjects, 142 patients were diagnosed with CSFP (LAD and/or LCX), and 5 patients had CSFP of RCA excluded, while 44 patients without CSFP served as the control group. Patients with chest pain and CHD were enrolled and assigned to the CSFP group according to these criteria: (1) 18 – 75 years of age and (2) slow passage of contrast agent through the normal or near-normal (<30 % stenosis) coronary lumen, which was confirmed using coronary angiography (CAG).

The following exclusion criteria were applied: (1) absence of evidence of CSFP, (2) presence of coronary artery dilatation or myocardial infarction, (3) presence of chronic congestive heart failure, hypertrophic/dilated cardiomyo-pathies, congenital heart disease, or valvular dysfunction, (4) presence of moderate-to-severe kidney disorder (glomerular filtration rate <60 ml/min/1.73m^2), severe non-cardiovascular disease (e.g., thyroid disorders, infections, or tumors), or serious liver disorder (aspartate/ alanine aminotransferase ≥ 3 times higher than normal upper limit); (5) diagnosis of any arrhythmias such as a history of frequent premature ventricular contractions (PVCs) and ventricular tachycardia, and bundle branch block, or persistent/paroxysmal atrial fibrillation/flutter; as well as (6) refusal to sign informed consent. In line with the thrombolysis in myocardial infarction (TIMI) frame count (TFC), 142 patients (99 males and 43 females) served as the CSFP group, while the 44 patients (28 males and 16 females) without CSFP or significant epicardial coronary stenosis (< 30%) served as the control group.

Dobutamine stress tests have been widely used as a check for coronary heart disease. They are routine tests at the Department of Cardiology in our hospital. This study was approved by the First Affiliated Hospital of Dalian Medical University Ethics Committee (approval no. PJ-KY-2018-109) and it conformed to the ethical guidelines of the 1975 Declaration of Helsinki [10]. All participants signed written consent forms.

CSFP assessment

Selective CAG was carried out via the femoral or radial approach with Judkins catheters in all patients, using Philips advanced Allura Xper FD20 X-ray system (Eindhoven, Noord Brabant, Holland). Complete images were obtained at different body positions. Left anterior descending (LAD) and left circumflex (LCX) images were obtained from the right anterior oblique position with 30° caudal angulation, and RCA images were collected from left anterior oblique position with 20° cranial angulation. Upon completion of coronary angiogram, digital images were assessed by two experienced cardiologists.

Based on TIMI frame counting, the first frame was confirmed when contrast agent entered the artery with the antegrade flow. The final frame was ascertained when the dye entered the distal landmark branch in each vessel. For the LAD,

the distal branch closest to the vertex was considered as the landmark. Distal bifurcation of the major obtuse marginal artery was used as the landmark for the LCX images. For the RCA images, the first branch of the posterolateral segment was employed.

Usually, compared with LCX or RCA, LAD is longer. Therefore, frame counts for LAD were often divided by 1.7 to acquire a corrected TIMI frame count (CTFC). For each patient, mean CTFC was calculated by dividing total number of frames of three coronary arteries by 3. Normal TFC values were 36.2 ± 2.6 (corrected count = 21.1 ± 2.1), 22.2 ± 4.1 and 20.4 ± 3.0 for LAD, LCX and RCA (acquisition speed: 30 frames per second), respectively. If the TFC of at least one branch of the coronary artery was greater than the normal value for a given patient, the patient was considered to have CSFP.

Transthoracic echocardiographic analysis

Vivid 7 Dimension ultrasound system (GE Healthcare, Waukesha, USA) was used to perform echocardiography (ECG). Ultrasound images of the resting heart were obtained at first. Patients were connected to an ECG monitor that recorded the electrical activity of the heart during the test, using small electrodes placed on the chest. For each patient, three consecutive cardiac cycles were recorded. Images were obtained in a left lateral decubitus position. Left ventricular wall motion was observed from parasternal long. Short axis (at the level of the mitral valves, papillary muscles and the apex); and apical 4- and 2-chamber views were also observed. Left ventricular ejection fraction (LVEF) was obtained with Simpson's biplane method.

From 4- and 2-chamber views, the following measured values were acquired with tissue Doppler imaging (TDI): peak early diastolic mitral filling velocity (E), peak late diastolic mitral filling velocity (A), early systolic mitral annular velocity (s') and early diastolic mitral annular velocity (e'). At the level of the mitral valve, tissue Doppler was employed to measure the peak of early diastolic velocity in the left ventricular lateral wall and septum, and then the average e' velocity was calculated. The ratio of peak early diastolic mitral filling velocity to early diastolic mitral annular velocity (E/e') was also calculated [11].

Dobutamine stress test

Under continuous ECG monitoring, continuous intravenous pumping was performed at the rates of 5, 10, 15, and 20 μg/kg/min at each dose of dobutamine, and each dose lasted for 8 min. The infusion was terminated if the test encountered the following conditions: (1) apparent increase in systolic blood pressure (>220 mmHg or >120 mmHg); (2) symptoms of ventricular arrhythmia, (3) systolic blood pressure no greater than 100 mmHg or decreased more than 40 mmHg, compared with baseline value; (4) new abnormal ventricular wall motion, (5) 85 – 90 % of the age-adjusted maximum heart rate, and (6) patient's request to stop.

Statistical analysis

SPSS 22.0 software (SPSS, Chicago, USA) was utilized for statistical analyses. Enumeration data are presented as percentages (%), while measurement data are presented as mean ± SD. An independent sample *t*-test was employed to compare continuous variables between two groups. Single-factor analysis of variance was conducted to compare normally distributed quantitative data among three or more groups, while the *H*-test was performed to compare quantitative data that did not follow a normal distribution. Significance tests of data were determined using Dunnett's test (heterogeneous variable) and Fisher's LSD method (homogeneous variable). For all statistical analyses, $p < 0.05$ was considered as indicative of statistically significant difference.

RESULTS

Dobutamine stress

As shown in Table 1, at the infusion rates of 15 and 20 μg/kg/min, 4.9 and 7.7% of all subjects reached the target heart rate; the incidents of systolic blood pressure ≥220 mmHg were 0.7 and 2.8 %, while the incidents of non-cardiac side effects (e.g., headache, nausea, and palpitations) were 14.7 and 30.9 %; respectively. At zero infusion rate and infusion rate of 5 μg/kg/min, no termination occurred. Three (3) patients (2.1 %) suffered from chest tightness when the infusion rate was adjusted to 10 μg/kg/min; and the chest tightness exhibited a steady upward trend when the infusion rate was increased, reaching 11.9 at the infusion rate of 15 μg/kg/min, and 29.5% at the infusion rate of 20 μg/kg/min.

Safety of the dobutamine stress test

There was no induced arrhythmias in the absence of infusion. Patients with CSFP had no atrial fibrillation or flutter at rest or at different stages of the test. As shown in Figure 1, LV peak systolic longitudinal strain (LS) of a CSF patient

Table 1: Reasons for termination of the dobutamine stress test

Patients (incidents)	10 μg/kg/min	15 μg/kg/min	20 μg/kg/min
Reaching target heart rate	0 (0)	7 (4.9)	11 (7.7)
Chest tightness	3 (2.1)	17 (11.9)	42 (29.5)
ST segment depression ≥1 mm	0 (0)	13 (9.1)	21 (16.9)
SBP ≥220 mmHg	0 (0)	1 (0.7)	4 (2.8)
SBP ≤100 mmHg	0 (0)	0 (0)	0 (0)
New abnormal ventricular wall motion	0 (0)	0 (0)	3 (2)
Non-cardiac side effects	0 (0)	21 (14.7)	44 (30.9)

SBP, systolic blood pressure

Table 2: Arrhythmias induced at different infusion rates during dobutamine stress test

Patients (incidents)	0 μg/kg/min	5 μg/kg/min	10 μg/kg/min	15 μg/kg/min	20 μg/kg/min
Atrial fibrillation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Atrial flutter	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
PAC	0 (0)	4 (3)	17 (12)	27 (19)	39 (28)
SVT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Junctional rhythm	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
NSVT	0 (0)	0 (0)	0 (0)	0 (0)	3 (2)
PVC	0 (0)	7 (5)	24 (17)	37 (26)	48 (34)

PAC: premature atrial contraction; SVT: supraventricular tachycardia; NSVT: non-sustained ventricular tachycardia; PVC: premature ventricular contraction

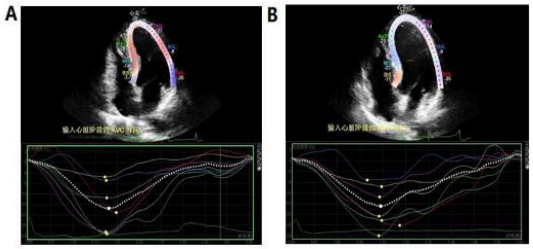

Figure 1: LV peak systolic longitudinal strain (LS) of a CSF patient at rest (A), and under dobutamine stress (20 μg/kg/min)

was decreased from rest to dobutamine stress (20 μg/kg/min). Table 2 shows that at infusion rates of 5, 10, 15, and 20 μg/kg/min, incidents of premature atrial contractions (PACs) were 3, 12, 19, and 28 %; while PVCs occurred in 5, 17, 26, and 34 % of the patients, respectively. When the infusion rate reached 20 μg/kg/min, three patients (2 %) had non-sustained ventricular tachycardia. Slow flow occurred in the LAD of one patient. In addition, slow flow was found in LAD and LCX of two patients. At the infusion rates of 15 and 20 μg/kg/min, the incidents of ST segment depression ≥1 mm were 9.1 and 16.9%, respectively.

Heart ultrasound

No significant difference was detected in the echocardiogram results between CSFP and control group. At the infusion rate of 20 μg/kg/min, three patients (2%) in the CSFP group had abnormal ventricular wall motion, as presented in Table 3.

Table 3: Comparison of 2D echocardiography and TDI results between patients in the CSFP and control groups

Parameter	CSFP group (n=142)	Control group (n=44)	*P*-value
LVEF	63.7±7.9	64.3±7.2	0.63
E	77.4±16.4	78.3±13.4	0.30
A	75.6±17.6	77.5±18.1	0.84
s'	8.7±1.9	9.0±2.0	0.58
e'	8.8±1.7	8.9±1.8	0.71
E/e'	8.8±1.4	8.0±1.9	0.06

Results are expressed as mean ± SD

After the dobutamine stress test, blood pressure and ECGs were monitored until they returned to baseline. All patients received cardiac marker tests a day after the dobutamine infusion, and all results were in the normal range. In addition, no myocardial infarctions or sudden deaths occurred during the test.

DISCUSSION

In this study, the feasibility and safety of the dobutamine stress test in CSFP patients were investigated

A low dose of dobutamine had weaker effects on heart rate and blood pressure, as well as a higher rate of non-cardiac side effects. With increasing doses of dobutamine, patients experienced different degrees of chest tightness. Few patients had ST segment depression and regional ventricular wall motion abnormalities. The incidence of arrhythmias such as PACs and PVCs, rose with increasing doses of dobutamine.

Dobutamine is a synthetic catecholamine and a racemic mixture of two enantiomers [8]. It increases heart rate and myocardial contractility through stimulation of β1 receptor in a dose-dependent manner. In patients with decreased coronary flow reserve, dobutamine may also induce myocardial ischemia. Therefore, the dobutamine stress test has been used to evaluate CHD. Generally, there are two protocols for the dobutamine stress test: (1) dobutamine is administered by intravenous infusion at the rates of 5, 10, 15, and 20 μg/kg/min for 8 min at each dose; or (2) dobutamine is administered intravenously at the rates of 5, 10, 15, 20, 25, and 30 μg/kg/min for 3 min at each dose. It is universally acknowledged that the first protocol corresponds better with *in vivo* pharmacokinetics of dobutamine [12].

Some studies have used high doses of dobutamine to stimulate the heart and assess how well it tolerates dobutamine activity. It has been reported that low doses of dobutamine produce an inotropic effect which promotes the recruitment of viable myocardium and wall thickening/motion in the myocardia [13]. Nevertheless, researchers are cautious about high doses of dobutamine due to the potential risks associated with them [13]. A study involving a consecutive series of 1,118 patients without CHD was carried out by Mertes *et al* [14]. In this study, dobutamine was infused in a piece-wise incremental method, and the mean and maximum doses of dobutamine were 36.6 and 50.0 μg/kg/min, respectively. There were no incidents of fatal arrhythmias, MI, or syncope. In a study by Minardi *et al*, dobutamine was administered directly at a constant dose of 50 μg/kg/min for 10 min [15]. The incidents of common arrhythmias (e.g., PVCs and PACs), nausea, and dizziness were not obviously increased, compared with the standard infusion protocol. However, not all enrolled subjects had CHD, and some of the subjects only had risk factors for cardiovascular disease, but not the disease itself. In a study with small sample size (65 patients), Jiang *et al* found that real-time myocardial contrast echocardiography under low-dose dobutamine stress could be an efficient tool for evaluating CHD patients without side-effects [16]. Nevertheless, to the best our knowledge, there are no studies so far on the safety of this procedure in patients with CSFP.

In the present study, no patient completed 85 – 90 % of target heart rate at the infusion rates of 5 – 10 μg/kg/min, while 4.9 – 7.7 % of patients achieved the target heart rate at the infusion rate of 15 – 20 μg/kg/min. It was also found that patient tolerance decreased apparently with increasing dobutamine dose. At the infusion rates of 15 and 20 μg/kg/min, 14.7 and 30.9% of patients, respectively, requested discontinuation of the dobutamine infusion due to discomfort. The patients exhibited symptoms such as chest tightness and palpitations. Despite the small dose of dobutamine used in the present study, the subjects experienced higher incidence of discomfort than was reported in other studies (30.9 vs. 26.0 %) [14]. Such an increased frequency of side effects could be due to the slow metabolic breakdown of dobutamine in patients with CSFP, as a result of impairments of microvascular, endothelial and microcirculatory perfusions.

Dobutamine, a synthetic catecholamine, stimulates β1-adrenergic receptors and increases myocardial oxygen consumption, leading to myocardial ischemia and ventricular arrhythmias [17].

Dobutamine also induces hypokalemia which is pertinent to a high risk of malignant arrhythmias. The most common arrhythmias were PVCs and PACs, with the highest occurrence at the infusion rate of 20 μg/kg/min. Malignant arrhythmias such as ventricular fibrillation and sustained ventricular tachycardia, were not observed in this study. Nevertheless, after infusion with dobutamine at the rate of 20 μg/kg/min, an apparent decrease in LV peak systolic longitudinal strain (LS) was observed. Moreover, 3 patients experienced non-sustained ventricular tachycardia with no significant hemodynamic changes; 2 patients who presented with CSFP in the LAD and LCX, also had chest tightness. Echocardiography monitoring revealed that ST-segment depression in the precordial leads and a heart ultrasound had uncoordinated ventricular wall motion. These symptoms were relieved when the dobutamine infusion was interrupted or when inorganic nitrates were used [18]. However, ST-segment depression was not observed in other patients with LAD or LCX disease who also had chest tightness.

All non-sustained ventricular tachycardia occurred at the infusion rate of 20 μg/kg/min. Blood pressure, ECGs, and cardiac markers of the patients were in their normal ranges after the dobutamine infusion test. In addition, no myocardial infarctions or sudden deaths occurred during the test. These results have demonstrated the safety and feasibility of the low-dose dobutamine stress test in CSFP patients.

Limitations of this study

Firstly, this study is single-center investigation.

This may limit the generalizability of the results. Furthermore, the limited study population and a small number of enrolled patients, which could be ascribed to low prevalence of CSFP, ethical considerations, and practical considerations, could affect the strength of this study. In subsequent follow-up of patients in the present study, the sample size will be enlarged. Another limitation in this study is that the pharmacokinetics of dobutamine in the patients was not studied.

CONCLUSION

Low-dose dobutamine stress test can be employed in patients with CSFP due to its safety and feasibility. However, larger prospective investigations are required to validate these results and demonstrate that a low-dose dobutamine stress test is safe and feasible in CSFP patients.

DECLARATIONS

Acknowledgement

This study was supported by the Beijing United Heart Foundation, Cardiacare Sponsored Optimizing Antithrombotic Research Fund (Grant no. BJUHFCSOARF 201801-02) (Beijing, China) and Summit talent Plan, Beijing Hospital Management Center (Plan no. DFL20190101) (Beijing, China).

Conflict of interest

No conflict of interest is associated with this study.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Jian Wu and Rongchong Huang contributed equally to this study. Jian Wu contributed to the analysis of data and manuscript preparation. Rongchong Huang contributed to study design, collection of data, and reviewing and rewriting the manuscript. Shuang Meng performed clinical studies. Yanzong Yang designed the study and reviewing and rewriting the manuscript. All authors gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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