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Original Research Article

Impact of intravenous administration of anisodamine on coronary microvascular dysfunction in patients with obstructive epicardial coronary artery disease after percutaneous coronary intervention

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Abstract

Purpose: *To analyze intravenous administration of anisodamine's impact on coronary microvascular dysfunction (CMD) in obstructive epicardial coronary artery disease (CAD) patients who had undergone percutaneous coronary intervention (PCI).*
Methods: *Enrollment of 210 patients in Shanghai Chest Hospital, Shanghai Jiaotong University with CMD was done in a randomized-controlled study. They were divided randomly into groups, viz, anisodamine (A) group and nitrate (N) group. A 14-day course of treatment was carried out in each group. 99mTc-MIBI myocardial perfusion imaging (MPI), treadmill exercise test (TET) and two-dimensional echocardiography (TDE) were performed, and the symptoms of angina pectoris were recorded before and after treatment according to the classification, frequency, and duration of angina, as defined by Canadian Cardiovascular Society (CCS).*
Results: *After treatment, summed stress score (SSS) and summed rest score (SRS) of MPI in group A significantly decreased after treatment ($p < 0.001$, respectively) and were remarkably lower than those in group N ($p < 0.001$, respectively). The CCS class in group A improved after treatment ($p < 0.001$) and was also better than in group N ($p < 0.001$). The frequency and duration of angina attack in group A significantly reduced after treatment ($p < 0.001$, respectively) and were notably lower than in group N ($p < 0.001$, respectively). Left ventricular ejection fraction in group A after treatment was higher than that before treatment ($p = 0.046$) and than that in group N ($p = 0.048$). Furthermore, the side effects of anisodamine were slight and tolerable.*
Conclusion: *Intravenous administration of anisodamine is a potentially suitable optional treatment for CMD in patients with obstructive epicardial CAD who have undergone PCI.*

Keywords: *Coronary microvascular dysfunction, Coronary artery disease, Percutaneous coronary intervention, Anisodamine, Intravenous administration*

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INTRODUCTION

Coronary artery disease (CAD), especially acute myocardial infarction (AMI) is a main reason of morbidity and mortality of cardiac disease worldwide. In the last decades, the considerable advances in reperfusion treatments, such as the technology of percutaneous coronary

intervention (PCI), have contributed to the recanalization of the obstruction-related epicardial coronary arteries, which significantly improved the prognosis of patients with CAD. However, there are still a large number of patients with recurrent angina or progressive heart failure after PCI. It has been recognized that this phenomenon can mainly be attributed to the condition which is frequently referred to as coronary microvascular dysfunction (CMD) at present [1].

The coronary microvasculature covers extra-myocardial prearterioles with diameters ranging from 100 to 500 μm, which is able to maintain pressure at the origin of arterioles within a narrow range when coronary perfusion pressure or flow changes, and intramural arterioles < 100 μm whose function is the matching of myocardial oxygen consumption and blood supply [1,2]. Though it could not be seen in CAG and hard to access, the coronary microvasculature directly influenced myocardial metabolism and cardiac function by regulating myocardial perfusion. Therefore, CMD mediated myocardial ischemia and may even result in an elevated risk of cardiovascular events such as angina pectoris, acute coronary syndrome (ACS), and heart failure in patients with obstructed and angiographically unobstructed coronary arteries [1,3]. Therefore, CMD has become an important clinical therapeutic targeted symptom. Nitrates, β-blockers, calcium antagonists, ivabradine, ranolazine, statins, and angiotensin-converting enzyme inhibitors (ACEI) are usually administered to relieve angina symptoms. Unfortunately, management of symptomatic patients with CMD is often frustrating for the patients and their physicians [4]. Further effective therapeutic methods for CMD patients with CAD, especially, who had undergone PCI require further investigation.

Anisodamine (6-hydroxyhyoscyamine), as a non-subtype-selective muscarinic cholinergic antagonist, which was first separated from the Chinese medicinal herb *Scopolia tangutica* Maxim in 1965 [5], has been proved to relieve microvascular spasm, inhibit calcium overload, scavenge superoxide, inhibit platelet aggregation, depress microthrombosis, and improve vascular endothelium function [6]. Therefore, it is applied in circulatory disorders' cure such as disseminated intravascular coagulation and septic shock, and it provides clear cardioprotection against ischemia/ reperfusion damage [7].

Currently, however, there is still no such technology to directly display coronary microvessels in human body. Up to now, coronary microvascular function can only be mediately assessed via a few invasive or noninvasive techniques such as positron emission tomography, intracoronary Doppler flow velocity wires, myocardial contrast echocardiography, transthoracic Doppler echocardiography, and cardiac magnetic resonance imaging [1]. Technetium-99m-sestamibi (^{99m}Tc-MIBI) myocardial single-photon emission computed tomography (SPECT) might offer another non-invasive option for coronary microvascular function assessment [8]. Therefore, this study aims to analyze the therapeutic effects of intravenous administration of anisodamine on CMD in obstructive epicardial patients with CAD after PCI via ^{99m}Tc-MIBI SPECT imaging.

METHODS

Patient information

From April 2014 to March 2018, 210 consecutive patients aged 60.2 ± 8.5 years (156 men) were admitted to hospital who had undergone treatment with PCI because of ST-segment elevation myocardial infarction (STEMI) or unstable angina pectoris (UAP) at least 3 months before admission. In all of the patients, chest x-ray, electrocardiogram (ECG), ^{99m}Tc-MIBI myocardial perfusion scintigraphy, treadmill exercise test (TET), two-dimensional echocardiography (TDE) and CAG were performed, and the serum myocardial indicators creatine kinase-MB (CK-MB) and cardiac troponin I (cTnI) were assured as well.

The inclusion criteria for this study were as follows: (a) a history of PCI, (b) symptoms of recurrent angina, graded by Canadian Cardiovascular Society (CCS) Angina Classes of CCS I to III [9], (c) resting left ventricular ejection fraction (LVEF) ≥ 35 %, (d) positive symptoms in myocardial perfusion scanning, (e) a positive symptom in TET, (f) a normal coronary angiogram (the residual stenosis in epicardial coronary artery < 30 %).

The exclusion criteria included ACS, right ventricular myocardial infarction, serious arrhythmia (atrioventricular block, tachycardia, atrial fibrillation, frequent premature contractions), uncontrolled hypertension (systolic blood pressure (SBP) > 160 mmHg and/or diastolic blood pressure (DBP) > 100 mmHg), hypotension (SBP < 100 mmHg and/or DBP < 55 mmHg). Patients with left ventricular hypertrophy, valvular heart disease, pulmonary embolism, congenital heart disease, pulmonary heart

disease, various types of myocarditis and cardiomyopathy (except ischemic cardiomyopathy), pericardial disease, glaucoma, myasthenia gravis, prostatic hyperplasia, chronic renal insufficiency, severe liver dysfunction, malignant tumour, obstructive gastrointestinal disorders, febrile disorders or acute infection were also excluded.

Approval for this study protocol was obtained from the medical ethics committee of Shanghai Chest Hospital, Shanghai Jiaotong University (approval no. 20M128). Signature of written informed consent was obtained from all patients. All procedures were implemented in line with the guidelines of Helsinki declaration [10].

Study design

All enrolled patients were randomly divided into anisodamine group (group A, *n* = 110) and nitrate group (group N, *n* = 100). In group A, treatment with intravenous infusion of anisodamine (Minsheng Pharmaceutical Group Co., Ltd, China) diluted in 50 mL normal saline (1 mL: 10 mg;) was administered at the rate of 0.05 mg/kg/h (10 h/day) via micro-infusion pump for 14 days. With the same method, isosorbide dinitrate (10 mL: 10 mg; UCB Pharma Co., Ltd, China) in group N was injected. Bedside ECG and blood pressure (BP) monitoring should be performed continuously during the medication course.

During the 14-day course of treatment, routine medicines such as ACEI, angiotensin receptor blockers (ARB), calcium channel blockers (CCB), statins, aspirin, β-blockers, and clopidogrel were continued, except that orally administered organic nitrates were discontinued in all patients. If the BP decreased significantly (SBP < 100 mmHg and/ or DBP < 55 mmHg), especially in group N, CCB was withdrew immediately. And then the dose of ISDN be reduced appropriately.

^{99m}Tc-MIBI myocardial perfusion scintigraphy

Each patient underwent a one-day dobutamine stress and rest ^{99m}Tc-MIBI myocardial perfusion scintigraphy prior to and after the 14-day treatment. Vasodilator and β-blocker were discontinued 48 h before examination. Dobutamine (2 mL: 20 mg; First Biochemical Pharmaceutical Co. Ltd., China) was given by intravenous infusion at 5 μg/kg/min, which was increased by 5 μg/kg/min every 3 min, ultimately to 40 μg/kg/min. Heart rate (HR), blood pressure, ECG and symptoms of the patients at each level were recorded. If target HR (85 % of maximum predicted HR for age and gender or ≥ 130 bpm) was not achieved at peak dobutamine dose, up to 1 mg of atropine IV was administrated [11].

Administration with 370 MBq of ^{99m}Tc-MIBI (radiochemical purity > 95 %, Xinke Pharmaceutical Co. Ltd, China) by intravenous injection was performed on the appearance of the termination index for stress imaging, and that with 1110 MBq of 99mTc-MIBI was conducted after 4 h for rest imaging. Images were acquired 1.0-1.5 h after each injection with a GE Discovery NM/CT 670. On a 180° semicircular arc ranging from 45° right anterior oblique to 45° left posterior oblique, 30 projections were obtained at an interval of 60 s. All data were stored in a 64 × 64 matrix and processed using Xeleris workstation. Ordered Subsets Expectation Maximization was used to reconstruct the images acquired.

Interpretation of images was performed by two experienced nuclear physicians who were unknown about patient identity or clinical history. To assess myocardial perfusion, the left ventricle was divided into 17 standard segments according to the American Heart Association statement [12]. Each segment was analyzed (0 = normal tracer uptake, 1 = slightly reduced, 2 = moderately reduced, 3 = severely reduced, and 4 = absent tracer uptake). Summed stress score (SSS) and summed rest score (SRS) were obtained by summation of all the scores at stress and rest, respectively. Then, the summed difference score (SDS) was used to indicate the difference between the SSS and SRS (SSS - SRS). Images were classified as normal (scores = 0 to 3) or abnormal (score ≥ 4) based on the SSS. Abnormal images, in turn, were defined as fixed defect (SDS ≤ 2) or reversible defect (SDS > 2) based on SDS.

Treadmill exercise test

In the light of the standard Bruce protocol [13], TET was performed for all the patients before and after treatment via GE T2100 stress treadmill (GE Healthcare, USA). No drugs, except short lasting nitrates for pain relief, were permitted during 24 h prior to TET, meanwhile, eating and drinking were forbidden for at least 2 h prior to the test. ECG monitoring was conducted continuously throughout the test. A resting 12-lead ECG was recorded prior to TET and then done every 3 min. In addition, whenever any abnormality was presented, the ECG would be recorded rapidly. Measurement of BP was carried out at rest and then every 2-3 min during exercise and recovery. Similarly, BP was measured as soon as any abnormality occurred.

Definition of a positive TET was determined as horizontal or down-sloping ST-segment depression of ≥ 0.1 mV or upsloping depression of ≥ 0.2 mV (80 ms after the J-point) for ≥ 2 min in ≥ 2 adjacent leads when vs. the baseline measurement, ST-segment elevation of ≥ 0.2 mV (20 ms after the J-point) for ≥ 1 min in ≥ 2 adjacent leads, SBP decrease > 10 mmHg when vs. the baseline measurement, or occurrence of typical symptom of angina pectoris [14,15].

During the TET, the following parameters were monitored and recorded: duration of exercise (DE), total exercise load, time to 0.1 mV ST-segment depression ($STD_{0.1}$), maximal ST depression (STDmax), maximum HR (HRmax), the maximal ST/HR-slope (ST/HRmax), time to ST normalisation (STnorm).

Clinical follow-up

According to CCS Angina class, the grade, frequency and duration (without the use of nitroglycerin) of angina attack in all patients 3 months before admission and 3 months after discharge were recorded respectively. A standard TDE applying the modified Simpson method was used for assessment of LVEF on admission and at the 3-month follow-up after discharge.

Statistical analysis

All statistical analyses were carried out applying SAS 9.13 software (SAS institute Inc., Cary, USA). Continuous variables were clarified as mean ± standard deviation (SD) and were compared between two groups applying the student's t-test. Categorical variables were displayed as percentage (%) and were compared applying Chi-square test. A p value < 0.05 was considered statistically significant.

RESULTS

Clinical characteristics

The baseline characteristics of the patients enrolled in this study are summarized in Table 1 and 2. No significant differences in gender, age, BMI, risk factors (smoking, hypertension, hyperlipidemia, and diabetes), basic medication use, CCS class, LVEF, Vital signs (HR, SBP/DBP), and seizure frequency were found among the two groups.

Myocardial perfusion imaging (MPI)

No clear differences were presented in such MPI parameters as SSS, SRS and SDS of two groups before treatment (P = 0.691, 0.682 and 0.892, respectively) (Table 2). In group A, both SSS and SRS decreased significantly after treatment, and the proportion of the patients with SSS ≤ 3 was clearly higher than that before treatment (71.8 vs 0 %, P < 0.001). In the patients with SSS ≥ 4 (31, 28.2 %), 9 patients had SDS of ≤ 2 (the same as that before treatment).

Table 1: Clinical characteristics of all patients enrolled (mean ± SD)

Variable	Group A (n=110)	Group N (n=100)	*P*-value
Gender (male)	84 (76.4)	72 (72.0)	0.470
Age (years)	59.1 ± 8.3	61.3 ± 8.7	0.363
BMI (kg/m^2)	25.2 ± 3.8	24.8 ± 4.2	0.386
Risk factors			
Current smoker	61 (55.5)	58 (58.0)	0.710
Hypertension	68 (61.8)	57 (57.0)	0.477
Hyperlipidemia	51 (46.4)	48 (48.0)	0.813
Diabetes	25 (22.7)	18 (18.0)	0.397
Medications			
ACEI/ARB	74 (67.3)	62 (62.0)	0.424
CCB	23 (20.9)	23 (23.0)	0.715
Statin	110 (100)	100 (100)	—
Aspirin	110 (100)	100 (100)	—
β-blockers	89 (80.9)	82 (82.0)	0.839
Clopidogrel	110 (100)	100 (100)	—
Long-acting nitrates	32 (29.1)	33 (33.0)	0.541
Vital signs			
HR (bpm)	76.3 ± 7.3	74.8 ± 7.5	0.510
SBP (mmHg)	125.2 ± 12.7	128.7 ± 11.9	0.375
DBP (mmHg)	70.1 ± 9.4	71.7 ± 10.3	0.610

Data are expressed as mean ± SD or as number (%). BMI; body mass index; CCB; calcium channel blockers; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure DBP, diastolic blood pressure

Then in group N, treatment could reduce both SSS and SRS, but there were no significant differences (both $P > 0.05$) despite the proportion of the patients with SSS ≤ 3 increased notably (19.0 vs 0 %, $P < 0.001$). Likewise, in the patients with SSS ≥ 4 (81, 81.0 %), there were 11 cases had SDS of ≤ 2 (the same as that before treatment). There were significant differences in SSS and SRS between group A and group N after treatment ($p < 0.001$). The typical images before and after treatment are shown in Figure 1.

Treadmill exercise results

The results of TET are shown in Table 2. Before treatment, all of the parameters including DE, total exercise load, $STD_{0.1}$, STDmax, HRmax, ST/HRmax and STnorm were similar in group A and group N ($p > 0.05$, all). Apparent differences were displayed in group A ($P \leq 0.001$, all) after treatment, while no significant difference was found in group N ($P > 0.05$, all) in all parameters above when compared with those before treatment. More concretely, after treatment, longer duration of exercise, higher exercise load, longer time to 0.1 mV ST-segment depression were presented in group A compared with the baseline measurement. Lower maximal depth of ST-segment depression, higher maximal exercise heart rates, lower maximal ST/HR-slope and shorter time to ST-segment normalisation was able to be seen in patients of group A after treatment than before treatment or patients in group N. Distinct differences were illustrated in all the parameters of two groups after treatment ($P < 0.01$, all).

Symptoms and LVEF

According to the CCS Angina Class, 26 (23.6 %) patients in group A before admission were classified in class I, 70 (63.6 %) in class II, 14 (12.8 %) in class III, compared with 19 (19.0 %) in class I, 69 (69.0 %) in class II, 12 (12.0 %) in class III in group N ($P = 0.679$). However, 3 months after treatment, there were 53 (48.2 %) patients in class I, 51 (46.4 %) in class II, 6 (5.4 %) in class III in group A, compared with 21 (21.0 %) in class I, 65 (65.0 %) in class II, 14 (14.0 %) in class III in group N ($P < 0.001$).

Table 2: Parameters of auxiliary examinations and clinical symptoms before and after treatment

Variable	Group A (n=110)			Group N (n=100)			P (A/N)	
	BT	*AT*	*P*	*BT*	*AT*	*P*	*BT*	*AT*
MPI parameters								
SSS	4.9 ± 0.9	2.1 ± 1.5	<0.001	4.8 ± 0.9	4.3 ± 1.1	0.129	0.691	<0.001
≤ 3	0 (0)	79 (71.8)	<0.001	0 (0)	19 (19.0)	<0.001	—	<0.001
≥ 4	110 (100)	31 (28.2)		100 (100)	81 (81.0)			
SRS	1.5 ± 1.1	0.5 ± 0.9	<0.001	1.4 ± 1.2	1.0 ± 1.2	0.290	0.682	<0.001
SDS*	3.4 ± 0.8	2.7 ± 1.6		3.4 ± 0.9	3.4 ± 1.4		0.892	
≤ 2	9 (8.2)	9 (8.2)		11 (11.0)	11 (11.0)		0.487	
> 2	101 (91.8)	21 (19.1)		89 (89.0)	69 (69.0)			
TET parameters								
DE (min)	7.1 ± 0.7	8.0 ± 0.8	<0.001	7.3 ± 0.6	7.2 ± 0.6	0.632	0.480	<0.001
Load (METs)	9.8 ± 1.2	11.8 ±1.6	<0.001	10.0 ± 0.9	10.2 ± 1.1	0.436	0.695	<0.001
$STD_{0.1}$ (min)	4.9 ± 0.6	5.8 ± 0.8	<0.001	5.1 ± 0.6	4.9 ± 0.7	0.570	0.331	<0.001
STDmax (mm)	2.4 ± 0.6	1.0 ± 0.4	<0.001	2.1 ± 0.5	2.2 ± 0.5	0.721	0.117	<0.001
HRmax (bpm)	148.6 ± 7.1	155.7 ± 5.6	0.001	151.3 ± 6.6	149.9 ± 6.9	0.478	0.197	0.005
ST/HRm x (μm/bpm)	16.0 ± 4.2	6.4 ± 2.6	<0.001	13.8 ± 3.6	14.4 ± 3.7	0.615	0.082	<0.001
STnorm (min)	4.2 ± 0.7	2.6 ± 0.7	<0.001	4.0 ± 0.8	4.1 ± 0.6	0.665	0.325	<0.001
CCS class			<0.001			0.830	0.679	<0.001
Class I	26 (23.6)	53 (48.2)		19 (19.0)	21 (21.0)			
Class II	70 (63.6)	51 (46.4)		69 (69.0)	65 (65.0)			
Class III	14 (12.8)	6 (5.4)		12 (12.0)	14 (14.0)			
Angina attack								
Frequency(times/month)	4.4 ± 1.2	1.5 ± 0.9	<0.001	4.2 ± 1.1	3.9 ± 0.8	0.449	0.705	<0.001
Duration (min)	8.3 ± 3.0	4.8 ± 1.6	<0.001	7.9 ± 2.3	8.1 ± 2.4	0.787	0.681	<0.001
LVEF (%)	52.9 ± 7.5	57.1 ± 6.1	0.046	53.8 ± 7.2	53.2 ± 6.5	0.783	0.712	0.048

Data are expressed as mean ± SD or as number (%). ***Key:*** SSS: summed stress score SRS: summed rest score; SDS: summed difference score (= SSS – SRS); DE: duration of exercise; METs: metabolic equivalents; $ST_{0.1}$: time to 0.1 mV ST-segment depression compared with the baseline measurement; STDmax, maximal ST-segment depression (1mm = 0.1 mV); HRmax: maximal heart rate; bpm, beats per minute; ST/HRmax, maximal ST/HR-slope: SBPmax, maximal systolic blood pressure; STnorm: time to ST-segment normalisation; CCS: Canadian Cardiovascular Society; LVEF: left ventricular ejection fraction; BT: before treatment; AT: after treatment; A/N, Group A vs. Group N; *, Calculated and classified only in the images with SSS ≥ 4

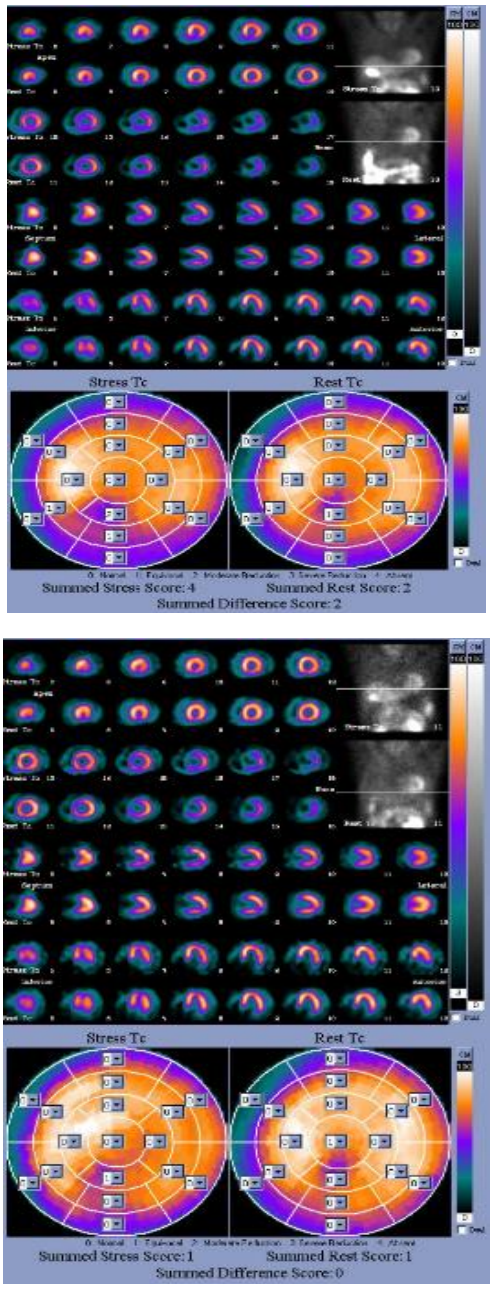

Figure 1: ^{99m}Tc-MIBI myocardial perfusion images in typical case before and after treatment with intravenous administration of anisodamine. The Figures were obtained from a patient aged 49 years old who had undergone PCI in left anterior descending artery (LAD) one year before admission. CAG was performed again before treatment only to find a < 30% residual stenosis in LAD. Left picture (acquired before treatment) shows severe reduction of radiotracer uptake in left ventricular inferior wall close to apex at stress phase (SSS = 4) and mild reduction at rest phase (SRS = 2). Right picture (acquired after 14-day treatment with intravenous administration of anisodamine) revealed mild reduction at stress and rest phase (SSS = 1, SRS = 1), respectively, in original segment.

Between before and after treatment, there was significant difference in group A (P < 0.001) but no significant difference in group N (P = 0.830) in CCS class.

Frequencies of angina attack were 4.4 ± 1.2 times per month in group A and 4.2 ± 1.1 times per month in group N (P = 0.705) during 3 months before treatment, which were 1.5 ± 0.9 and 3.9 ± 0.8 times per month in two groups (P < 0.001) in 3 months after treatment. The mean durations of angina attack in two groups, respectively, were 8.3 ± 3.0 and 7.9 ± 2.3 minutes (P = 0.681) during 3 months before treatment, which were 4.8 ± 1.6 and 8.1 ± 2.4 minutes (P < 0.001) in 3 months after treatment. There were significant differences in group A (P < 0.001) but no significant differences in group N (P > 0.05) in frequency and duration of angina attack before and after treatment.

No apparent difference was displayed in LVEF on admission in the two groups (52.9 ± 7.5 % vs. 53.8 ± 7.2 %, P = 0.712). In group A, the LVEF measured at the 3-month follow-up after discharge was remarkably higher than that was measured on admission (57.1 ± 6.1 % vs. 52.9 ± 7.5 %, P = 0.046). Nevertheless, in group N, the LVEF 3 months after treatment did not differ from that on admission (53.2 ± 6.5 % vs. 53.8 ± 7.2 %, P = 0.783). The comparisons of clinical symptoms and LVEF between before and after treatment are presented in Table 2.

Side effects

There were some side effects which were observed during the course of treatment (Table 3). Thirst (87.3 %), blurred vision (19.1 %), dysuria (12.7 %), and flushing (9.1 %) were observed in group A but not in group N (P < 0.01). In contrast, headache (16.0 %) and hypotension (11.0 %) were observed in group N but not in group A (P < 0.001). 17 patients in group A and 4 patients in group N (15.5 % vs. 4.0 %; P = 0.006) developed symptomatic tachycardia or palpitation. However, these side effects were mild, tolerable and controllable, and none of the patients withdrew from the study. All adverse effects in group A disappeared within 2 - 3 h after intravenous administration. In group N, headache and symptomatic tachycardia also disappeared rapidly after administration. Among the 11 patients with hypotension in group N, 7 cases needed to discontinue CCB and 4 cases needed to discontinue CCB, as well as adjusting the rate of ISDN to 0.04 mg/kg/h (12 h/d), and all of them achieved stable BP. No clinical sequela was noticed.

Table 3: Side effects during the course of treatment

Variables	Group A (n=110)	Group N (n=100)	*P*-value
Thirst	96 (87.3)	0 (0)	<0.001
Blurred vision	21 (19.1)	0 (0)	<0.001
Palpitation/tachycardia	17 (15.5)	4 (4.0)	0.006
Dysuria	14 (12.7)	0 (0)	<0.001
Flushing	10 (9.1)	0 (0)	0.002
Headache	0 (0)	16 (16.0)	<0.001
Hypotension	0 (0)	11 (11.0)	<0.001

Data are expressed as number and percentage (%)

DISCUSSION

The typical cardiovascular disorder caused by CMD is known as cardiac syndrome X (CSX), which was firstly brought forward by Kemp in 1973 and defined as ST-segment depression during angina, exercise-induced and angina-like chest discomfort, normal epicardial coronary arteries on angiography, no spontaneous or induced epicardial coronary artery spasm upon ergometrine or acetylcholine stimulation, no associated cardiac or microvascular dysfunction systemic diseases such as hypertrophic cardiomyopathy or diabetes [16]. However, there are increasing evidences that CMD also occurs in obstructive CAD which is originally characterized by stenosis or obstruction in epicardial coronary [17]. Unlike the remarkable effect of revascularization on epicardial coronary arteries, the current treatments on CMD are not really effective because of its complex pathogenesis and the lack of direct and efficient detection methods.

In the present study, CAG was performed in each patient to exclude significant residual stenosis or obstruction in epicardial coronary arteries. The TET was designed to identify the presence of myocardial ischemia under exercise loads and to analyze cardiac reserve in patients with recurrent angina or progressive heart failure undergoing PCI. Furthermore, MPI performance validated the abnormalities of myocardial perfusion and assessed the extent of myocardial ischemia. Thus, the diagnosis of CMD in this study was based on a comprehensive assessment by above detection methods.

The CMD can be caused by several pathogenic mechanisms such as microvascular remodelling, endothelial dysfunction and vasospasm, smooth muscle dysfunction and autonomic dysfunction [1,17]. Meanwhile, CMD can occur not only in patients with obstructive CAD and myocardial diseases absence, but also in the presence of myocardial diseases, even in the presence of obstructive CAD, and may also result from iatrogenic factors [1,17]. The presence of CMD significantly reduces the effect of revascularization and will remarkably increase adverse cardiovascular events' risk in obstructive CAD patients. Several drugs, as mentioned above, which are usually administered in the patients with obstructive epicardial CAD to relieve angina symptoms, are recommended for the treatment of CMD. However, the clinical outcomes are not so encouraging. Therefore, new therapeutic approaches for CMD need to be further investigated. Organic nitrates such as ISDN, whose main mechanism of vasodilatation is to act as a sort of non-endothelium dependent exogenous nitric oxide (NO) donor in biological systems [18], are commonly used in treatment of ischemic heart disease [19]. Nevertheless, nitrates' dilation effects on coronary microvasculature have been shown to be poor in previous studies [20]. This result may be related to a low ability of coronary microvasculature to convert nitrates into their active products such as NO.

However, Anisodamine, has shown a significant advantage in improving the microcirculation. In recent years, intracoronary administration has been used to treat coronary no-reflow (CNR), which is mainly caused by CMD. Treatment with anisodamine by intracoronary administration perfected myocardial reperfusion and reduced major adverse cardiac events in patients with STEMI undergoing primary PCI [21]. This treatment by intracoronary administration is not suitable for patients who have not undergo CAG or PCI. Maybe treatment using intravenous administration would be more suitable for such patients. So far, few studies have explored the therapeutic effect of anisodamine by intravenous administration on CMD in patients with obstructive epicardial CAD after PCI. Encouragingly, in a previous study, treatment with intravenous administration of anisodamine effectively mitigated myocardial perfusion and decreased angina attacks in patients with CSX and variant angina (VA) [22].

The results of this study clarified intravenous administration of anisodamine was superior to

ISDN in the treatment of CMD. After 14 days of treatment, both SSS and SRS of MPI in patients treated with anisodamine decreased significantly and were markedly lower than those in patients treated with ISDN. This outcome suggests that intravenous administration of anisodamine improved myocardial perfusion much more effectively than that of ISDN. Then, by comparing the results of TET before and after treatment, it was observed that intravenous administration of anisodamine prolonged the patients' duration of exercise, enhanced the exercise load, postpone the time to 0.1 mV ST-segment depression (compared with the baseline measurement), reduce the maximal depth of ST-segment depression and the maximal ST/HR-slope, shorten the time to ST-segment normalization more significantly than that of ISDN. It was suggested that anisodamine could more effectively ameliorate myocardial ischemia and improve cardiac reserve than ISDN. Furthermore, through the follow-up of the patients' symptoms and LVEF, it was observed that the treatment with intravenous administration of anisodamine significantly reduced the frequency and duration of angina attacks, improve the cardiac function. However, ISDN did not show a similar effect. Finally, the side effects of anisodamine were slight and tolerable. Compared with ISDN, anisodamine had never caused a decline in blood pressure which would probably lead to some iatrogenic risks.

Limitations of study

The study has several limitations. Firstly, for patients with CMD who suffered from obstructive epicardial CAD and had undergone PCI, the sample size was relatively small, this research limitation is supposed to be improved by expanding study scale. In addition, no drug-free group was clarified for contrast. In future research, a placebo group is supposed to be included. It was also limited by the short duration of follow-up. A 3-month follow-up was relatively short and at least 1 year is supposed to be preferred instead. Furthermore, the dose of anisodamine applied in the research was followed the protocol in the previous investigations. Different dose groups should be established to determine the optimum dose of anisodamine in further studies. Moreover, this study has only figured out the therapeutic impact of intravenous administration of anisodamine on CMD in patients with obstructive epicardial CAD who had undergone PCI. However, this method's exact mechanism is still not yet fully determined. More clinical, animal, isolated heart, and cell culture studies are required for a better understanding of the definite mechanism involved. Finally, this study did not determine whether prolonging or shortening the treating period may have different therapeutic effects. More investigations are needed to clarify it.

CONCLUSION

By comparing the results of MPI, TET and the clinical symptoms as well as LVEF, it was observed that intravenous administration of anisodamine improves coronary microvascular perfusion, ameliorate myocardial ischemia, increase cardiac reserve, alleviate symptoms of angina much more effectively than that of ISDN. Furthermore, anisodamine was not only mild in side effects, but it is also affordable. Therefore, this will be an optional cure for CMD in patients with obstructive epicardial CAD receiving PCI.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

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. Liang Chen conceived and designed the study, and drafted the manuscript. Bei Lei and Ying Lou collected, analyzed and interpreted the experimental data. Lixiu Chen and Jinqi Jiang revised the manuscript for important intellectual content. All authors read and approved the final manuscript for publishing.

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