Adenosine triphosphate stress ^{99m}Tc-methoxyisobutylisonitrile gated myocardial perfusion imaging efficacy in diagnosing stent restenosis following coronary stent implantation

PENGFEI ZHANG[1], SONG CHEN[2], YANG LI[1], QIUHONG DU[1], LIJUAN WANG[1], YINGXIAN SUN[1] and YAMING LI[2]

Departments of [1]Cardiology and [2]Nuclear Medicine, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning 110001, P.R. China

Received October 1, 2015; Accepted September 20, 2016

DOI: 10.3892/etm.2016.3875

Abstract. Coronary stent restenosis rate following implantation is considerably high. The adenosine stress gated myocardial perfusion imaging (G-MPI) method has been widely used in the diagnosis, risk stratification and prognosis evaluation of coronary heart disease; however, the high cost of adenosine limits its clinical application. The aim of the present study was to investigate the efficacy of adenosine triphosphate (ATP) stress ^{99m}Tc-methoxyisobutylisonitrile (^{99m}Tc-MIBI) G-MPI for diagnosis in-stent restenosis following coronary stent implantation. Data from 66 patients with typical angina pectoris symptoms who had undergone percutaneous coronary stent implantation >3 months prior to participation in the study were analyzed. All the patients underwent ATP stress ^{99m}Tc-MIBI G-MPI and coronary artery angiography as the criterion diagnostic standard within 1 month. The sensitivity, specificity, and accuracy of ATP stress ^{99m}Tc-MIBI G-MPI in the assessment of in-stent restenosis were calculated. In addition, Fisher's exact probability methods were used to compare differences between experimental groups. Among 66 patients with a total of 99 implanted coronary arterial branches, 39 patients (59%) with 45 coronary arteries (45%) presented in-stent restenosis. The diagnostic sensitivity, specificity, accuracy, positive predictive and negative predictive value of ATP stress ^{99m}Tc-MIBI G-MPI for assessing stent restenosis in all patients were 85, 89, 86, 92 and 80%, respectively. Similarly, these values in patients with myocardial infarction were 79, 88, 83, 88 and 78%, respectively, while in patients without myocardial infarction the values were 90, 91, 90, 95 and 83%, respectively. Therefore, the diagnostic efficacy of ATP stress ^{99m}Tc-MIBI G-MPI in patients without myocardial infarction was higher compared with those with myocardial infarction; however, no significant difference was observed between the two groups. Furthermore, the sensitivity, specificity and accuracy for diagnosing LAD stent restenosis were higher compared with LCX and RCA stent restenosis, but with no significant differences observed (P>0.05). The present results indicated that ATP stress ^{99m}Tc-MIBI G-MPI had a high clinical application value for diagnosing in-stent restenosis following coronary stent implantation as a non-invasive examination tool, with the advantages of safety and low cost.

Correspondence to: Professor Lijuan Wang, Department of Cardiology, The First Affiliated Hospital of China Medical University, 155 Nanjing Bei Street, Shenyang, Liaoning 110001, P.R. China
E-mail: wlj199810@163.com

Key words: adenosine triphosphate, ^{99m}Tc-methoxyisobutylisonitrile, gated myocardial perfusion imaging, coronary artery disease, stent, restenosis

Introduction

Intracoronary stent implantation has been widely used in the treatment of coronary heart disease (CHD). It has also reduced the incidence rate of restenosis after intracoronary intervene-tional therapy; however, the stent restenosis rate is as high as 20% at 3-6 months after surgery (1). Albertal *et al* (2) and Singh *et al* (3) have reported that the morbidity rate of patients with of in-stent restenosis in left anterior descending (LAD) is higher than that in left circum-flex (LCX) and right coronary artery (RCA), and remains the main factor to influence long-term prognosis in the patients with CHD. Coronary angiography (CAG) and intravascular ultrasound were typically considered as the criterion diagnostic standard for the evaluation of in-stent restenosis, but they are invasive and expansive (4). Therefore, in order to determine an efficient treatment strategy, a more convenient and accurate evaluation method for clinical screening of patients with coronary stent restenosis is required.

Gated myocardial perfusion imaging (G-MPI) is a convenient, non-invasive and accurate assessment method for myocardial blood perfusion. In addition, G-MPI is a simultaneous measurement tool for cardiac function parameters, namely left ventricular ejection fraction (LVEF) and ventricular wall motion (5-7). Adenosine stress G-MPI has been widely used in the diagnosis, risk stratification, and prognosis evaluation of CHD (8,9). However, adenosine is costly and, thus, there is reason to identify similar pharmaceuticals to replace it. Adenosine triphosphate (ATP) is a similar compound to adenosine regarding its pharmacological mechanism, but also inexpensive and thus more suitable for use in clinical practice (10).

Coronary angiography (CAG) is typically considered as the criterion diagnostic standard for the evaluation of stent restenosis. In the present study, the CAG diagnosis was determined and used to investigate the clinical application efficacy of ATP stress ^{99m}Tc-methoxyisobutylisonitrile (^{99m}Tc-MIBI) G-MPI in the evaluation of coronary artery stent restenosis, by comparing the results of the two methods.

Patients and methods

Ethical approval. The study protocol was approved by the Ethics Review Board of the First Affiliated Hospital of China Medical University (Shenyang, China). Written informed consent was obtained from all study participants. All the procedures were conducted in accordance with the Declaration of Helsinki and relevant policies in China.

Patient population. A total of 71 patients with typical angina pectoris symptoms from the hospital ward or outpatient service of the First Affiliated Hospital of China Medical University between January 2012 and December 2014 were enrolled into the current study (Table I). All patients had undergone coronary stent implantations (108 coronary arteries in total) 3 months to 10 years (2.5±2.1 years) before enrollment. Typical angina pectoris symptoms included chest pain, stuffy chest, left upper limb pain and left shoulder pain.

All the patients underwent CAG and one-day ATP stress/rest ^{99m}Tc-MIBI G-MPI on the same day within 1 month. The contraindications for the exclusion of ATP stress were as follows: i) Acute coronary syndrome; ii) bronchial asthma or chronic obstructive pulmonary disease; iii) sick sinus syndrome, with second- or third-degree atrioventricular block; iv) severe cardiac insufficiency, with cardiac function level III or IV; and v) high systolic blood pressure (≥180 mmHg) or low systolic blood pressure (≤90 mmHg).

Instruments and medicines. The instrument used was a VG double-probe single-photon emission computed tomography (SPECT) scanner with a low-energy high-resolution parallel hole collimator, which was provided by the General Electric Healthcare (Chicago, IL, USA). ATP was provided by Tianjin Pharmaceutical Jiaozuo Co. Ltd. (Jiaozuo, China). ^{99m}Tc was provided by Yuanzi Gaoke Co., Ltd. (Beijing, China), and MIBI was provided by the Jiangyuan Pharmaceutical Factory of the Jiangsu Institute of Atomic Medicine (Jiangsu, China).

ATP-induced stress experiment. Prior to the experiments, the patients discontinued the administration of any β-blockers, nitrate angiotensin-converting enzyme inhibitors and calcium ion antagonist for at least 48 h. In addition, administration of theophylline drugs was discontinued for at least 12 h. A double venous pathway was established, one for the injection of ATP and the other for the injection of ^{99m}Tc-MIBI. Using an intravenous tracer pump, ATP was injected at 0.16 mg/kg/min at a constant speed for 6 min.

Table I. Clinical characteristics of the patients in the study.

Characteristic	Value
Age, years	60.2±9.5
Gender, n (%)	
Men	56 (79)
Women	15 (21)
Condition, n (%)	
Myocardial infarction	36 (51)
Angina pectoris	35 (49)
Single-vessel disease	17 (24)
Double-vessel disease	23 (32)
Triple-vessel disease	31 (44)
Vessel, n (%)	
LAD artery	45 (42)
LCX artery	24 (22)
RCA	39 (36)

LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

After 3 min, ^{99m}Tc-MIBI 740 MBq was injected from the other pathway. Prior to the intravenous ATP injection, a 12-lead electrocardiogram (ECG), blood pressure test, heart rate and symptoms were recorded at various time points, as follows: At 3 min before injection, right after injection, 3 min after injection, and we monitored them during the entire procedure (10).

One-day stress/rest ^{99m}Tc-MIBI G-MPI. At 30 min after the ATP stress experiment, the subjects were provided with high-fat food (sour milk) to promote liver radioactivity removal. After 1 h from the meal, the cardiac images were collected using a VG double-probe SPECT scanner with a low-energy high-resolution parallel hole collimator, from the right anterior oblique 45˚ to the left posterior oblique 45˚ planes (6˚/view, 40 sec/view, with 8 frames per cardiac cycle) using a 64x64 matrix, and observed under x1.45 magnification. The gated slicing image by the ECToolbox Slicing software (Emory University; Syntermed, Inc., Atlanta, GA) was calibrated, and the slicing image was reconstructed using Butterworth low-pass filter back-projection, at a 6.59-mm thickness. The short axis, vertical long axis and horizontal axial slicing images were obtained, and the function parameters of LVEF were measured using QPS 2009 and QGS 2009 software (Siemens Medical Systems) . After 3-4 h, ^{99m}Tc-MIBI 740 MBq injection was administered in the state of rest. At 30 min after the intravenous injection, the patients were fed a high-fat meal, and 1 h later an image was obtained. The same collection method was used as that for stress imaging (7).

Scintigraphic image interpretation. On the image obtained by ^{99m}Tc-MIBI G-MPI, the left ventricle along the short-axis was divided into the apex, central and basal departments. These three segments were then respectively divided into the anterior, septum, inferior and lateral walls, combined with the cardiac apex department of the vertical long axis, with a total of 13 segments formed. Coronary blood vessels dominated the areas, as shown in Fig. 1. Using the conventional visual method, two experienced nuclear medicine physicians evaluated the nuclide distribution of each segment of the ATP stress ^{99m}Tc-MIBI G-MPI, without reference to the clinical data and the CAG findings of the patients. Scored visually in four classes (0-3), normal, mildly reduced, moderately reduced and severely reduced. Reduction of nuclide distribution were observed on two or more consecutive slices in the same place was considered a nuclide distribution anomaly. On a combined stress/rest G-MPI examination, a reversible or partially reversible nuclide distribution anomaly in the dominating region with stent blood vessels was defined as myocardial ischemia, and in-stent resenosis, while myocardial infarction combined with myocardial ischemia was defined as coronary in-stent restenosis (11,12).

CAG examination. Within a month after ATP stress ^{99m}Tc-MIBI G-MPI, experienced cardiovascular interventional physicians performed selectively left and right CAG using Judkin's method, and divided the coronary artery into the LAD artery, LCX artery and RCA. Without reference to the ATP stress ^{99m}Tc-MIBI G-MPI, a stenosis of ≥50% of the vascular inner diameter appearing in the coronary stent or within a 5-mm range from the stent was defined as restenosis. In cases where stenosis appeared at a distance of >5 mm from the stent, this was defined as a new stenosis of other region (13).

Statistical analysis. SPSS version 17 software (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Enumeration data are expressed as rate and percentages. Using CAG as the criterion diagnostic standard, the sensitivity, specificity, accuracy, positive predictive value and negative predictive value of ATP stress ^{99m}Tc-MIBI G-MPI in the evaluation of stent restenosis were calculated. The Fisher exact probability method was used to compare the rates, and $P<0.05$ was considered to show statistically significant differences.

Results

CAG results. Of the 71 patients originally included in the present study, data for 5 patients were excluded from the final analysis due to the occurrence of new stenosis. Therefore, the study included a total of 66 patients with stent implantation performed in 99 coronary arteries. Among these, 39 patients (59%) presented in-stent restenosis, 19 presented myocardial infarction and 20 presented non-myocardial infarction. In-stent restenosis was observed in 45 coronary arteries out of the 99 arteries subjected to stent implantation (~45%), including 24 LAD arteries, 6 LCX arteries and 15 RCAs.

ATP stress ^{99m}Tc-MIBI G-MPI efficacy in diagnosing stent restenosis. The ability of ATP stress ^{99m}Tc-MIBI G-MPI to diagnose stent restenosis was analyzed against the diagnostic ability of CAG. In those 39 positive patients diagnosed by CAG, 33 were diagnosed positve by ATP stress ^{99m}Tc-MIBI G-MPI. In those 27 negative patients diagnosed by CAG, three were diagnosed positive by ATP stress ^{99m}Tc-MIBI G-MPI. The diagnostic sensitivity, specificity, accuracy, positive predictive value and negative predictive value of ATP stress ^{99m}Tc-MIBI G-MPI for all the patients were found to be 85, 89, 86, 92 and 80%, respectively (Table II). This result indicated that ATP stress ^{99m}Tc-MIBI G-MPI has higher clinical value in diagnosing in-stent restenosis.

Table II. Values of adenosine triphosphate stress ^{99m}Tc-MIBI G-MPI for evaluating stent restenosis.

	CAG		
^{99m}Tc-MIBI G-MPI	Positive	Negative	Total
Positive	33	3	36
Negative	6	24	30
Total	39	27	66

MIBI, methoxyisobutylisonitrile; G-MPI, gate myocardial perfusion imaging; CAG, coronary angiography.

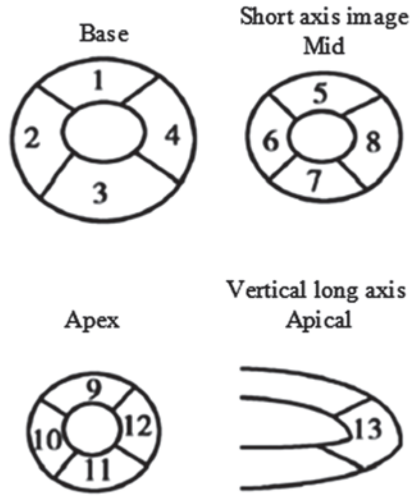

Figure 1. Coronary artery supply territories in adenosine triphosphate stress ^{99m}Tc-methoxyisobutylisonitrile gated myocardial perfusion imaging. Segments 1, 2, 5, 6, 9, 10 and 13 refer to the left anterior descending supply territories. Segments 4, 8 and 12 indicate the left circumflex supply territories. Segments 3, 7 and 11 indicate the right coronary artery territories.

ATP stress ^{99m}Tc-MIBI G-MPI efficacy in diagnosing stent restenosis in different types of CHD. The diagnostic sensitivity, specificity, accuracy, positive predictive value and negative predictive value of ATP stress ^{99m}Tc-MIBI G-MPI were 79, 88, 83, 88 and 78%, respectively, when evaluating stent restenosis in patients with myocardial infarction. Similarly, these values were 90, 91, 90, 95 and 83%, respectively, when evaluating patients with non-myocardial infarction (Table III). Therefore, the diagnostic values were higher in patients with non-myocardial infarction compared with those in patients with myocardial infarction; however, no statistically significant difference was observed between the two patient groups ($P>0.05$).

ATP stress ^{99m}Tc-MIBI G-MPI efficacy in diagnosing stent restenosis in different coronary arteries. The diagnostic

Table III. ATP stress ^{99m}Tc-MIBI G-MPI efficacy in diagnosing stent restenosis in different types of CHD.

	CAG in myocardial infarction patients			CAG in non-myocardial infarction patients		
^{99m}Tc-MIBI G-MPI	Positive	Negative	Total	Positive	Negative	Total
Positive	15	2	17	18	1	19
Negative	4	14	18	2	10	12
Total	19	16	35	20	11	31

ATP, adenosine triphosphate; ^{99m}Tc-MIBI G-MPI, ^{99m}Tc-methoxyisobutylisonitrile gated myocardial perfusion imaging; CHD, coronary heart disease; CAG, coronary angiography.

Table IV. ATP stress ^{99m}Tc-MIBI G-MPI efficacy in diagnosing stent restenosis in different coronary arteries.

	CAG in LAD artery			CAG in LCX artery			CAG in RCA		
^{99m}Tc-MIBI G-MPI	Positive	Negative	Total	Positive	Negative	Total	Positive	Negative	Total
Positive	20	2	22	5	3	8	12	5	17
Negative	4	16	20	1	13	14	3	15	18
Total	24	18	42	6	16	22	15	20	35

ATP, adenosine triphosphate; ^{99m}Tc-MIBI G-MPI, ^{99m}Tc-methoxyisobutylisonitrile gated myocardial perfusion imaging; CAG, coronary angiography; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

Table V. ATP stress ^{99m}Tc-MIBI G-MPI efficacy in diagnosing stent restenosis in patients with a different number of diseased vessels.

	CAG in single-vessel patients			CAG in double-vessel patients			CAG in triple-vessel patients		
^{99m}Tc-MIBI G-MPI	Positive	Negative	Total	Positive	Negative	Total	Positive	Negative	Total
Positive	8	0	8	10	2	12	15	1	16
Negative	2	5	7	1	9	10	3	10	13
Total	10	5	15	11	11	22	18	11	29

ATP, adenosine triphosphate; ^{99m}Tc-MIBI G-MPI, ^{99m}Tc-methoxyisobutylisonitrile gated myocardial perfusion imaging; CAG, coronary angiography.

sensitivity, specificity, accuracy, positive predictive value and negative predictive value of ATP stress ^{99m}Tc-MIBI G-MPI in the evaluation of stent restenosis in different artery types were as follows: 83, 89, 86, 91 and 80%, respectively, in LAD arteries; 83, 81, 82, 63 and 93%, respectively, in LCX arteries; 80, 75, 77, 71 and 83%, respectively, in RCAs (Table IV). These results indicate that the sensitivity, specificity and accuracy of diagnosis with ATP stress ^{99m}Tc-MIBI G-MPI were higher for the LAD artery stent restenosis compared with the LCX artery and RCA stent restenosis diagnoses; however, no statistically significant differences were observed among the three different artery categories ($P>0.05$).

ATP stress ^{99m}Tc-MIBI G-MPI efficacy in diagnosing stent restenosis in the patients with different number of diseased vessels. The diagnostic sensitivity, specificity, accuracy, positive predictive value and negative predictive value of ATP stress ^{99m}Tc-MIBI G-MPI according to the number of diseased vessels in the patients were as follows: Patients with single-vessel disease, 80, 100, 87, 100 and 71%, respectively; patients with double-vessel disease, 91, 82, 86, 83 and 90%, respectively; and patients with triple-vessel disease, 83, 91, 86, 94 and 77%, respectively. The results showed no significant difference in diagnosing in-stent restenosis by ATP stress ^{99m}Tc-MIBI G-MPI between these different number of diseased vessels ($P>0.05$) (Table V).

Typical case. A 56-year-old male patient with angina pectoris, who underwent coronary stent implantation in the LAD artery 10 years previously, experienced intermittent episodes of chest pain that were persistent for 1 month. ATP stress/rest ^{99m}Tc-MIBI G-MPI was performed as shown in Fig. 2. It was

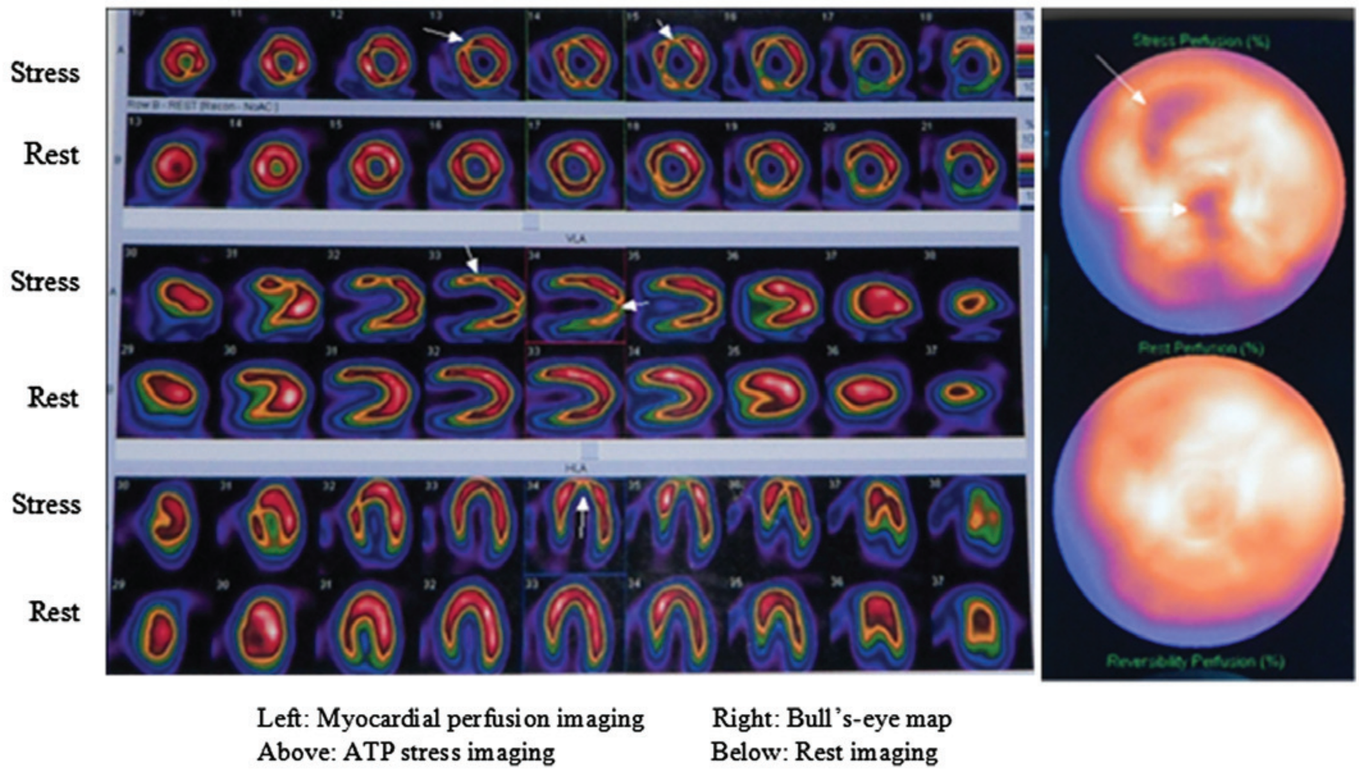

Figure 2. ATP stress/rest ^{99m}Tc-MIBI G-MPI in a representative case who underwent coronary stent implantation 10 years prior to participation in the present study. The nuclide distributions were mildly decreased and completely reversible in the anterior, anteroseptum and apex areas, whereas they were incompletely reversible in the inferoposterior and posterolateral areas. ATP, adenosine triphosphate; ^{99m}Tc-MIBI G-MPI, ^{99m}Tc-methoxyisobutylisonitrile gated myocardial perfusion imaging.

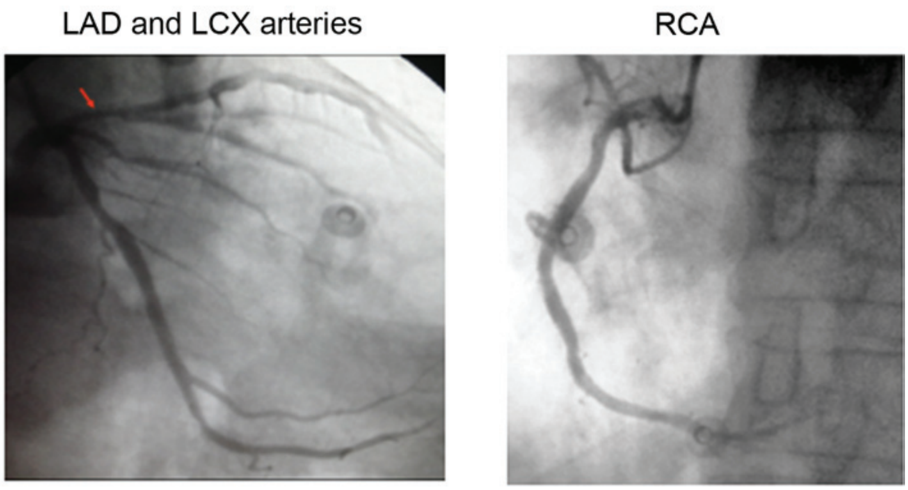

Figure 3. Coronary angiograms obtained 10 years after coronary stent implantation in the representative case of a 56-year-old patient with angina pectoris. The CAG images showed 80% stent restenosis in the LAD artery and 40% stenosis in the LCX artery and RCA. CAG, coronary angiography; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

observed that nuclide distribution was mildly decreased and completely reversible in the anterior, anteroseptum and apex areas, while it was incompletely reversible in the antero-posterior and posterolateral areas. Subsequently, CAG was performed 2 days after ATP stress/rest ^{99m}Tc-MIBI G-MPI. As shown in Fig. 3, 80% stent stenosis was observed in the LAD artery, as well as 40% stenosis in the RCA and LCX artery, confirming that the LAD artery had stent restenosis. Thus in this case, ATP stress/rest ^{99m}Tc-MIBI G-MPI agree with CAG.

Discussion

The methods currently used for diagnosing coronary stent restenosis mainly include CAG, exercise ECG, coronary computed tomography angiography (CTA) and stress MPI. Although CAG is known as the criterion standard for the diagnosis of coronary artery stenosis and stent restenosis, it is an invasive examination, with high cost and low patient compliance. In addition, although exercise ECG is a more affordable technique, it has low sensitivity. Buchler *et al* (14) reported that the sensitivity rates of exercise ECG for detecting coronary artery stent restenosis were 57.3, 54.5 and 38.5% at 6 weeks, 6 months and 1 year, respectively, after coronary stent implantation. So, the result indicated the presence of myocardial ischemia and LAD in-stent resenosis in this patient. Furthermore, coronary CTA image quality is easily affected, not only by arteriosteogenesis, but also by the patients' heart rate, heart rate fluctuations and partial stent volume. However, stress MPI is a non-invasive method that can accurately evaluate coronary in-stent restenosis.

The stress testing method mainly includes exercise-, adenosine-, dipyridamole-, dobutamine- and ATP-induced stresses. Exercise-induced stress is often not inducible in elderly people, while dobutamine-induced stress is time-consuming and not suitable for patients with high blood pressure. In addition, dipyridamole has a long half-life period and adenosine is expensive, thus limiting their application in stress testing. By contrast, ATP has a short half-life period (<20 sec) and is eliminated quickly from the body. In addition, ATP has relatively few adverse side effects, it is easily converted to adenosine in the body, and its cost is much lower than that of adenosine. Therefore, ATP has a more extensive application value compared with the other compounds (15).

ATP decomposes rapidly *in vivo,* producing adenosine diphosphate, adenosine phosphate and adenosine. The resulting adenosine then combines with vascular smooth muscle cells and binds with the A2 receptor, activating adenylate cyclase, which increases cycle adenosine monophosphate levels, activates potassium channels, reduces intracellular calcium uptake and expands coronary arteries. In addition, adenosine can significantly expand normal coronary arteries, although it does not significantly influence the increase in arterial blood flow in stenosis. The blood flow resistance is lower in the non-ischemic zone compared with that in the ischemic areas into the non ischemia areas are through the collateral circulation reflux to the non-ischemia area, which is namely the transverse vascular steal phenomenon (16). Furthermore, adenosine increases the coronary blood flow, which not only increases the pressure difference cross the stenosed coronary arteries, but also decrease the distal blood flows of stenosed vessels, and cause the blood flows of epicardium increasing and blood flows of endocardium decreasing, this is known as the longitudinal vascular steal phenomenon. This type of uneven blood flow distribution causes uneven myocardial nuclide uptake. In cases where G-MPI reveals radionuclide reduction or defects in stress state, the radionuclide defects may improve partly or fully in rest state (17).

In the present study, 59% of 66 patients presented in-stent restenosis,with 45% of 99 coronary arteries with in-stent restenosis, which is higher than the 20% incidence of patients previously reported in the literature (1). This may be explained by the fact that the present study selected patients with typical angina pectoris symptoms subsequent to stenting rather than randomly selecting patients who had undergone stenting.

Galassi *et al* (18) detected stent restenosis using sports stress ^{99m}Tc-tetrofosmin MPI in 97 patients subsequent to coronary stenting. This previous study observed sensitivity, specificity, accuracy, positive predictive value and negative predictive values of 82, 84, 83, 69 and 91%, respectively. By contrast, these values in the present study were 85, 89, 86, 92 and 86%, respectively, which are slightly higher compared with those reported by Galassi *et al* (18). In total, 6 patients in our study showed positive results on CAG and negative results on ATP stress ^{99m}Tc-MIBI G-MPI, mainly due to the presence of collateral circulation. In addition, the regulating function of the coronary artery itself was not affected in 50% of the critical coronary in-stent stenosis, the blood flow reserve capacity was close to normal, and the stress myocardial perfusion had no reversible defects in the state of stress. Furthermore, 3 patients demonstrated negative results on CAG and positive results on ATP stress ^{99m}Tc-MIBI G-MPI, as microangiopathy mainly led to the appearance of decreased perfusion in the non-stenosis coronary area by reducing the mild nuclide distribution.

Kósa *et al* (19) reported the sensitivity and specificity of stress MPI for detecting stent restenosis in 82 patients. The study identified that the sensitivity and specificity of MPI in the myocardial infarction area were 64 and 72%, respectively, while these values in the non-myocardial infarction area were 100 and 82%, respectively. In the present study, the sensitivity, specificity and accuracy of the G-MPI technique used were 79, 88 and 83%, respectively, in the myocardial infarction group, whereas these values in the non-myocardial infarction group were 90, 91 and 90%, respectively. It is evident that the sensitivity was lower for the myocardial infarction group compared with that for the non-myocardial infarction group, as scar tissue formed in the infarction area and the number of viable myocardial cells was reduced, leading to a significant reduction in myocardial cell nuclide uptake; thus, the stress/rest nuclide MPI reversible distribution was not clear. In addition, 5 patients in the current study developed complete myocardial infarction due to the stent implantation vessel governing area having no viable myocardium, namely the myocardial scar, and fixed defects were detected on stress/rest MPI. Although 2 patients presented stent restenosis on CAG, stress/rest MPI have not shown that radionucleotide distribute reberseibly or partly reversibly in rest state, and showed false negative results. Therefore, the sensitivity of ATP stress ^{99m}Tc-MIBI G-MPI for detecting in-stent restonosis was reduced in the patients with myocardial dysfunction.

In the present study, the sensitivity, specificity and accuracy of ATP stress ^{99m}Tc-MIBI G-MPI for evaluating stent restenosis in various arteries were as follows: In LAD arteries, 83, 89 and 86%, respectively; in LCX arteries, 83, 81 and 82%, respectively; and in RCAs, 80, 75 and 77%, respectively. These values were similar to those reported in the study of Elhendy *et al* (20). In general, the sensitivity, specificity, and accuracy of ATP stress ^{99m}Tc-MIBI G-MPI for evaluating coronary artery branch restenosis were high, particularly for the LAD artery, indicating that this technique is useful in determining the 'culprit vessel'. Furthermore, ^{99m}Tc-MIBI G-MPI in the present study was less sensitive and specific in detecting RCA restenosis compared with its detection ability in the other two coronary arteries. As there are numerous patients with inferior wall myocardial infarction in the current study, the inferior wall myocardial nuclide uptake was evidently reduced, which affected the refilling of the inferior wall myocardial nuclide distribution, leading to reduced sensitivity for the diagnosis of RCA restenosis. In addition, myocardial nuclide uptake was susceptible to the attenuation effect of the surrounding tissues, such as those of the liver and gall, due to the inferior wall. Although the present study corrected for attenuation, the inferior wall myocardial nuclide distribution unavoidably showed false positive results, particularly in certain obese patients; therefore, the specificity of ^{99m}Tc-MIBI G-MPI to detect right coronary artery restenosis was reduced.

The current research results also demonstrated the diagnostic sensitivity, specificity, accuracy, positive predictive value and negative predictive value of ATP stress ^{99m}Tc-MIBI in patients with different number of diseased arteries. In single-vessel disease patients, these values for G-MPI were 80, 100 and 87%, respectively; similarly, these values were 91, 82 and 86%, respectively, in patients with double-vessel disease, and 83, 91 and 86%, respectively, in patients with triple-vessel disease. These values are higher compared with those reported by Wei and Shi (21). Among these values, the sensitivity for diagnosis in patients with double- and triple-vessel disease was higher compared with that for single-vessel disease patients; this is due to the larger number of diseased vessels, and the greater scope and degree of myocardial ischemia. Thus, it was not easy to form collateral circulation, and only few false-negative results in the patients with double and triple vessel disease were detected.

In the ATP stress test performed in the present study, a total of 60 cases (85%) with adverse reactions were encountered, mainly in the form of chest pain (22 cases; 31%), stuffy chest (29 cases; 41%), dyspnea (7 cases; 10%) and ventricular premature beats (2 cases; 3%). However, these symptoms were mild, and therefore, ATP stress experiments were not stopped in these patients. In addition, the patients were relieved several minutes after the drug was discontinued, and none of them required administration of nitroglycerin or other drugs orally, similar to patients in previous studies (22,23). It is, thus, clear that ATP stress ^{99m}Tc-MIBI G-MPI is safe to use in such patients.

However, the present study presented certain limitations. Firstly, the number of cases in the study was small, and a higher number of cases will be analyzed in our future research. Furthermore, the patients did not undergo stress MPI prior to percutaneous coronary intervention; therefore, the results before and after this procedure cannot be compared. We will focus on this area in our future research study.

In conclusion, the present study observed that the ATP stress ^{99m}Tc-MIBI G-MPI technique showed characteristics of high sensitivity, specificity and accuracy, as well as non-invasiveness and relative affordability, for the diagnosis of stent restenosis. This method has high clinical application value for evaluating coronary restenosis following stent implantation.

Acknowledgements

The present study was supported by the Science and Technology Project Plan of Liaoning, China (grant no. 2007225004-2).

References

1. Mercado N, Boersma E, Wijns W, Gersh BJ, Morillo CA, de Valk V, van Es GA, Grobbee DE and Serruys PW: Clinical and quantitative coronary angiographic predictors of coronary restenosis: A comparative analysis from the balloon-to-stent era. J Am Coll Cardiol 38: 645-652, 2001.
2. Albertal M, Abizaid A, Munoz JS, Mintz GS, Abizaid AS and Feres F: A novel mechanism explaining early lumen loss following balloon angioplasy for the treatment of in-stent restenosis. Am J Cardiol 95: 751-755, 2005.
3. Singh M, Gersh BJ, MeClelland RL, Ho KK, Willerson JT and Penny WF: Clinical and angiographic predictors of restenosis after percutaneous coronary intervention. Circulation 109: 2727-2731, 2004.
4. Veselka J, Cadova P, Tomasov P, Theodor A and Zemanek D: Dual-source CT angiography for detection and quantification of in-stent restenosis in the left main coronary artery: comparison with intracoronary ultrasound and coronary angiography. J Invasive Cardiol 23: 460-464, 2011.
5. Dowsley T, Al-Mallah M, Ananthasubramaniam K, Dwivedi G, McArdle B and Chow BJ: The role of noninvasive imaging in coronary artery disease detection, prognosis, and clinical decision making. Can J Cardiol 29: 285-296, 2013.
6. Uebleis C, Hellweger S, Laubender RP, Becker A, Sohn HY, Lehner S, Haug A, Bartenstein P, Cumming P, Van Kriekinge SD, *et al*: Left ventricular dyssynchrony assessed by gated SPECT phase analysis is an independent predictor of death in patients with advanced coronary artery disease and reduced left ventricular function not undergoing cardiac resynchronization therapy. Eur J Nucl Med Mol Imaging 39: 1561-1569, 2012.
7. Akalin EN, Yaylali O, Kıraç FS, Yüksel D and Kılıç M: The role of myocardial perfusion gated SPECT study in women with coronary artery disease: A correlative study. Mol Imaging Radionucl Ther 21: 69-74, 2012.
8. Shaw LJ, Hendel R, Borges-Neto S, Lauer MS, Alazraki N, Burnette J, Krawczynska E, Cerqueira M and Maddahi J; Myoview Multicenter Registry: Prognostic value of normal exercise and adenosine triphosphate (99m) Tc-tetrofosmin-SPECT imaging: Results from the multicenter registry of 4,728 patients. J Nucl Med 44: 134-139, 2003.
9. Wang LJ, Li XJ, Sun YX, Li N and Li YM: The clinical value of adenosine stress ^{99m}Tc-MIBI gated myocardial perfusion imaging in diagnosis of coronary artery disease. Zhong Guo Xun Huan Za Zhi 26: 170-173, 2011 (In Chinese).
10. Karpova IE, Samoĭlenko LE, Soboleva GN, Sergienko VB, Karpov IuA, Chernysheva IE and Ioseliani DG: Adenosine triphosphate stress (99m)Tc-MIBI single-photon emission computed tomography in the diagnosis Miocardial Iscemia in patients with Microvascular Angina. Kardiologiia 54: 4-8, 2014 (In Russian).
11. Milavetz JJ, Miller TD, Hodge DO, Holmes DR and Gibbons RJ: Accuracy of single-photon emission computed tomography myocardial perfusion imaging in patients with stents in native coronary arteries. Am J Cardiol 82: 857-861, 1998.
12. Xu ZN, Li DF, Li JH, Feng JL and Cheng X: The value of gated myocardial perfusion imaging for evaluating stent restenosis after percutaneous coronary interventions. Lin Chuang Xin Xue Guan Bing Za Zhi 25: 302-305, 2009 (In Chinese).
13. Coroleu SF, De Vita M, Burzotta F, Trani C, Porto I, Niccoli G, Leone AM, Tommasino A, Talarico GP, Schiavoni G and Crea F: Angiographic and clinical outcome of percutaneous coronary intervention for in-stent restenosis of bifurcated lesions. EuroIntervention 8: 701-707, 2012.
14. Buchler RD, Ribeiro EE, Mansur Ade P, Smanio P, Meneghelo RS, Chalela WA, Buchpiguel CA, Buchler JR, Bates ER and Martinez EE: Noninvasive assessment of patients undergoing percutaneous intervention in myocardial infarction. Arq Bras Cardiol 95: 555-562, 2010 (In English, Portuguese).
15. Ohtaki Y, Chikamori T, Hida S, Tanaka H, Igarashi Y, Hatano T, Usui Y, Miyagi M and Yamashina A: Clinical characteristics in patients showing ischemic electrocardiographic changes during adenosine triphosphate loading single-photon emission computed tomography. J Cardiol 55: 370-376, 2010.
16. Conti A, Mariannini Y, Canuti E, Petrova T, Innocenti F, Zanobetti M, Gallini C and Costanzo E: Nuclear scan strategy and outcomes in chest pain patients value of stress testing with dipyridamole or adenosine. World J Nucl Med 13: 94-101, 2014.
17. Chen GB, Wu H, He XJ, Huang JX, Yu D, Xu WY and Yu H: Adenosine stress thallium-201 myocardial perfusion imaging for detecting coronary artery disease at an early stage. J Xray Sci Technol 21: 317-322, 2013.
18. Galassi AR, Foti R, Azzarelli S, Coco G, Condorelli G, Russo G, Musumeci S, Tamburino C and Giuffrida G: Usefulness of exercise tomographic myocardial perfusion imaging for detection of restenosis after coronary stent implantation. Am J Cardiol 85: 1362-1364, 2000.

19. Kósa I, Blasini R, Schneider-Eicke J, Neumann FJ, Matsunari I, Neverve J, Schömig A and Schwaiger M: Myocardial perfusion scintigraphy to evaluate patients after coronary stent implantation. J Nucl Med 39: 1307-1311, 1998.
20. Elhendy A, Schinkel AF, van Domberg RT, Bax JJ, Valkema R and Poldermans D: Non-invasive diagnosis of in stent stenosis by stress 99m technetium tetrofosmin myocardial perfusion imaging. Int J Cardiovasc Imaging 22: 657-662, 2006.
21. Wei HY and Shi RF: The clinical value of SPECT ^{99m}Tc-MIBI ST/RE myocardial imagings in restenosis after percutaneous coronary angioplasty. Zhong Guo Xin Xue Guan Za Zhi 9: 199-201, 2004 (In Chinese).
22. AlJaroudi WA, Alraies MC, Cerquiera MD and Jaber WA: Safety and tolerability of regadenoson in 514 SPECT MPI patients with and without coronary artery disease and submaximal exercise heart rate response. Eur J Nucl Med Mol Imaging 40: 341-348, 2013.
23. Karamitsos TD, Arnold JR, Pegg TJ, Cheng AS, van Gaal WJ, Francis JM, Banning AP, Neubauer S and Selvanayagam JB: Tolerance and safety of adenosine stress perfusion cardiovascular magnetic resonance imaging in patients with severe coronary artery disease. Int J Cardiovasc Imaging 25: 277-283, 2009.