Short Communication

The role of oral dipyridamole stress gated SPECT in assessing the response of the left ventricle to stress: Re-evaluation of an old method

Doğangün Yüksel[1], Suna Kıraç[1], Olga Yaylalı[1], Beyza Akdağ[2], Dursun Dursunoğlu[3]

[1]Department of Nuclear Medicine, [2]Department of Biostatistics,
[3]Department of Cardiology, Medical Faculty, Pamukkale University, Denizli, Turkey

(Received 25 September 2014, Revised 20 November 2014, Accepted 1 December 2014)

ABSTRACT

Introduction: We aimed to assess whether the vasodilator effect of oral dipyridamole on the left ventricular systolic function in patients with suspected CAD is different from that of intravenous (IV) dipyridamole using Tc-99m MIBI myocardial perfusion gated SPECT.

Methods: Eighty-nine patients (17 male, 72 female; 61±10 years) were enrolled in this study. The patients underwent a dipyridamole stress test for the gating study. Forty-one patients were given oral dipyridamole (OD), and 48 patients were given intravenous dipyridamole (ID). Each group was divided into two subgroups according to whether they had normal or abnormal myocardial perfusion scintigraphy (MPS) findings (reversible perfusion defect). A two-day dipyridamole pharmacologic stress-rest Tc-99m MIBI myocardial perfusion gated SPECT protocol was performed in all patients. The LV ejection fraction (EF), end diastolic volume (EDV) and end systolic volume (ESV) were calculated from the gated data.

Results: In the ID group, LV myocardial perfusion was normal in 28 cases and abnormal in 20 cases. In abnormal ID cases, a significant difference between rest and stress EDV was detected (P = 0.017). In the OD group, the LV myocardial perfusion was normal in 20 and abnormal in 21 cases. In the OD normal cases, the rest EF (P = 0.012) and EDV (P = 0.029) were significantly different from the stress cases.

Conclusion: The effect of ID test continues during gated SPECT and results in LV diastolic dysfunction in patients with abnormal myocardial perfusion. Oral administration is also highly effective for detecting real myocardial ischemia that causes LV systolic and diastolic dysfunction.

Key words: Dipyridamole; Gated SPECT; Left ventricular function; Myocardial perfusion imaging; Tc-99m; Sestamibi

Iran J Nucl Med 2015;23(2):116-123
Published: June, 2015
http://irjnm.tums.ac.ir

Corresponding author: Doğangün Yüksel, Pamukkale Üniversitesi, Tıp Fakültesi, Nükleer Tıp Anabilim Dalı, Pau Sarum Hastanesi, Kınıklı. 20070 Denizli, Turkey. E-mail: dyuksel@pamukkale.edu.tr

INTRODUCTION

The left ventricular (LV) function is a major determinant of the prognosis of patients with coronary artery disease (CAD) [1]. Gated single photon emission computerized tomography (Gated SPECT) offers the possibility of simultaneously assessing both myocardial perfusion and left ventricular function and provides useful diagnostic and prognostic information for CAD [2, 3].

Dipyridamole, a potent coronary vasodilator, has indirect effects via adenosine on the small coronary resistance vessels. The increase in coronary blood flow that is achieved with dipyridamole in normal vessels is three- to five-fold greater than basal blood flow; myocardial ischemia occurs as a result of the reduced blood flow in the territory supplied by the stenotic artery, which is defined as myocardial steal phenomenon [4]. The intravenous form of dipyridamole (ID) is commonly preferred to the oral form (OD) in myocardial perfusion scintigraphy (MPS) for coronary vasodilatation [5]. Because its serum levels have too different a range because of the individual variability in gastrointestinal absorption, oral dipyridamole is not a preferred coronary vasodilator agent. The maximal effect duration of dipyridamole on the coronary vessels varies from patient to patient [6]. The effects are apparent within approximately 24 minutes and persist for approximately 3 hours [7]. The hemodynamic effects of intravenous dipyridamole reached the maximum level in approximately 7-10 minutes and returned to the basal level 25 minutes after infusion [8, 9]. Myocardial perfusion gated SPECT scintigraphy is performed 30–60 minutes after the intravenous injection of technetium-labeled myocardial perfusion agents [8]. Some previously published studies evaluated the functional parameters of LV under the effect of dipyridamole. The techniques used in these studies included cardiac echography, radionuclide ventriculography during intravenous infusion of dipyridamole and gated SPECT during or after the intravenous infusion of dipyridamole [9-11]. The gated SPECT parameters acquired 30-60 minutes after intravenous dipyridamole are reported to show the left ventricular dysfunction if there is post-stress stunning [9-19]. Therefore, it is still controversial whether the effect of intravenous dipyridamole continues during acquisition. The effect of OD on the coronary vessels seems to be maintained during Gated SPECT acquisition because of its prolonged intestinal absorption and variety in metabolism. However, no previous studies have investigated the LV functional parameters after oral dipyridamole intake.

We aimed to assess whether the vasodilator effect of oral dipyridamole on left ventricular systolic function in patients with suspected CAD using Tc-99m MIBI myocardial perfusion gated SPECT is different from that of IV dipyridamole.

METHODS

Patient Population

We investigated 89 patients (17 men, 72 women; mean age 61 ± 10 years, range 38 to 89 years) who were referred for myocardial perfusion scintigraphy (MPS) because of suspected CAD. Approval of the Faculty Ethical Committee was obtained. Informed consent forms were obtained from all participants.

All patients underwent a dipyridamole stress test for myocardial perfusion Gated SPECT. Dipyridamole was administered orally (n = 41) and intravenously (n=48). Each group was divided into two subgroups according to the visual evaluation of MPS images as normal (ODN and IDN) or abnormal (ODA and IDA). Abnormal myocardial perfusion was defined as evidence of a reversible perfusion defect or defects in the MPS images.

The major risk factors of cardiac events for patients were determined according to the patient's risk profile. The major risk factors for CAD were sex, age, blood pressure, obesity, chest pain, family history of cardiac disease, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, smoking behavior and diabetes status. Then, the global risk scores of patients were calculated using a risk prediction program developed from the Framingham Heart Study [20]. The clinical cardiac events were categorized as low risk < 15%, medium risk = 15 - 20%, high risk = 20 - 30% and very high risk > 30%.

The exclusion criteria were the presence of a left bundle branch block, cardiac pacemaker, recent myocardial infarction, coronary revascularization, significant valvular disease, arrhythmia, or a fixed defect in MPS and aminophylline use before MPS.

Two-day dipyridamole pharmacologic stress-rest myocardial perfusion gated SPECT imaging protocol

This study was performed according to the procedural guidelines of EANM/ESC for dipyridamole pharmacologic stress-rest Tc-99m MIBI myocardial perfusion Gated SPECT using a 2-day protocol [8].

In the ID group, dipyridamole (Persantine® ampul, Krebs, Offenbach, Germany) was administered intravenously as a continuous infusion at 0.14 mg/kg/min (max. dose of 0.56 mg/kg) over 4 minutes while the patient was in the supine position. In the OD group, 300 mg (four 75 mg tablets) dipyridamole (Drisentin® draje, SANOVEL, İstanbul, Türkiye) was administered peroral [21]. Technetium-99m

MIBI (740 MBq) was injected at the end of the stress test (at 3-5 minutes, IV and at 45-50 minutes, oral dipyridamole). The blood pressure, heart rate, ECG and complaints were recorded during the test. Two-day dipyridamole pharmacologic stress-rest myocardial perfusion Gated SPECT images were obtained 45 minutes after the injection of radiopharmaceutical while the patient was in the supine position. If there were any side effects, aminophylline was applied before the patient left the department.

The short-axis, vertical long-axis, and horizontal long-axis myocardial perfusion images for dipyridamole stress and rest MPS SPECT studies were displayed in gray scale. The left ventricle was divided into 17 segments. Two experienced nuclear physicians visually evaluated the myocardial perfusion images to reach consensus.

Gated SPECT analysis

The gated data were processed using the Emory Cardiac Toolbox – ECT eNTEGRA. The LV wall motion and wall thickening were visually and semi quantitatively evaluated; then, the ejection fraction (EF), end diastolic volume (EDV) and end systolic volume (ESV) were automatically calculated. The LV wall motion and wall thickening were scored using a 4-point scale (0: normal regional function is defined when wall thickening and motion are normal; 1: a hypokinetic region is defined when wall thickening and/or motion is decreased; 2: an akinetic region is defined by the absence of wall thickening and motion; and 3: a dyskinetic region is defined by paradoxical wall motion).

Statistical analysis

Data were analyzed using the Kruskal Wallis Variance Analysis, the Mann Whitney U Test with Bonferroni Correction, the Wilcoxon Signed Rank Test and the Chi-Square Test. All analyses were performed with the SPSS (version 10.0) statistical package program. The results for continuous variables are given as the mean ± standard deviation, and categorical variables are given as the frequencies and percentages. The statistical significance was set at $P < 0.05$.

RESULTS

The demographic data, CAD risk factors and Framingham scores of the patient groups are presented in Table 1. Also, Table 2 shows the results of Gated SPECT MPS parameters.

Intravenous dipyridamole group

The mean age was 61 ± 11 years (range: 39 - 79 years) for the 28 patients (22 F / 6 M) with normal myocardial perfusion. The mean Framingham Score was 6.7 ± 5.2%.

Table 1: The descriptive statistics of patient groups with regard to demographic data and CAD risk factors and significance levels.

Groups	Oral dipyridamole		Intravenous dipyridamole		P
Subgroups for MPS	Normal	Abnormal	Normal	Abnormal	
Number of patients	20	21	28	20	
Mean age (year) (Range)	57±7 (39-71)	63±12 (46-89)	61±11 (39-79)	63±11 (38-79)	NS
Gender: F/M (%)	20/0 (100/0)	15/6 (71/29)	22/6 (79/2)	15/5 (75/25)	NS
Obesity	12 (60%)	7 (33%)	12 (43%)	11 (55%)	NS
Hypertension	13 (65%)	15 (71 %)	16 (57%)	17 (85%)	NS
Smoking	3 (15%)	4 (19%)	7 (25%)	3 (15%)	NS
Family history	8 (40%)	8 (38%)	14 (50%)	8 (40%)	NS
Hyperlipidemia	16 (80%)	8 (38%)	10 (36%)	7 (35%)	0.007
Diabetes Mellitus	11 (55%)	6 (29%)	13 (46%)	8 (40%)	NS
Mean risk score (%)	4.7±3.8	10.0±8.2	6.7±5.2	9.5±9.3	NS

NS: Not significant

Table 2: The results of Gated SPECT MPS parameters.

	Patient Number	EF% Stress vs. Rest	EDV (ml) Stress vs. Rest	ESV (ml) Stress vs. Rest
IDN	28	75±8 vs. 78±8	88± 6 vs. 89±25	22±11 vs. 20±11
IDA	20	65±14 vs. 66±15	119±40 vs. 111±30, P = 0.017	46±37 vs. 41±28
ODN	20	80±6 vs. 77±5, P=0.012	79±11 vs. 80±15	15±6 vs. 19±6, P=0.029
ODA	21	74±16 vs. 72±15	111±61 vs. 103±43	36±51 vs. 34±35

EDV: End diastolic volume, EF: Ejection fraction, ESV: End systolic volume, IDA: Intravenous dipyridamole abnormal group, IDN: Intravenous dipyridamole normal group, ODA: Oral dipyridamole abnormal group, ODN: Oral dipyridamole normal group

Four patients were in the moderate risk group, and 24 patients were in the low risk group. There was no significant difference in any of the parameters between the rest and stress study in the IDN group. Of the 20 patients (15 F/5 M) who underwent ischemic MPS study, the mean age was 63 ± 11 years (range: 38 - 79 years). The mean Framingham Score was 9.5 ± 9.3%. Four patients were in the high risk group, and 16 patients were in the low risk group.

In the IDN subgroup, the difference between the rest and stress parameters was not meaningful. In the IDA subgroup, the stress EDV measurement was significantly higher than rest in this group (119 ± 40 ml and 41 ± 28 ml, respectively; P = 0.017). Though no deterioration in the LV systolic wall thickening and wall movements after the stress test was observed in the MPS normal group, it was detected in 12 patients and 45 segments (33 hypokinesia, 6 akinesia and 6 dyskinesia) in the IDA group.

Oral dipyridamole group

In this group, 20 cases (20 F/0 M) had normal left ventricular myocardial perfusion on MPS images. The mean age was 57 ± 7 years (range: 39 - 71 years). The mean Framingham Score was 4.7 ± 3.8%, and all patients were in the low risk group. Twenty-one patients (15 F/6 M, 63 ± 12 years of mean age) with ischemic MPS had an age ranging from 46 - 89 years. The mean Framingham Score was 10.0 ± 8.2%; two patients were in the high risk group, four patients were in the moderate risk group, and 15 patients were in the low risk group.

In the ODN group, significant differences were observed in the EF (80 ± 6% and 77 ± 5%, P = 0.012) and ESV (15 ± 6 ml and 19 ± 6 ml, P = 0.029) values between the stress and rest studies. All patients in the ODN group had normal LV function. In the ODA group, a significant difference was not detected for any of the parameters between rest and stress. Assessing the LV systolic wall thickening and wall movements, deterioration in the LV wall motion and myocardial thickening after the stress test was observed in 6 patients and 21 segments (14 hypokinesia, 5 akinesia and 2 dyskinesia) in this group.

Subgroup comparison

The Kruskal Wallis Test shows significant differences for all LV parameters between the groups ($P < 0.05$). Additionally, all parameters in the IDA group that were obtained under stress and at rest were significantly different than those in the ODN and IDN groups ($P < 0.001$).

The stress EF and ESV were significantly different in the ODN group compared with the IDN group and in the ODA group compared with the IDA group ($P < 0.05$). Additionally, a significant difference was observed between the ODN and ODA groups for EDV values obtained under stress ($P < 0.05$) (Table 3, Figure 1).

We did not observe any severe side effects with either form of dipyridamole.

DISCUSSION

The basis for dipyridamole echography and dipyridamole radionuclide ventriculography includes both coronary and systemic vasodilatation [22-24]. Systemic vasodilatation induced by dipyridamole reduces the ventricular afterload. There is an inverse relationship between the afterload and LV fiber shortening [25-27].

Table 3: The P values for LV parameters of each group.

	Stress			Rest		
	EF	EDV	ESV	EF	EDV	ESV
All subgroups*	0.001	0.001	0.0001	0.033	0.003	0.013
ODN-ODA**	0.333	0.042	0.064	0.497	0.098	0.166
ODN-IDN**	0.005	0.281	0.016	0.537	0.164	0.925
ODN-IDA**	0.0001	0.0001	0.0001	0.018	0.0001	0.003
ODA-IDN**	0.436	0.203	0.840	0.199	0.353	0.253
ODA-IDA**	0.018	0.159	0.030	0.162	0.151	0.188
IDN-IDA**	0.024	0.001	0.002	0.007	0.004	0.004

*: Kruskal Wallis Test, **: Mann Whitney U Test. EDV: End diastolic volume, EF: Ejection fraction, ESV: End systolic volume, IDA: Intravenous dipyridamole abnormal group, , IDN: Intravenous dipyridamole normal group, ODA: Oral dipyridamole abnormal group and ODN: Oral dipyridamole normal group

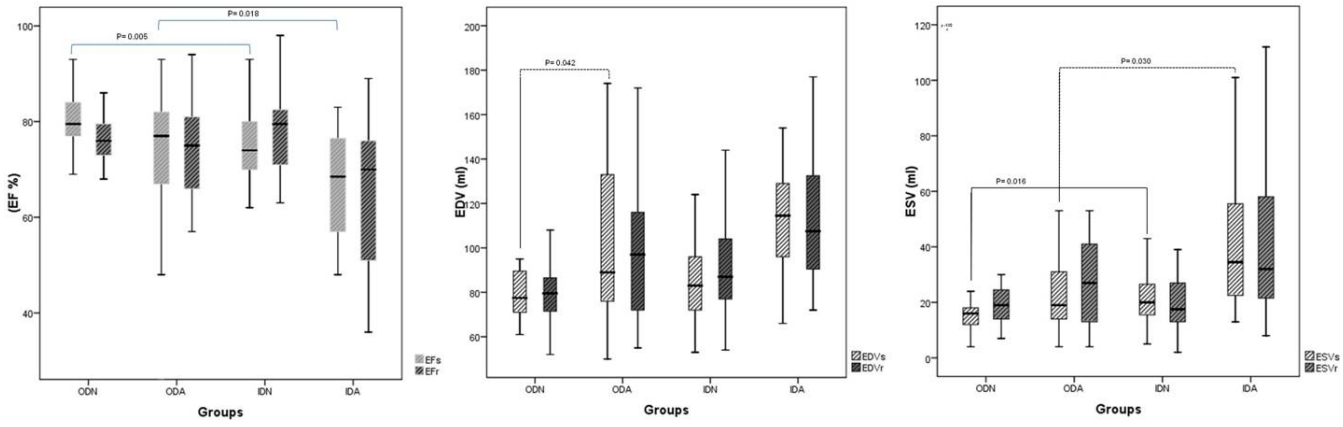

Fig 1. The stress EF and ESV were significantly different in ODN from IDN and in ODA from IDA. These findings suggested that the effect of oral dipyridamole is different from intravenous dipyridamole during imaging. The most likely explanation of this situation is that the effect of oral dipyridamole continues during gated study. A significant difference was observed between ODN and ODA group for EDV values obtained under stress. Abbreviations, ODN: Oral dipyridamole normal group; ODA: Oral dipyridamole abnormal group; IDN: Intravenous dipyridamole normal group; IDA: Intravenous dipyridamole abnormal group; EF: Ejection fraction; EDV: End diastolic volume; ESV: End systolic volume; EFs: Stress ejection fraction; EDVs: Stress end diastolic volume; ESVs: Stress end systolic volume; EFr: Rest ejection fraction; EDVr: Rest end diastolic volume; ESVr: Rest end systolic volume.

Weinmann et al. [19] reported that the quantitative Gated SPECT parameters obtained an hour after the infusion were nearly the same as for the rest values in patients with low risk CAD during dipyridamole infusion. Klein et al. [9] reported an increase in the EF value during dipyridamole infusion compared to the baseline value in patients who had a low risk for CAD and who lacked a perfusion defect in Tl-201 myocardial perfusion scintigraphy in a study on the LV functions evaluated by radionuclide ventriculography. In another study, Fleming et al. [28] detected an increase in the EF with high dose dipyridamole infusion. Similarly, Kakhki et al. [29] demonstrated an increased EF and decreased ESV in post-dipyridamole stress Gated SPECT performed 90 minutes after radiotracer injection compared with rest

Gated SPECT in patients with normal myocardial perfusion. The authors of that study administered a higher dipyridamole dose (0.142 mg/kg/min) compared with the routine doses (0.56 mg/kg/min or 0.76 mg/kg/min). For that reason, the effect of the drug most likely continued until the late period (90 minutes).

In contrast with these studies, we did not find any significant difference between the rest and stress LVEF or ESV values in patients with both normal and ischemic myocardial perfusion in the ID group. Though there was no change in the EDV between rest and stress in the IDN group, a significant increase was detected in patients with IDA during the stress test. The change in the EDV after IV dipyridamole seems to be due to the severity of diastolic dysfunction or stunned myocardium in patients with coronary artery stenosis, as reported in previously published studies [12, 14].

We found that the effect of oral dipyridamole might continue longer than the intravenous application because of individual absorption changes. Additionally, when we gave oral dipyridamole, there was a significant increase in the LVEF and a significant decrease in the ESV during post-stress Gated SPECT in the ODN group. Many studies have reported these results in subjects with normal coronary arteries or low risk CAD while under the effects of dipyridamole [9, 19, 25, 27]. The increase in the LVEF and decrease in ESV may be the result of an increase in the LV myocardial perfusion and contraction rate, depending on the vasodilator effect of oral dipyridamole to the normal coronary vessels in the cases with normal myocardial perfusion. Therefore, it seems that the change in the functional parameters of the LV during the oral dipyridamole stress test is real and continues to act on the LV during a Gated SPECT study acquired at approximately 90 minutes post-stress. Our oral dipyridamole cases with normal myocardial perfusion were in the low risk group, as observed in previously published studies (Table 1), and our results were similar to those in the previously published studies [9, 19, 25, 27].

Conversely, the LV EF, EDV and ESV at rest and stress values were similar in our ODA group. Klein et al. [9] showed that as the number of affected vessels increased, the EF values that were obtained on radionuclide ventriculography with dipyridamole decreased in patients with a Tl-201 perfusion defect. A similar finding was reported by Fleming et al. [28] during high dose dipyridamole infusion in Tc-99m MIBI Gated SPECT. Although most cases (n = 15) had a low risk for CAD in the ODA group, the EDV was higher (P = 0.042) under stress compared to the ODN group. These findings may be the result of a decrease in the coronary vasodilator reserve and of the reduced contractile reserve in the ischemic myocardium. In patients with severe CAD, dipyridamole may cause systolic dysfunction by inducing myocardial ischemia with two mechanisms; the LVEF fails to increase or may even decrease; finally, wall motion abnormalities may depend on the severity of ischemia. In CAD patients, the first mechanism is known as the coronary steal phenomenon [22, 30]. This phenomenon likely only occurs in the presence of severe stenosis associated with abundant collateral circulation [31, 32]. The second mechanism for inducible regional systolic dysfunction during dipyridamole stress is the reduced endocardial myocardial blood flow reserve [33]. Bin et al. [33] suggested that the reduction in the myocardial blood flow reserve can also be due to a drop in the coronary perfusion pressure that is caused by systemic hypotension, which is frequently associated with dipyridamole administration. Based on our finding of the prominently increased LVEF and decreased ESV in the normal group, the effect of oral dipyridamole might continue during the MPS gated study. However, the high EDV and ESV at rest compared with the normal group indicate the presence of ischemic LV dysfunction in the ODA group and may explain the non-significant difference between the rest and stress measurements in our study (Figure 1).

Although the mean risk score for CAD is similar in the ODA and IDA groups, the number of patients with deterioration in systolic wall motion and thickening is higher in the IDA group. This is most likely related to the number of stenotic coronary arteries and the extent of severe ischemia in the IDA group. In published studies performed after IV dipyridamole infusion, it has been shown that the stunned myocardium can be visualized using hemodynamic changes detected in post-stress Gated SPECT [12-14]. These hemodynamic changes originate from the continuation of the severe ischemia that occurs during pharmacological stress test, particularly in cases with moderate and severe CAD [10, 13]. Though it is presented by LV wall motion deterioration, there is no significant change in the quantitative parameters, such as the EF, EDV and ESV [1]. In our study, the stress EDV value was higher than the rest value in the IDA group. Conversely, the LV EF is decreased, whereas the EDV and ESV are increased on stress-gated analysis obtained by intravenous dipyridamole administration in the IDA group compared with the parameters for the IDN group. We observed a highly increased EDV on stress (P = 0.042), but there was no difference in the ESV and EF in the ODA group compared with parameters for the ODN group (Figure 1). The deterioration in the LV systolic wall thickening and wall motion was observed in both the ODA and IDA groups.

In conclusion, our results support that both the intravenous and oral forms of dipyridamole provoke a stunned myocardium and that the effect of dipyridamole continues during the gated study. Post-stress stunning shows the persistent contractile dysfunction in the myocardium after reperfusion of ischemic segments, and this condition usually improves with time. Complete recovery may occur within a few minutes after myocardial reperfusion; in some cases, it may take hours, days, or even weeks, depending on the severity of the ischemic episode [10]. The best predictor of post-stress stunning is the presence of stress-induced ischemia [13, 34, 35].

Study limitations

We could not determine the effect of both the intravenous and oral form on myocardial perfusion and function in the same patient because administering both forms to the same patient was not allowed in the study design approved by the ethics committee.

The number of patients in the study subgroups was too low to draw strong conclusions.

CONCLUSION

We found that Gated SPECT with oral and IV dipyridamole is useful for assessing the function of the LV under stress. In CAD patients, both dipyridamole stress test types cause a long-term stunning effect that can be used to define myocardial ischemia. The effect of the ID test continues during Gated SPECT and results in LV diastolic dysfunction in the patients with abnormal myocardial perfusion. Oral administration might also be effective in the detection of real myocardial ischemia (acute dipyridamole-induced ischemia), causing LV systolic and diastolic dysfunction. Although we did not observe, serious adverse effects are disadvantageous for oral dipyridamole. Future randomized studies that include large sample size of patients with oral and IV dipyridamole stress test or other vasodilator stress agents (adenosine or regadenoson) and the angiographic demonstration of the number of affected vessels in different risk groups will demonstrate the role of these techniques in assessing LV functions.

Acknowledgment

This work was supported by the Scientific Research Projects Unit of Pamukkale University (2011).

REFERENCES

1. Gerson MC. Test accuracy, test selection and test result interpretation in chronic coronary artery disease. In: Gerson MC (Editor). Cardiac nuclear medicine. 3th edition. New York: McGraw-Hill Companies; 1997. p.527-79.
2. Paul AK, Nabi HA. Gated myocardial perfusion SPECT: basic principles, technical aspects, and clinical applications. J Nucl Med Technol. 2004 Dec;32(4):179-87.
3. Sciagrà R, Leoncini M. Gated single-photon emission computed tomography. The present-day "one-stop-shop" for cardiac imaging. Q J Nucl Med Mol Imaging. 2005 Mar;49(1):19-29.
4. Follansbee WP. Alternatives to leg exercise in the evaluation of patients with coronary artery disease: Functional and pharmacologic stress modalities. In: Gerson MC (Editor). Cardiac nuclear medicine. 3th edition. New York: McGraw-Hill Companies; 1997. p.193-235.
5. Taillefer R, Lette J, Phaneuf DC, Léveillé J, Lemire F, Essiambre R. Thallium-201 myocardial imaging during pharmacologic coronary vasodilation: comparison of oral and intravenous administration of dipyridamole. J Am Coll Cardiol. 1986 Jul;8(1):76-83.
6. Segall GM, Davis MJ. Variability of serum drug level following a single oral dose of dipyridamole. J Nucl Med. 1988 Oct;29(10):1662-7.
7. Drug information online. Persantine. Revised: 12/2007 Boehringer Ingelheim. Available from: URL: http://www.drugs.com/pro/persantine.html
8. Hesse B, Tägil K, Cuocolo A, Anagnostopoulos C, Bardiés M, Bax J, Bengel F, Busemann Sokole E, Davies G, Dondi M, Edenbrandt L, Franken P, Kjaer A, Knuuti J, Lassmann M, Ljungberg M, Marcassa C, Marie PY, McKiddie F, O'Connor M, Prvulovich E, Underwood R, van Eck-Smit B; EANM/ESC Group. EANM/ESC procedural guidelines for myocardial perfusion imaging in nuclear cardiology. Eur J Nucl Med Mol Imaging. 2005 Jul;32(7):855-97.
9. Klein HO, Ninio R, Eliyahu S, Bakst A, Levi A, Dean H, Oren V, Beker B, Kaplinsky E, Gilboa S, Di Segni E. Effects of the dipyridamole test on left ventricular function in coronary artery disease. Am J Cardiol. 1992 Feb 15;69(5):482-8.
10. Ambrosio G, Betocchi S, Pace L, Losi MA, Perrone-Filardi P, Soricelli A, Piscione F, Taube J, Squame F, Salvatore M, Weiss JL, Chiariello M. Prolonged impairment of regional contractile function after resolution of exercise-induced angina. Evidence of myocardial stunning in patients with coronary artery disease. Circulation. 1996 Nov 15;94(10):2455-64.
11. Mut F, Beretta M, Vidal I, Rener A, Alonso O, Nunez M, Alvarez B. Identification of myocardial stunning by means of gated perfusion SPECT in patients undergoing ischaemic stress myocardial tests. World J Nucl Med. 2003;2:122–5.
12. Ben-Haim S, Gips S, Merdler A, Front A, Tamir A. Myocardial stunning demonstrated with rest and post-stress measurements of left ventricular function using dual-isotope gated myocardial perfusion SPECT. Nucl Med Commun. 2004 Jul;25(7):657-63.
13. Lee DS, Yeo JS, Chung JK, Lee MM, Lee MC. Transient prolonged stunning induced by dipyridamole and shown on 1- and 24-hour poststress 99mTc-MIBI gated SPECT. J Nucl Med. 2000 Jan;41(1):27-35.

14. Feldman RL, Nichols WW, Pepine CJ, Conti CR. Acute effect of intravenous dipyridamole on regional coronary hemodynamics and metabolism. Circulation. 1981 Aug;64(2):333-44.

15. Kim C, Kwok YS, Heagerty P, Redberg R. Pharmacologic stress testing for coronary disease diagnosis: A meta-analysis. Am Heart J. 2001 Dec;142(6):934-44.

16. Noguchi Y, Nagata-Kobayashi S, Stahl JE, Wong JB. A meta-analytic comparison of echocardiographic stressors. Int J Cardiovasc Imaging. 2005 Apr-Jun;21(2-3):189-207.

17. de Albuquerque Fonseca L, Picano E. Comparison of dipyridamole and exercise stress echocardiography for detection of coronary artery disease (a meta-analysis). Am J Cardiol. 2001 May 15;87(10):1193-6; A4.

18. Picano E, Bedetti G, Varga A, Cseh E. The comparable diagnostic accuracies of dobutamine-stress and dipyridamole-stress echocardiographies: a meta-analysis. Coron Artery Dis. 2000 Mar;11(2):151-9.

19. Weinmann P, Moretti JL. Effects of dipyridamole on left ventricular function. J Nucl Cardiol. 2000 Mar-Apr;7(2):103-6.

20. Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA. 2001 May 16;285(19):2486-97.

21. Homma S, Callahan RJ, Ameer B, McKusick KA, Strauss HW, Okada RD, Boucher CA. Usefulness of oral dipyridamole suspension for stress thallium imaging without exercise in the detection of coronary artery disease. Am J Cardiol. 1986 Mar 1;57(8):503-8.

22. Picano E, Lattanzi F. Dipyridamole echocardiography. A new diagnostic window on coronary artery disease. Circulation. 1991 May;83(5 Suppl):III19-26.

23. Gould KL. Noninvasive assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilatation. I. Physiologic basis and experimental validation. Am J Cardiol. 1978 Feb;41(2):267-78.

24. Cates CU, Kronenberg MW, Collins HW, Sandler MP. Dipyridamole radionuclide ventriculography: a test with high specificity for severe coronary artery disease. J Am Coll Cardiol. 1989 Mar 15;13(4):841-51.

25. Indolfi C, Betocchi S, Piscione F, Perrone-Filardi P, Salvatore M, Chiariello M. Assessment of Left Ventricular Function Using Radionuclide Angiography After Dipyridamole lnfusion. Chest. 1989 Nov;96(5):1026-30.

26. Sochor H, Pachinger O, Ogris E, Probst P, Kaindl F. Radionuclide imaging after coronary vasodilation: myocardial scintigraphy with thallium-201 and radionuclide angiography after administration of dipyridamole. Eur Heart J. 1984 Jun;5(6):500-9.

27. Ross J Jr. Covell JW, Sonnenblick EH, Braunwald E. Contractile state of the heart characterized by force-velocity in variable afterloaded and isovolumic beats. Circ Res. 1966 Feb; 18(2):149-63.

28. Fleming RM. High-dose dipyridamole and gated sestamibi SPECT imaging provide diagnostic resting and stress ejection fractions useful for predicting extent of coronary artery disease. Angiology. 2002 Jul-Aug;53(4):415-21.

29. Kakhki VRD, Jabari H. Dipyridamole stress and rest gated 99mTc-sestamibi myocardial perfusion SPECT: left ventricular function indices and myocardial perfusion findings. Iran J Nucl Med. 2007;15(1):1-7.

30. Akinboboye OO, Idris O, Chou RL, Sciacca RR, Cannon PJ, Bergmann SR. Absolute quantitation of coronary steal induced by intravenous dipyridamole. J Am Coll Cardiol. 2001 Jan;37(1):109-16.

31. Gould KL. Coronary steal. Is it clinically important? Chest. 1989 Aug;96(2):227-8.

32. Seiler C, Fleisch M, Meier B. Direct intracoronary evidence of collateral steal in humans. Circulation. 1997 Dec 16;96(12):4261-7.

33. Bin JP, Le E, Pelberg RA, Coggins MP, Wei K, Kaul S. Mechanism of inducible regional dysfunction during dipyridamole stress. Circulation. 2002 Jul 2;106(1):112-7.

34. Hale SL, Kloner RA. Acetaminophen and myocardial stunning after transient ischemia in rabbit hearts. J Cardiovasc Pharmacol Ther. 2005 Jun;10(2):121-9.

35. Otto AC, van Staden J, van Aardt A, van Aswegen E, Joubert G, Englebrecht H. Evaluation of exercise-induced stunning using myocardial perfusion imaging. Cardiovasc J S Afr. 2001 Oct-Nov;12(5):259-62.