DIPYRIDAMOLE MYOCARDIAL PERFUSION TOMOGRAPHY IN PATIENTS WITH SLOW CORONARY FLOW

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Increase in velocity of contrast dye following intravenous dipyridamole infusion has been reported in patients with slow flow pattern (SFP) on coronary arteriography. We evaluated the results of coronary arteriography and exercise myocardial perfusion tomography (MPT) in patients with SFP. We also investigated the changes in myocardial perfusion using pharmacological stress test with dipyridamole.

The study included 60 patients who revealed SFP in their coronary arteriograms. The Thrombolysis in Myocardial Infarction flow count method was used for the assessment of slow coronary flow. Single day rest-exercise Technetium-99m hexadic-2-methoxy-isobutyl isonitril (Tc-99m MIBI) MPT was performed in all study patients. It was detected that the patients of the study group who were found to have ischemia on their exercise MPT, had changes in myocardial perfusion following dipyridamole infusion.

Patients with SFP revealed higher counts in both native coronary arteries as well as higher mean frame counts. In control patients, mean frame count was 26.4±3.5. In patients with SFP, mean frame count was 64.4±16.64 ($p<0.001$). Exercise MPT showed ischemia in 17 patients (group 1), while 43 patients in group 2 revealed no perfusion defect. There was no statistically significant difference between the two groups in frame counts. Normal myocardial perfusion was observed in all the 17 patients on dipyridamole MPT.

In patients with SFP, ischemic changes improve with dipyridamole infusion. It is possible to show this improvement with dipyridamole MPT. In addition, there is no correlation between the time needed to fill the native coronary artery and ischemia, even if there is SFP.

Key words: Coronary slow flow, coronary arteriography, myocardial perfusion tomography, dipyridamole.

When a patient with chest pain, suggestive of angina pectoris, was referred for diagnostic coronary arteriography, which subsegmently showed the typical phenomenon of "slow contrast medium progression" in the absence of any coronary artery stenosis, there is no conclusive evidence available on etiopathogenesis of slow coronary blood flow.

Coronary artery ectasia, abnormal increase in microvascular resistance, has been proposed to be the possible underlying mechanism of coronary slow flow (1-4). The abnormalities of left ventricular function with exercise have been reported in this patient group (5). In some of these patients, ischemia can also be detected on exercise myocardial perfusion scintigraphy (5,6). Ischemia mechanism in patients with slow flow was not understood exactly.

On coronary arteriography, significant increase in the speed of contrast medium following intravenous dipyridamole infusion has been shown in the patients with slow flow pattern (SFP) (3). However, we do not know whether myocardial perfusion improved due to this increase.

In the present study, we assessed coronary arteriographic and scintigraphic characteristics in patients with SFP. In addition, we examined the changes in myocardial perfusion with intravenous dipyridamole infusion in patients with proven ischemia on exercise myocardial perfusion scintigraphy.

METHOD

Patients

The study group consisted of 60 patients with angina pectoris, suggestive of ischemic heart disease, and a pattern of slow coronary flow detected on their coronary arteriography (48 male, 12 female; mean age 54±11 years). None of the patients had hypertension, diabetes, glucose intolerance, cardiomyopathy, valvular heart disease, congenital heart disease or rhythm disturbances. Patients with atherosclerotic lesions or coronary artery ectasia were not included as well. Control group consisted of 50 patients with normal coronary arteries (38 male, 12 female; mean age 48±12 years). All patients in the study group underwent coronary arteriography, contrast ventriculography and exercise myocardial perfusion tomography (MPT). We also examined changes in myocardial perfusion using pharmacological stress test with dipyridamole in patients of the study group who were found to have ischemia on exercise MPT.

Coronary Arteriography

Study group and control group patients underwent selective coronary arteriography using standard Judkins technique (Siemens Coroscop-TOP). Coronary arteries in the left and right oblique planes and cranial and caudal angles were visualized. Injection of contrast medium was carried out by an automatic injector (Angiomat 6000), at a speed of 3-4 ml/sec for the left coronary artery and 2-3 ml/sec for the right coronary artery. Iopromide (Ultravist-370, Schering AG), a contrast agent, was used. Arteriographies were recorded at a speed of 25 frame/sec using a 35mm cinefilm (Fuji). Heart rate (beat per minute) and both systolic and diastolic blood pressures were monitored before, during and after the procedure.

The method of TIMI frame count was used for measuring filling of contrast medium in the coronary arteries and for diagnosis of SFP (7). Frames from the origin to the distal part of the arteries which must be filled with contrast agent were counted.

The frame where contrast medium filled the origin of the coronary artery was considered as the first frame. The following distal landmark branches were used for determination of the last frame: the distal bifurcation (the mustache) of the left anterior descending artery (LAD); in the circumflex artery (LCx), the distal bifurcation of the segment with the longest total distance; and in the right coronary artery (RCA), the first branch of the postero-lateral artery. To estimate the number of frames, firstly, coronary artery was filled with opaque medium to the distal point described above. Then, moving back frame by frame, we assessed the frame where contrast

medium entered the origin of the coronary artery. The number of frames necessary for filling the arteries was estimated by subtracting the number of the first frame from the number of the last frame. Average frame number of the three major coronary arteries was accepted as the mean frame count. All these calculations were done by two invasive cardiologists working individually. Pattern of slow flow was decided to be present according to the previously determined frame count of control patients.

Exercise Test

Symptom-limited treadmill exercise was performed using the standard Bruce protocol, with a 12-lead electrocardiography recording for each minute of exercise and continuous monitoring of leads V2, V5 and aVF. Anti-ischemic medications were withheld for 48h before stress testing. Criteria for interrupting the test were reaching target heart rate (220 minus age), severe chest pain, complex ventricular arrhythmia, hypotension, exhaustion, ST segment depression of ≥ 2mm, ST segment elevation of ≥ 2mm. At near-maximal exercise, 22-30 mCi of technetium-99m hexadic-2-methoxy-isobutyl isonitril (Tc-99m MIBI) was injected with dose variation based on the patient weight. The patients continued to exercise maximally for an additional minute. Positive test criteria were > 0.5 mm downsloping, >1.0 mm horizontal or >1.5 mm upsloping ST segment depression if they occurred newly compared to resting electrocardiography (ECG) and 0.08 second after the J point.

Myocardial Perfusion Tomography

Myocardial perfusion single photon emission computed tomography (SPECT) with Tc-99m MIBI was obtained according to rest and stress protocol. Rest images were obtained 60 minutes after injection of 296-370 MBq (8-10 mCi) Tc-99m MIBI intravenously in fasting. Thirty minutes prior to imaging, the patients were given chocolate and milk to diminish hepato-biliary activity. Images were obtained with gamma camera (Sopha DS 7-France) equipped with low-energy, parallel-hole, high-resolution collimator. The system was adjusted to 140 keV energy peak with 20% window for Tc-99m. The data was collected with 64x64 matrix, zoom factor of 1 at 45° right anterior oblique (RAO) projection initially and thereafter in 32 continuos sections for 30 seconds each along 180° arch. 3-4 hours after the rest images, treadmill exercise testing was performed. At near maximal exercise or if positive test criteria have developed, 814-1110 MBq (22-30 mCi) Tc-99m MIBI was injected. Stress imaging was done 15-30 minutes later using the same method as the resting study (20 seconds/frame). Filtered back projection method was applied to the raw data and reconstruction was done in oblique-transverse, sagittal and coronal planes using a Butterworth filter (cut of frequency 0.28, filter order 5). No attenuation correction was performed.

Dipyridamole Stress Test

The patients underwent pharmacological stress test with IV dipyridamole infusion protocol (0.56mg/kg/4 minutes) within a week of ischemia detection. It was followed in 3-4 minutes by the injection of 296-370 MBq (8-10mCi) Tc-99m MIBI in fasting. Imaging was done 15-30 minutes later with the same method used in the rest study (30 seconds/frame). Beta adrenergic blocking agents and calcium antagonists were withheld for 48 hours, and long acting nitrates for 6 hours before the dipyridamole test. Xanthine derivatives and caffeine-containing products were discontinued 48 and 12 hours before testing, respectively. Images were compared with the segments found to have ischemia on previously performed exercise myocardial perfusion tomography.

Evaluation of Perfusion Images

The images were interpreted without the knowledge of clinical and coronary arteriographic results. For evaluation, the previously reported 20 segmental SPECT analysis method was used (8). Accordingly, segmental perfusion was determined and scored as 0=normal, 1=mild decrease, 2=moderate decrease, 3=marked decrease, 4=absent. In patients with normal rest study, scores of 2 or above found at least on 2 consecutive sections and 2 planes on stress images were interpreted as abnormal.

Statistical Analysis

All continuous measures were summarized as mean value±SD. Mean differences for continuous variables were compared using the Student's t test. A p value of < 0.05 was considered statistically significant. The kappa statistic and its standard error was used for interobserver agreement analysis. A value of 1 denotes perfect agreement, and 0 indicates no agreement beyond chance. In general, kappa values ≥ 0.6 are considered indicative of good agreement. The Microsoft Excel statistical software package (version 97) was used to perform all statistical calculations.

RESULTS

Clinical And Exercise Testing Data

Twenty-one patients (35%) had stable angina pectoris; two patients (3%) had emotional angina; and 37 patients (62%) had atypical chest pain. There was no abnormality on resting ECG. No complication developed during exercise test. All patients achieved at least 85% of maximum heart rate (220-age) on exercise test. Eight patients (13%) had positive treadmill test. Six of them had chest pain complaint with exercise.

Table 1. Dipyridamole myocardial perfusion tomography in patients with slow coronary flow

Hemodynamic parameters of patients with slow coronary flow and controls.

	Slow flow	Control	p value
BPM-R	79±21	82±24	NS
SBP-R (mmHg)	129±20	130±16	NS
DBP-R (mmHg)	73±12	77±10	NS
BPM-CA	88±13	93±15	NS
SBP-CA (mmHg)	118±21	120±16	NS
DBP-CA (mmHg)	62±9	66±8	NS
CAP (mmHg)	120±22/64±8	124±20/65±7	NS

BPM: Beat per minute, CA: Coronary arteriography, CAP: Central aortic pressure, DBP: Diastolic blood pressure, NS: Not significant, R: Rest, SBP: Systolic blood pressure.

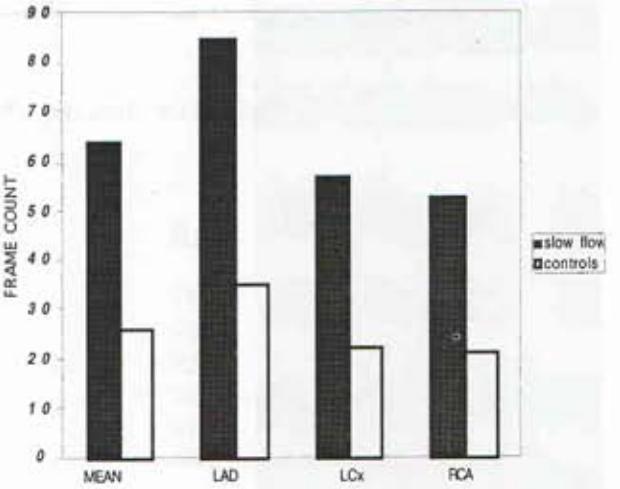

Figure 1. Comparison between patients with slow flow pattern and controls according to frame counts.

Coronary Arteriography

There was no statistically significant difference in values of heart rate, systolic and diastolic blood pressures during both rest and examination and thereafter between the study and control groups. Central aortic pressure during coronary arteriography did not show difference between the controls and patients with SFP (Table 1).

Calibrations of the coronary arteries were normal. There was no observed luminal irregularity in the major coronary arteries and their branches. The flow of dye in the visualized vessels featured a strikingly slow flow velocity resulting in marked delay in the clearance of the contrast medium from the coronary arterial tree in patients with SFP.

There was a high degree of concordance between the two observer in the calculation of frame count. Exact agreement ratio was 88% (kappa= 0.82, $p< 0.001$).

Frame counts found in patients with slow coronary flow were considerably higher compared to those of the controls (Figure 1). In control patients, mean frame count was 26.4±3.5. Average frame count was 35.4 ± 3.3, 22.5±4.5 and 21.5±2.8 for LAD, LCx and RCA, respectively. In patients with slow coronary flow, mean frame count was 64.40±16.64. Average frame count was 85.75±24.39, 57.21±15.25 and 53.75±17.81 for LAD, LCx and RCA, respectively ($p<0.001$).

The left ventricles were normal in size. Resting left ventricular wall motion was found normal in all patients.

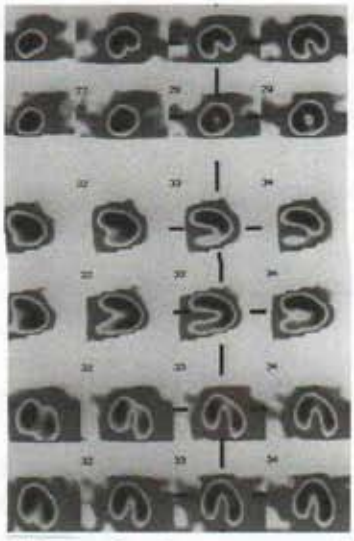

Figure 2a. In group 1 patient (no: 15, mean frame count: 64), infero-apical and inferior reversible perfusion defects are seen.

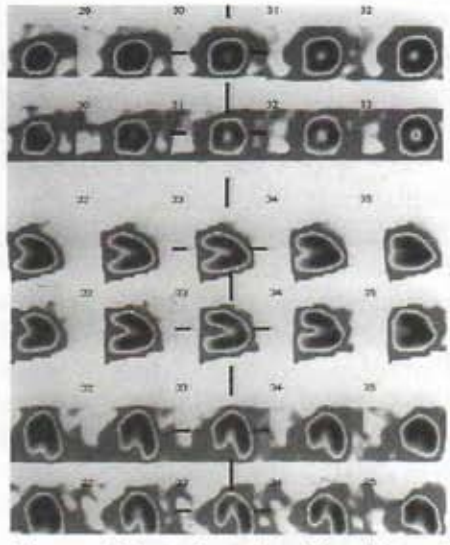

Figure 2b. Following dipyridamole infusion, normal myocardial perfusion is seen on perfusion images.

Exercise Myocardial Perfusion Tomography

Seventeen patients (28.3%) with slow coronary flow (13 male; 4 female; mean age 52±12 years) were found to have ischemia on exercise MPT (group 1) (Fig 2a). The remaining 43 patients (71.7%; 35 male, 8 female; mean age 55±10 years) were not found to have a perfusion defect (group 2) (fig 3). Treadmill test was positive in seven patients in group 1 and in only patient in group 2. In group 1, overall six patients had chest pain complaint during the exercise. Mean frame count was 61.50±18.99 in group 1 and 64.15±18.18 in group 2 (p=NS). Average frame count was 84.11±18.55, 56.23±11.79 and 54.94±15.79 for LAD, LCx and RCA, respectively in group 1. In group 2, average frame count was 86.39±26.51, 57.6±16.54 and 53.27±18.71 for LAD, LCx and RCA, respectively. There was no statistically significant difference in frame counts for LAD, LCx and RCA between the patients with or without ischemia . The frame counts of major coronary arteries of group 1 and group 2 patients are shown in Table 2-3.

Eleven patients had ischemia located in LAD, four in RCA, one in RCA and LAD and one in LCx artery regions. Frame count of the coronary artery, indicator of ischemia was calculated only for LAD. There was no statistically significant difference in frame counts between the patients with and without ischemia in LAD region.

Dipyridamole Test Data

No major complications such as severe hypotension, chest pain, dyspnea and arrhythmia developed during and after dipyridamole infusion. Four patients had mild and transient headache, two had dyspnea and one flushing. None of these complications were severe enough to administer aminophylline. After dipyridamole stress test, normal myocardial perfusion was observed in the patients of group 1 on perfusion scintigraphy (Fig 2b).

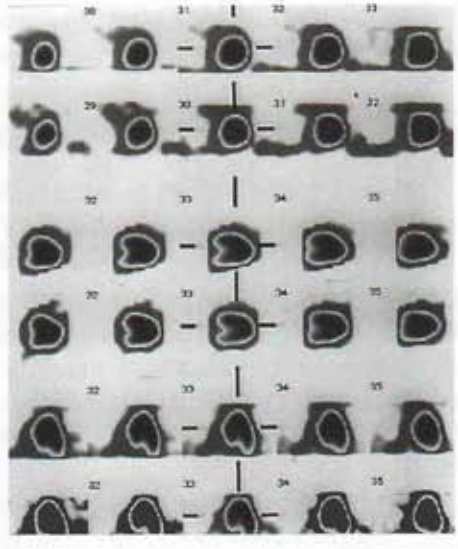

Figure 3. In group 2 patient (no: 40, mean frame count: 67.6), normal myocardial perfusion is seen.

Table 3.

Dipyridamole myocardial perfusion tomography in patients with slow coronary flow

Frame counts of group 2 patients.

	Age/Sex	LAD	LCx	RCA	Mean
1	64/F	106	78	19	67.6
2	51/F	108	79	59	82
3	59/F	60	62	25	49
4	63/F	57	37	58	50.6
5	61/F	49	24	91	54.6
6	41/F	76	40	48	54.6
7	58/F	109	51	30	63.3
8	69/F	116	67	67	83.3
9	53/M	40	36	38	38
10	52/M	156	81	95	110.6
11	71/M	58	50	23	43.6
12	49/M	110	52	53	71.6
13	46/M	122	74	56	84
14	68/M	87	49	81	72.3
15	61/M	53	48	30	43.6
16	57/M	66	57	29	50.6
17	53/M	153	93	28	91.3
18	70/M	56	40	62	52.6
19	44/M	56	37	41	44.6
20	41/M	68	43	40	50.3
21	39/M	84	54	46	61.3
22	61/M	104	66	60	76.6
23	62/M	90	54	65	69.6
24	55/M	88	45	53	62
25	40/M	63	38	36	45.6
26	36/M	59	44	51	51.3
27	46/M	102	55	70	76
28	51/M	67	39	37	48.3
29	63/M	74	41	43	52.6
30	60/M	71	58	39	56
31	38/M	82	51	46	59.6
32	45/M	115	68	63	82
33	39/M	92	77	80	83
34	55/M	90	66	59	71.6
35	51/M	118	76	70	88
36	62/M	69	48	42	52.6
37	48/M	77	56	51	61.3
38	67/M	94	78	80	84
39	72/M	85	67	66	72.6
40	71/M	79	61	73	67.6
41	55/M	123	97	78	99.3
42	60/M	88	71	49	69.3
43	48/M	95	69	61	75

F: Female, LAD: Left anterior descending artery, LCx: Left circumflex artery, M: Male, RCA: Right coronary artery.

Table 2. Dipyridamole myocardial perfusion tomography in patients with slow coronary flow frame counts and ischemia localization of group 1 patients.

	Age/Sex	LAD	LCx	RCA	Mean	Exercise test	Ischemia localization
1	58/F	86	59	55	66.6	P	Ap, Ant
2	65/F	112	57	72	80.3	N	Ap, Ant, AL
3	42/F	83	68	76	75.6	N	Ap, AS
4	70/F	74	47	46	55.6	N	Inf
5	35/M	81	48	51	60	P	Ap, Antap
6	51/M	86	66	62	71.3	P	Ap, Ant, AS
7	49/M	92	54	41	62.3	N	Ap, AS, S
8	68/M	98	69	60	75.6	N	Lat, IL
9	40/M	107	59	91	85.6	N	Inf
10	56/M	93	79	71	81	N	Ap, Ant, AS, Inf
11	54/M	91	50	48	63	N	Ap, Ant
12	39/M	42	36	31	36.3	P	Ap, AS, Antap
13	33/M	72	61	53	62	N	Ap, Ant, AL
14	64/M	82	46	44	57.3	P	Inf
15	61/M	76	69	47	64	P	Infap, Inf
16	47/M	106	51	54	70.3	N	Ap, Ant, AS
17	55/M	49	37	32	39.3	P	Ap, Antap, AL

Ant: Anterior, Antap: Antero-apical, AL: Antero-lateral, Ap: Apical, AS: Antero-septal, F: Female, IL: Infero-lateral, Inf: Inferior, Infap: Infero-apical, LAD: Left anterior descending artery, Lat: Lateral, LCx: Left circumflex artery, M: Male, N: Negative, P: Positive, RCA: Right coronary artery, S: Septal.

DISCUSSION

15% of the patients with typical chest pain were found to have normal epicardial coronary arteries (9). A pattern of slow coronary flow, which means a decrease in filling velocity of contrast agent during coronary arteriography, has also been detected in some of these patients. There is no conclusive evidence available on etiopathogenesis of slow coronary flow.

In 1972, Tambe et al (2). first described the clinical and hemodynamic features of a group of six patients with angina pectoris and slow flow velocity of contrast agent in coronary arteries. Three of these patients had ischemic results on exercise test, three showed mild hemodynamic abnormalities, and two had moderate left ventricular enlargement with segmental dyskinesia. The authors suggested that an abnormal increase of small vessel resistance was the cause of the slow progression of the dye at selective coronary arteriography.

Angina in patients with slow coronary flow is generally atypical. Resting ECG is normal or nonspecific. As in our trial, ischemia was found by some of the investigators on myocardial perfusion scintigraphy in patients with SFP (5,6). Cesar et al. (6) found ischemia in 76.4% of patients with SFP on myocardial perfusion scintigraphy. The rate of ischemia was 28.3% in our study.

Van Lierde et al. (1) found that coronary flow reserve and coronary blood flow on intracoronary Doppler examination were normal in one patient with SFP which was caused by coronary artery ectasia and in turn caused coronary artery thrombosis. Coronary artery ectasia was not observed in our study.

In 1986, Mosseri et al (4). performed a clinical, angiographic, and ultrastructural study of 54 patients with normal coronary arteries. However, of the six patients with the evidence of SFP, rest ECG abnormalities and hypertension were present in four patients, and diabetes and hypertension in one patient. The echocardiographic study showed that all patients had myocardial hypertrophy, while there was left ventricular enlargement in two cases, and enlargement of both ventricles in one case. Biotic samples showed abnormalities of small coronary arteries with myocardial

hypertrophy, patchy fibrosis, and markedly swollen capillaries that in our opinion could well be provoked by the concomitant diseases. In another study, histopathological features, suggesting small vessel disease which might lead to increase in flow resistance, were detected in endomyocardial biopsy of the left ventricle and electron microscopy in six patients with SFP without any underlying disease (3).

Mangieri et al. (3) showed that flow speed increased without a change in luminal diameter following IV dipyridamole infusion in six patients with SFP. They also found that flow speed did not increase while luminal diameter did so following intracoronary nitroglycerin infusion. This study had some limitations in that it included a small sample size and changes in myocardial perfusion caused by increase in the speed of coronary blood flow were not detected.

Nitroglycerin was effective on vascular structures with a diameter of more than 200 mm but not so in vessels with a diameter less than that, probably because the mechanism which turns nitroglycerin into its active metabolite nitrosocysteine does not exist in vessels with small diameter (10,11). As for dipyridamole, it is effective on arterioles with a diameter of less than 200 mm. Dipyridamole is a pyrimidopyrimidine compound. It inhibits uptake of adenosine by vascular endothelium and erythrocytes (10,12,13). It also prevents adenosine from turning into its inactive metabolite inosine by inhibiting adenosine deaminase (12). Adenosine induces vasodilation by redistributing vascular resistances, thus increasing coronary blood flow rate (10,13). As a foregone view, it is possible to conclude that SFP is a pathology involving small arteries with a diameter of less than 200 mm.

In our study, myocardial perfusion improved with dipyridamole infusion in all of the seventeen patients with ischemia proven on exercise myocardial perfusion tomography, which indicated that SFP was associated with the obstruction of microvascular structures which was improved by dipyridamole infusion. The finding above also supported the idea that problem of SFP was typical of vessels with a diameter of less than 200 mm.

Yet, it is not possible to determine whether slow coronary flow was due to changes in microvessels and increased resistance of these vessels or vice versa. We think that the latter is more reasonable because ischemia is seen in a certain proportion of the patients with SFP. Ischemic changes may occur in nonischemic patients during the follow-up period. Effects of slow coronary flow in chronic stage are not well known. Tendency to microvascular obstruction and coronary thrombosis may increase in the long term. Therefore, patients need a long follow-up period.

This study also compared the number of frames of patients, determined by the method of TIMI frame count, with proven ischemia with those of the patients without ischemia and found no statistically significant difference, which indicated that coronary filling time alone was not involved in formation of ischemia in patients with SFP.

Thrombolysis in Myocardial Infarction (TIMI) frame count method was developed by Gibson et al. (7) Count of frames for filling coronary arteries was also estimated with TIMI frame count method by Gibson et al. Estimations we made in normal controls were almost the same as those found by Gibson et al., which lends support to the objectivity of our findings (LAD: 36.2±2.6, LCx: 22.2±4.1, RCA: 20.4±3.0 versus LAD: 35.4±3.3, LCx: 22.5±4.5, RCA: 21.5±2.8).

CONCLUSION

Coronary slow blood flow is a pathological condition due to an obstruction of vessels with a diameter of less than 200 mm, which causes an increase in vascular tone in arteriolar level and in microvascular resistance, as a consequence of which ischemic changes occur. These changes improve with dipyridamole infusion. It is possible to show this improvement with dipyridamole myocardial perfusion scintigraphy, which suggests that dipyridamole can be used in treatment of these patients. Effect of this treatment on symptomatic patients is beyond the scope of this study and should be investigated in another study.

Perfusion changes may develop in the long term in the patients who were found to have no ischemia on myocardial perfusion tomography. Determination of prognosis is of importance in the patients who were found to have ischemia. Follow-up of perfusion changes and determination of prognosis will help to understand the clinical course and investigate the reason for the increase in microvascular tone.

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