Abnormal Myocardial Blood Flow Distribution in Patients With Angina Pectoris and Normal Coronary Arteriograms

Akihiko Shiraishi, MD; Hisao Ikeda, MD; Nobuya Haramaki, MD; Toyoaki Murohara, MD; Takahiro Matsumoto, MD; Takafumi Ueno, MD; Tsutomu Imaizumi, MD

To evaluate coronary microvascular function and its relation to the genesis of chest pain and ST-segment depression during exercise in patients with syndrome X, pacing-induced changes in transmural myocardial blood flow distribution were quantitatively assessed by 2-dimensional myocardial contrast echocardiography. Of 25 patients with a history of chest pain and normal coronary arteries with the negative ergonovine test, 11 had exercise-induced chest pain and ST-segment depression (syndrome X), and 14 did not (controls). Myocardial blood flow distribution before and after pacing stress was assessed by measuring the ratio of the endocardial to epicardial gray level (ie, endo/epi gray level ratio) in the territory of the left anterior descending coronary artery. Pacing-induced chest pain and ST-segment depression were observed in syndrome X, but not in controls. The endo/epi gray level ratio in syndrome X significantly decreased after pacing (from 0.98 ± 0.10 to 0.76 ± 0.17 , $p < 0.01$), but not in controls (from 0.97 ± 0.08 to 0.99 ± 0.08 , NS). Abnormal myocardial blood flow distribution may play an important role in exercise-induced chest pain and ST-segment depression in these patients. (*Jpn Circ J* 2000; 64: 566–571)

Key Words: Angina pectoris; Coronary arteries; Myocardial blood flow distribution; Myocardial contrast echocardiography

The term 'syndrome X,' originally coined by Kemp et al,¹ is used to describe patients who have angina and angiographically normal coronary arteries. Exercise-induced chest pain and ST-segment depression are demonstrated in some patients with syndrome X, but previous studies have not provided convincing metabolic data, such as myocardial lactate production after pacing stress, as evidence of myocardial ischemia,^{2–5} although recently, acetylcholine-induced lactate production was reported.⁶ It has been suggested that the exercise-induced chest pain and ST-segment depression in syndrome X may be closely related to impaired coronary flow reserve of the small coronary arteries because of the limited increase in coronary blood flow in response to pacing^{3,7} or pharmacologic vasodilator, dipyridamole^{2,8} and pacing or dipyridamole after infusion of ergonovine.^{9,10} However, Camici et al, using positron emission tomography, which enables quantitative measurement of regional myocardial blood flow, could not demonstrate a correlation between coronary flow reserve and the presence of chest pain and/or ST-segment depression after dipyridamole infusion.¹¹ Thus, although the consistent finding in syndrome X appears to be impairment of coronary flow reserve, this is not always the genesis of the chest pain and changes on ECG.

The 2-dimensional myocardial contrast echocardiography (MCE) directly assesses coronary microvascular circulation¹² and provides important information on regional myocardial perfusion, including perfusion bed size,^{13–18} infarct size,^{17,19–22} collateral circulation,^{23,24} and myocardial

blood flow distribution in the different layers of the myocardium.^{25,26} Because an abnormality in the microvasculature is implicated in the pathophysiology of syndrome X,^{27–29} it is reasonable to assume that MCE may provide new information and so we investigated the correlation between changes in transmural myocardial blood flow distribution after pacing stress, evaluated by MCE, and ECG changes during exercise and pacing stress in patients with a history of chest pain and normal coronary arteriograms.

Methods

Patients

The study population consisted of 25 patients with a history of chest pain and angiographically normal coronary arteries (12 men, 13 women; age range, 27–67 years, mean 49). None had evidence of other cardiac or extracardiac disease, including coronary artery disease or hypertrophic cardiomyopathy, conduction disturbance on ECG, hypertension, hyperlipidemia or diabetes mellitus.

Before MCE was performed, the patients underwent a maximal symptom-limited treadmill exercise test according to the Bruce protocol, at least 48 h after medication was discontinued. Of the 25 patients, 11 developed typical chest pain with horizontal or downsloping ST-segment depressions of 1 mm or more from the baseline in the anterior ECG leads during the exercise test and they comprised the syndrome X group (5 men, 6 women; age range, 34–67 years, mean 52). The remaining 14 patients with a negative response to the exercise test served as the control group (7 men, 7 women; age range, 27–63 years, mean 46). The syndrome X group included 2 smokers and the control group had 3 smokers ($p = \text{NS}$). Written informed consent was obtained from all subjects.

(Received December 24, 1999; revised manuscript received April 24, 2000; accepted April 27, 2000)

Department of Internal Medicine III, Kurume University School of Medicine, Kurume, Japan

Mailing address: Hisao Ikeda, MD, Department of Internal Medicine III, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan

Fig 1. Representative images of myocardial contrast echocardiography (MCE). Two echocardiograms show parasternal short-axis view at the midpapillary muscle level before and after injection of contrast agent. Right schemata indicates the locations of the region of interest (ROI) in the endocardium and epicardium.

Myocardial Contrast Echocardiography

Standard medications, including long-acting nitrates, calcium channel blockers, β -blockers, angiotensin converting enzyme inhibitors, and aspirin, were discontinued throughout all procedures. Cardiac catheterization and coronary angiography were performed by a standard technique. All patients had normal ventriculograms, coronary angiograms and negative responses to the pharmacological provocation test with ergonovine ($6\text{--}9\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). The interval between the exercise test and cardiac catheterization was 7 days or less.

After routine catheterization and angiography, a standard 12-lead ECG and aortic blood pressure were continuously monitored. MCE was then performed using a commercially available 2-dimensional echocardiographic system with a 3.5 MHz transducer (Model SSD-630, Aloka, Tokyo, Japan). Microbubbles as contrast agent were generated using the ultrasonic sonication technique (Model ms-50, Heat System-Ultrasonics, Framingham, NY, USA) with a sonomicroprobe (2.3 mm) as previously described by Feinstein et al.³⁰ Briefly, 8 ml of amidotrizoate sodium meglumine (Urografin-76) was placed in a plastic syringe and sonicated for approximately 30 s until a homogeneous solution was generated as a flow marker, based on its ability to enhance echo intensity. MCE was performed in the parasternal short-axis view at the midpapillary muscle level during the injection of contrast agent (2 ml) into the left coronary artery. Echocardiographic recordings were started before the injection of contrast agent and were continued until the contrast enhancement completely disappeared. The gain setting was optimized at the beginning of the study and kept constant in order to avoid the effect of gain setting on the regional echo amplitudes.³¹ During imaging gated to the ECG, patients were required to hold their breath at moderate inspiration. The MCE images were recorded on videotape using a video recorder (Model VO-5850, Sony, Tokyo, Japan).

After the ECG and hemodynamic values returned to the baseline, rapid atrial pacing was employed at a rate of 150

beats/min for 3 min in all patients. Immediately after the cessation of pacing, MCE was performed again as described. Major clinical complications related to the injection of the contrast agent were not observed in any of the patients.

Analysis of MCE Images

MCE image analysis was performed with an image-processing computer (Model GMS-55A, Toshiba, Tokyo, Japan). The obtained images were continuously digitized into 512×512 pixel matrix image with 256 gray scale levels per pixel. The end-diastolic echocardiographic image of the left ventricular short-axis view, which was synchronized to the peak of the R wave, was determined and then 2 rectangular regions of interest (2×4 mm, Fig 1) were set on 2 layers of the endocardial and epicardial myocardium in the territory perfused by the left anterior descending coronary artery by an observer using a computer-aided technique. The rectangular region of interest (ROI) was so placed in the middle of the myocardium that it was always apparent, even during cardiac movement. Peak gray levels in the endocardium and epicardium, which showed the maximal intensity per pixel, were measured in each ROI. This measurement was relative and not absolute, so we calculated the ratio of subendocardial gray level to epicardial gray level (ie, endo/epi gray level ratio), which is defined as an index of transmural myocardial blood flow distribution.

Reproducibility of Measurements

The reproducibility of the measurements was determined by repeating the injection of the contrast agent into the left coronary artery in 16 patients. Indexes, such as peak gray levels in the endocardium and epicardium, and the endo/epi gray level ratio, from the first and second measurements were assessed by an independent observer unaware of the study protocol and the 2 measurements correlated closely: endocardial peak gray level, $r=0.89$, $p<0.001$; epicardial peak gray level, $r=0.91$, $p<0.001$; endo/epi gray ratio, $r=0.70$, $p<0.005$.

Table 1 Hemodynamics, ST-Segment Depression, and Chest Pain at Rest and During Exercise

	Sex	Age (years)	Rest			Exercise test					Pain
			HR (beats/min)	SBP (mmHg)	RPP (mmHg·beats/min)	HR (beats/min)	SBP (mmHg)	RPP (mmHg·beats/min)	Duration (min)	ST dep (mV)	
Controls											
1	M	60	64	128	8,192	158	184	29,072	9.0	0	No
2	F	60	56	126	7,056	150	180	27,000	9.5	0	No
3	M	37	86	122	10,492	172	170	29,240	12.0	0	No
4	F	34	71	94	6,674	159	134	21,306	9.0	0	No
5	M	44	56	116	6,496	148	210	31,080	15.0	0	No
6	M	49	66	122	8,052	175	196	34,300	12.0	0	No
7	F	46	69	92	6,348	167	132	22,044	7.0	0	No
8	F	63	60	130	7,800	154	180	27,720	6.0	0	No
9	F	54	64	126	8,064	162	186	30,132	8.0	0	No
10	M	44	66	114	7,524	174	180	31,320	12.0	0	No
11	F	35	72	106	7,632	168	130	21,840	10.0	0	No
12	F	45	76	140	10,640	157	210	32,970	7.0	0	No
13	M	27	79	116	9,164	193	180	34,740	17.0	0	No
14	M	45	68	102	6,936	148	140	20,720	8.0	0	No
Mean		46	68	117	7,934	163	172	28,106	10.1	0	
SD		11	8	14	1,350	13	28	4,881	3.2	0	
Syndrome X											
1	F	51	85	134	11,390	151	176	26,576	9.0	0.10	Yes
2	M	41	64	124	7,936	166	220	36,520	8.0	0.15	Yes
3	M	56	51	150	7,650	123	196	24,108	7.0	0.25	Yes
4	F	34	72	110	7,920	169	146	24,674	9.0	0.15	Yes
5	M	53	83	130	10,790	168	214	35,952	8.0	0.10	Yes
6	F	49	76	120	9,120	152	158	24,016	8.0	0.15	Yes
7	M	56	66	128	8,448	160	190	30,400	9.0	0.20	Yes
8	F	61	87	98	8,526	159	172	27,348	8.0	0.15	Yes
9	F	60	67	130	8,710	148	160	23,680	6.0	0.10	Yes
10	M	43	75	116	8,700	162	140	22,680	9.0	0.20	Yes
11	F	67	77	138	10,626	157	188	29,516	10.0	0.10	Yes
Mean		52	73	125	9,074	156	178	27,770	8.3	0.15	
SD		10	11	14	1,278	13	26	4,846	1.1	0.05	

HR, heart rate; SBP, systolic blood pressure; RPP, rate pressure product; ST dep, ST-segment depression.

Statistical Analysis

Values are expressed as mean $\pm$ SD. Comparison among the groups was performed with a Student's *t* test for paired and unpaired data. A linear regression analysis was used to assess the reproducibility of measurements between the first and the second injection. The hemodynamic values obtained at different time periods were compared by repeated-measures ANOVA with the Scheffé test. Differences were considered to be statistically significant if probability (*p*) was less than 0.05.

Results

Exercise Testing

As shown in Table 1, there were no differences in the resting hemodynamics between the 2 groups. The duration of the treadmill exercise and the peak rate–pressure product also did not differ. Typical chest pain with horizontal or downsloping ST-segment depression developed in all patients with syndrome X during exercise testing, whereas no symptoms or ST-segment changes were observed in the controls.

Rapid Atrial Pacing

Table 2 shows the hemodynamics, chest pain and ST-segments before and during pacing stress. There were no differences in hemodynamics before pacing between the 2 groups. During pacing, both groups recorded significant increases in heart rate, but not systolic blood pressure, and

so the rate–pressure product in both groups also significantly increased, but did not differ between the 2 groups.

Pacing-induced chest pain with horizontal or downsloping ST-segment depression was observed in all patients with syndrome X, but neither symptoms nor ST-segment depression was observed in controls. Pacing-induced ST-segment depression was observed in the identical anterior ECG leads to those in whom exercise-induced ST-segment depression was observed (data not shown).

MCE Study

Fig 2 shows the endo/epi gray level ratio before and immediately after the cessation of pacing in the 2 groups. In the controls, the endo/epi gray level ratio remained unchanged (*p*=NS), but was significantly decreased in patients with syndrome X (*p*<0.01).

Discussion

In the present study, endo/epi gray level ratio obtained from MCE, which is defined as an index of change in myocardial blood flow distribution, significantly decreased after pacing stress in 11 patients diagnosed with syndrome X from a total of 25 patients with a history of chest pain and angiographically normal coronary arteries without evidence of coronary vasospasm. These 11 patients also had exercise-induced chest pain and ST-segment depression. In contrast, the 14 patients without evidence of exercise-induced chest pain or ST-segment depression did not show

Table 2 Hemodynamics, ST-Segment Depression, and Chest Pain at Rest and During Rapid Atrial Pacing

	Before atrial pacing			During atrial pacing				Pain
	HR (beats/min)	SBP (mmHg)	RPP (mmHg-beats/min)	HR (beats/min)	SBP (mmHg)	RPP (mmHg-beats/min)	ST dep (mV)	
Controls								
1	81	140	11,340	150	130	19,500	0	No
2	47	160	7,520	136	142	19,312	0	No
3	60	120	7,200	125	117	14,625	0	No
4	63	110	6,930	136	107	14,552	0	No
5	50	140	7,000	135	130	17,550	0	No
6	81	150	12,150	136	175	23,800	0	No
7	56	144	8,064	130	137	17,810	0	No
8	60	150	9,000	130	137	17,810	0	No
9	68	180	12,240	136	185	25,160	0	No
10	64	128	8,192	150	133	19,950	0	No
11	75	126	9,450	150	115	17,250	0	No
12	79	110	8,690	150	100	15,000	0	No
13	68	120	8,160	125	130	16,250	0	No
14	71	104	7,384	150	186	27,900	0	No
Mean	66	134	8,809	139	137	19,034	0	
SD	11	22	1,845	10	27	4,037	0	
Syndrome X								
1	83	180	14,940	150	187	28,050	0.10	Yes
2	86	150	12,900	136	140	19,040	0.10	Yes
3	48	130	6,240	150	137	20,550	0.25	Yes
4	65	118	7,670	143	120	17,160	0.15	Yes
5	65	168	10,920	142	157	22,294	0.10	Yes
6	56	140	7,840	125	128	16,000	0.10	Yes
7	65	180	11,700	136	168	22,848	0.15	Yes
8	60	134	8,040	125	140	17,500	0.10	Yes
9	65	100	6,500	150	95	14,250	0.10	Yes
10	88	150	13,200	130	148	19,240	0.15	Yes
11	73	120	8,760	150	116	17,400	0.10	Yes
Mean	69	143	9,883	140	140	19,485	0.13	
SD	13	26	2,975	10	25	3,837	0.05	

HR, heart rate; SBP, systolic blood pressure; RPP, rate pressure product; ST dep, ST-segment depression.

Fig 2. Endo/epi gray level ratios before and after pacing stress in controls (Left panel) and patients with syndrome X (Right panel). Note that the endo/epi gray level ratio significantly decreased after pacing stress in patients with syndrome X, but not in controls.

any significant reduction in the endo/epi gray level ratio after pacing stress. Thus, the pacing-induced decrease in the endo/epi gray level ratio may indicate abnormal myocardial blood flow distribution in patients with syndrome X, which may contribute to the exercise-induced chest pain and ST-segment depression.

Methodological Considerations

In this study, exercise testing was performed for the definition of syndrome X and rapid atrial pacing was performed for MCE investigation. The rate–pressure product during pacing stress ($\approx 19,000$) was lower than during exercise ($\approx 28,000$), but similar depression of the ST segment was observed (0.13 vs 0.15 mV). We also evaluated ST segment change at a rate–pressure product of almost 19,000 during exercise and the ST-segment depression was almost -0.11 mV. Although the precise mechanism for this is unclear from the current results, the difference in the relationship of the rate–pressure product and the changes in the ST segment may be due to methodological differences.

Sonicated non-iodinated and iodinated radio-opaque dyes have been widely used in experimental and clinical studies.¹² In the present study, we used the sonication method, as previously described by Feinstein et al,³⁰ because it makes more homogeneous microbubbles than the manually agitated method. Using a computer-basis analysis of the MCE images, we measured the peak gray level in both the endocardium and epicardium. A good correlation between the first and second measurements of the peak endocardial and epicardial gray levels as well as the endo/epi gray level ratio was observed with good reproducibility. Previous studies in an animal model of critical coronary stenosis demonstrated that the relative changes in the peak gray level detected by MCE were significantly correlated with absolute changes in myocardial blood flow assessed by the radioactive microspheres method.^{25,32–34} Nonetheless, because the peak gray level represents the relative flow value, the level varies from patient to patient, resulting in difficulty comparing patients. Furthermore, although we tried to inject the same amount of dye at the same speed in each patient, it is possible that some leaked into the systemic circulation and that it was injected at a slightly different speed in each case. However, the animal model demonstrated that in the ischemic region the decrease in the endo/epi gray level ratio obtained by MCE is similar in magnitude to that obtained by the microspheres technique²⁵ so it is reasonable to assess changes in transmural myocardial blood flow distribution by calculating the changes in the endo/epi gray level ratio in clinical studies. Indeed, a previous clinical study by Lim et al clearly demonstrated that the endo/epi gray level ratio significantly decreased after pacing stress in patients with coronary artery disease, which suggests that transient subendocardial ischemia can be detected by MCE.²⁶ Thus, we consider that the endo/epi gray level ratio used in the present study is useful in assessing regional myocardial blood flow distribution.

In the present study, the mean endo/epi gray level ratio before pacing stress was 0.97 in the controls and 0.98 in the patients with syndrome X, which are similar values to those obtained before pacing in patients with coronary artery disease in a previous study.²⁶ Thus, the mean endo/epi gray level ratio in humans is nearly equal to 1, indicating that transmural myocardial blood flow is

uniformly distributed from the endocardium to the epicardium at rest. Furthermore, the endo/epi gray level ratio at rest in humans is similar to that obtained by the radioactive microsphere technique in experimental animals.^{25,32,33} Therefore, the MCE method can detect myocardial blood flow distribution.

Abnormal Myocardial Blood Flow Distribution in Syndrome X

In the present study, although the changes in the rate–pressure product (ie, myocardial oxygen consumption) during pacing stress was similar between the 2 groups, the endo/epi gray level ratio significantly decreased after pacing stress, with accompanying pacing-induced chest pain and ST-segment depression, only in patients with syndrome X. Patients with syndrome X had normal coronary angiograms with a negative response to spasm provocation by ergonovine. These findings suggest that in syndrome X the abnormal transmural myocardial blood flow distribution is caused by an abnormality of the myocardial microvasculature, which may be the mechanism of the exercise-induced chest pain and ST-segment depression.

There are 2 hypotheses of the pathogenesis of syndrome X: microvascular angina, as proposed by Epstein and Cannon,^{27,28} and inappropriate constriction of the prearteriolar vessels of the coronary microvasculature, as proposed by Maseri et al.²⁹ Both hypotheses suggest that the coronary steal phenomenon of transmural myocardial blood flow is the cause of the ST-segment depression and chest pain. Defective endothelium-dependent dilatation of the resistance coronary arteries has also been suggested.³⁵ Although the mechanisms of the abnormal blood flow distribution in patients with syndrome X still remain unclear from the data of the present study, it is interesting to note that coronary steal occurred from the endocardium to the epicardium. It is therefore plausible that reduced, flow-dependent dilatation in response to pacing or exercise stress in the endocardium, by whatever mechanism, may cause the ST depression and chest pain.

Study Limitations

The myocardial contrast effect depends on a variety of physical and biological factors.³⁶ The physical factors include electronic signal processing, signal amplification and scattering elements; for example, the relation between contrast concentration and signal intensity may largely depend on the type of computer processing and this would limit the appropriate interpretation of data. The biological factors, including coronary blood flow, intramyocardial blood volume and coronary blood pressure, are not easily controllable, especially in the clinical setting. Thus, although MCE provides useful information about myocardial perfusion,^{12–26} the meaning of the absolute value of the myocardial contrast intensity remains elusive and clinical applications of MCE still remain unclear.³⁶ In the present study, we did not subtract the background gray level and, therefore, because the values of background gray level differ among patients, the obtained peak gray levels are semi-quantitative. To overcome this problem, we calculated the endo/epi gray level ratio.

From the present data, we were not able to demonstrate coronary steal phenomenon in the patients with syndrome X. Reduced coronary flow reserve in those patients can not be ruled out. Therefore, further study, which simultaneously records both MCE and coronary flow, will be needed.

It should also be noted that we did not assess whether the patients with syndrome X had myocardial ischemia because we did not measure myocardial lactate production.

In summary, this is the first demonstration that the endo/epi myocardial blood flow ratio assessed by MCE significantly decreases after pacing stress in patients with syndrome X, suggesting abnormal distribution of transmural myocardial blood flow, which may be the genesis of the exercise-induced chest pain and ST-segment depression seen in patients with this syndrome. Although our results could not explain the mechanism of the decreased endo/epi myocardial blood flow ratio, they may be helpful in understanding the pathophysiology of the coronary microcirculation.

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