

## Correlation Between Exercise Electrocardiography Test and Coronary Flow Reserve in Patients Without Organic Coronary Artery Stenosis

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### Abstract

**Objectives.** The exercise electrocardiography (ECG) test is frequently positive in patients without organic coronary artery stenosis. Although the reason for this false positive ST depression is not fully understood, one possibility may be related to coronary microvascular abnormality. The present study investigated the relationship between the exercise ECG test and coronary flow reserve (CFR) in patients with angiographically normal coronary arteries, but with positive ECG ST depression.

**Methods.** This study included 67 patients, 32 with chest pain syndrome, and 35 with vasospasm. The exercise ECG test was performed without drug administration in all patients, and the CFR was determined after diagnostic cardiac catheterization.

**Results.** Although a significant correlation was recognized between ST depression and CFR in patients with chest pain syndrome ( $p < 0.05$ ), there was no correlation in patients with epicardial coronary vasospasm.

**Conclusions.** In patients with chest pain syndrome, ST depression detected by the exercise ECG test may suggest coronary microvascular dysfunction. However, in patients with coronary vasospasm, ST depression may occur without decreased CFR, suggesting that coronary spasm or other mechanism(s) relating to ST changes are present during the exercise ECG test, and careful interpretation is needed.

J Cardiol 2007 Mar; 4(3): 109 - 114

### Key Words

■Exercise      ■Electrocardiography      ■Coronary artery disease (flow reserve)  
■Coronary vasospasm

### INTRODUCTION

The exercise electrocardiography (ECG) test is the first line test for coronary artery disease<sup>1,2</sup> in which ST depression of over 0.1 mV has reasonable predictive accuracy for significant coronary obstructive lesion(s). However, patients with various cardiovascular diseases frequently show posi-

tive exercise ECG test but have normal coronary arteries.<sup>3-7</sup> Epicardial coronary vasospasm<sup>8,9</sup> and chest pain syndrome<sup>10</sup> in particular are frequently associated with this false positive exercise ST depression. Recently, coronary flow reserve (CFR) has been evaluated using a Doppler guidewire inserted into the coronary artery to assess microvascular maximal dilatory function,<sup>11,12</sup> as well as the

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Manuscript received October 31, 2006; revised December 14, 2006; accepted December 20, 2006

presence of epicardial coronary artery organic stenosis.<sup>13,14</sup>) Accordingly, if CFR decreases corresponding to exercise-induced ECG ST depression despite the absence of significant coronary stenosis, the ST depression may be related to a coronary microvascular dilatory dysfunction. However, few studies<sup>10</sup>) have investigated the relationship between the impairment of CFR and appearance of a false positive ST depression in various cardiovascular diseases.

To clarify whether such a depression following exercise is closely related to decreases in CFR, the present study investigated the relationship between CFR and exercise-induced ST depression in patients with coronary spasm and chest pain syndrome.

## SUBJECTS AND METHODS

### Subjects

The study population consisted of 35 patients with epicardial coronary vasospasm (27 men and 8 women, mean age  $61.6 \pm 9.2$  years). In this study, patients with coronary vasospasm, diagnosed clinically as well as by the acetylcholine provocation test, showed no organic stenosis in epicardial coronary arteries. The study also included 32 consecutive patients with atypical chest pain (18 men and 14 women, mean age  $57.1 \pm 12.4$  years), but with normal epicardial coronary arteries and no coronary spasm on diagnostic cardiac catheterization. Patients with ST depression at rest were excluded due to the difficulty of evaluating their exercise ECG test. All medications except sublingual nitroglycerin were withdrawn before cardiac catheterization. Informed consent was obtained from all subjects before the study, which was approved by the ethics committee of Fukushima Medical University.

### Study protocol

Standard cardiac catheterization including pressure recording and coronary angiography was performed in all 67 patients using the femoral approach. After control coronary angiography, incremental doses of acetylcholine were infused into the left coronary artery (20, 50, and 100  $\mu\text{g}$ ) and subsequently into the right coronary artery (20 and 50  $\mu\text{g}$ ) during 30 sec. After the acetylcholine provocation test, multi-directional coronary angiography was performed following intracoronary injection of isosorbide dinitrate (ISDN) (1.25 - 2.5 mg in

each coronary artery) to diagnose the degree of coronary organic stenosis. Coronary vasospasm was diagnosed by the acetylcholine provocation test, in which test total and/or subtotal coronary artery narrowing including focal and diffuse patterns was observed. A Doppler guidewire (FloWire, Cardiometrics, Inc) was advanced into the proximal left anterior descending coronary artery through a 6 F coronary angiography catheter. The optimal Doppler signal was obtained by moving the guidewire slightly within the vessel lumen. Frequency analysis of the Doppler signals was carried out in real time by fast-Fourier transform using a velocimeter (FloMap, Cardiometrics, Inc). CFR was obtained from the ratio of maximal hyperemic to baseline time-averaged peak velocity at rest after intracoronary bolus injection of papaverine hydrochloride (10 mg)<sup>5</sup>) over 10 sec.

### Exercise ECG test

All patients underwent treadmill exercise ECG tests (Stress Test System ML-4500, Fukuda Denshi) having taken no medication on the day before cardiac catheterization. The Bruce protocol was used for the exercise test, and patients were considered positive if over 0.1 mV of a horizontal and downsloping, or over 0.2 mV of an upsloping ECG ST depression developed 0.08 sec from the J point in at least one lead. The level of ST depression was taken from the auto-measured value. The exercise ECG test was terminated when at least one of the following end points was reached: chest symptom, leg fatigue, diagnostic ST depression, frequent arrhythmias, and target heart rate. The ST depression with the maximum degree among all 12 leads was selected, and was averaged for each group of patients with chest pain syndrome and coronary vasospasm.

### Statistical analysis

All data are expressed as mean values  $\pm$  SD. Intergroup comparisons were performed by the unpaired Student's *t*-test. Correlation analysis was performed using Pearson's correlation coefficient. The proportions of men, smoking, hypertension, diabetes mellitus, and exercise positive patients were analyzed by Fisher's exact probability test. A *p* value of  $< 0.05$  was considered statistically significant.

**Table 1 Characteristics of study patients\***

	Chest pain syndrome			Coronary vasospasm		
	Overall (n = 32)	Exercise positive (n = 17)	Exercise negative (n = 15)	Overall (n = 35)	Exercise positive (n = 24)	Exercise negative (n = 11)
Age( yr )	57.1 ± 12.4	57.5 ± 12.6	56.7 ± 12.5	61.6 ± 9.3	61.7 ± 8.5	61.5 ± 11.1
Men/women	18/14	9/8	9/6	27/8	17/7	10/1
Total cholesterol( mg/dl )	201.2 ± 47.7	202.6 ± 41.4	199.7 ± 55.4	196.2 ± 41.7	194.0 ± 45.3	201.1 ± 33.8
Triglyceride( mg/dl )	113.0 ± 76.3	135.8 ± 91.5	87.1 ± 44.3	105.7 ± 57.5	104.4 ± 62.3	108.7 ± 48.1
HDL cholesterol( mg/dl )	56.5 ± 14.9	55.1 ± 15.0	58.1 ± 15.2	53.4 ± 14.9	55.3 ± 17.5	50.5 ± 13.4
Smoking <sup>§</sup>	15( 46.9 )	7( 41.2 )	8( 53.3 )	16( 45.7 )	9( 37.5 )	7( 63.6 )
Hypertension <sup>#</sup>	12( 37.5 )	6( 35.3 )	6( 40.0 )	12( 34.2 )	8( 33.3 )	4( 36.4 )
Diabetes mellitus <sup>†</sup>	5( 15.6 )	4( 23.5 )	1( 6.7 )	3( 8.6 )	2( 8.3 )	1( 9.1 )

Continuous values are mean ± SD. ( ): %. \**p* = NS for all comparisons. <sup>§</sup> ≥ 10 cigarettes/day for 10 years. <sup>#</sup>Blood pressure ≥ 140/90 mmHg or antihypertensive medication. <sup>†</sup>Fasting blood glucose ≥ 140 mg/dl or antidiabetic medication. HDL = high-density lipoprotein.

**Table 2 Hemodynamic variables**

	Chest pain syndrome			Coronary vasospasm		
	Overall (n = 32)	Exercise positive (n = 17)	Exercise negative (n = 15)	Overall (n = 35)	Exercise positive (n = 24)	Exercise negative (n = 11)
s-AP( mmHg )	150.4 ± 29.6	153.8 ± 29.7	146.7 ± 30.0	151.2 ± 23.7	152.4 ± 24.4	148.6 ± 23.0
d-AP( mmHg )	77.5 ± 12.1	78.3 ± 11.9	76.7 ± 12.7	75.8 ± 10.4	75.6 ± 11.1	76.4 ± 9.1
m-AP( mmHg )	107.1 ± 18.1	107.9 ± 17.8	106.1 ± 19.1	106.2 ± 15.9	105.8 ± 17.4	107.1 ± 12.8
s-LVP( mmHg )	150.6 ± 27.2	153.8 ± 28.4	146.9 ± 26.2	152.4 ± 22.8	153.5 ± 22.2	150.1 ± 25.2
Pcw( mmHg )	8.0 ± 2.7	9.2 ± 2.9	6.5 ± 1.7	9.8 ± 3.5*	9.8 ± 2.0	9.7 ± 5.7
s-PAP( mmHg )	24.2 ± 5.1	26.1 ± 5.8 <sup>#</sup>	22.1 ± 3.2	25.8 ± 4.6	26.1 ± 4.7	25.1 ± 4.7
CI( l/min/m <sup>2</sup> )	3.62 ± 0.77	3.52 ± 0.52	3.73 ± 1.00	3.41 ± 0.73	3.44 ± 0.79	3.34 ± 0.61
EF( % )	65.0 ± 7.3	64.4 ± 8.4	65.6 ± 6.1	64.2 ± 7.2	65.3 ± 7.3	62.0 ± 6.9

Values are mean ± SD. \**p* < 0.05 vs overall patients with chest pain syndrome. <sup>#</sup> *p* < 0.05 vs exercise negative patients with chest pain syndrome.

s-AP = systolic aortic pressure; d-AP = diastolic aortic pressure; m-AP = mean aortic pressure; s-LVP = systolic left ventricular pressure; Pcw = pulmonary artery wedge pressure; s-PAP = systolic pulmonary artery pressure; CI = cardiac index; EF = ejection fraction.

## RESULTS

Patient characteristics are presented in **Table 1**. Age, and values of total cholesterol, triglyceride, and high-density lipoprotein cholesterol were not significantly different between the two groups, and the proportions of men, smoking, hypertension, and diabetes mellitus were also not different. The results of hemodynamic variables during cardiac catheterization are shown in **Table 2**. Pulmonary wedge pressure in all patients with coronary vasospasm was significantly higher compared with that in all patients with chest pain syndrome, and systolic pulmonary arterial pressure in exercise positive patients with chest pain syndrome was sig-

nificantly higher than that in exercise negative patients with chest pain syndrome. The results of the exercise ECG tests are presented in **Table 3**. Positive ST depression in the exercise stress test was found in 17 with chest pain syndrome and 24 patients with coronary vasospasm.

CFRs of patients with chest pain syndrome and coronary vasospasm were  $3.53 \pm 0.75$  and  $3.61 \pm 0.82$ , respectively, with no significant difference. The rate of exercise ECG-positive seemed to be higher in patients with epicardial coronary vasospasm (24/35, 68.6%) compared to that in those with chest pain syndrome (17/32, 53.1%; **Tables 1 - 3**).

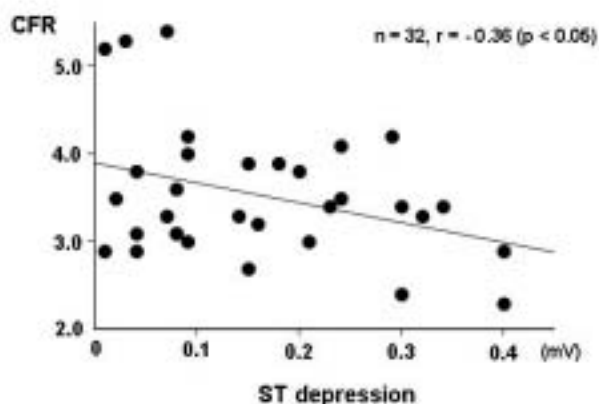
The relationship between ST depression and

**Table 3 Results of exercise electrocardiography test**

	Chest pain syndrome			Coronary vasospasm		
	Overall ( <i>n</i> = 32)	Exercise positive ( <i>n</i> = 17)	Exercise negative ( <i>n</i> = 15)	Overall ( <i>n</i> = 35)	Exercise positive ( <i>n</i> = 24)	Exercise negative ( <i>n</i> = 11)
Rest						
HR( beats/min )	71.9 ± 12.8	73.8 ± 13.3	69.9 ± 12.3	72.1 ± 11.9	70.9 ± 9.5	74.8 ± 16.2
s-BP( mmHg )	136.9 ± 14.8	138.4 ± 15.6	135.2 ± 14.2	141.3 ± 19.1	144.3 ± 19.3	135.0 ± 17.8
DP( × 10 <sup>2</sup> mmHg/min )	98.7 ± 21.5	101.9 ± 20.7	95.1 ± 22.4	101.9 ± 21.2	102.3 ± 19.6	101.1 ± 25.3
Maximal exercise						
ST depression( mV )	0.16 ± 0.12	0.25 ± 0.09 <sup>†</sup>	0.06 ± 0.03	0.19 ± 0.14	0.26 ± 0.11 <sup>†</sup>	0.05 ± 0.03
HR( beats/min )	146.5 ± 20.1	151.2 ± 15.4	141.2 ± 23.8	145.4 ± 18.1	147.0 ± 17.4	141.9 ± 19.8
s-BP( mmHg )	200.8 ± 33.9	205.5 ± 32.5	195.5 ± 35.8	198.7 ± 22.6	201.4 ± 24.9	193.0 ± 15.9
DP( × 10 <sup>2</sup> mmHg/min )	293.5 ± 61.5	310.3 ± 57.1	274.4 ± 62.7	289.4 ± 49.5	295.9 ± 48.5	275.4 ± 51.1

Values are mean ± SD. <sup>†</sup>*p* < 0.01 vs exercise negative patients.

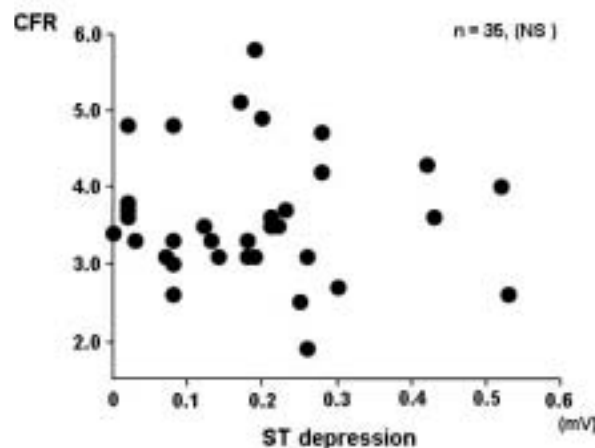
HR = heart rate ; s-BP = systolic blood pressure ; DP = double products.



**Fig. 1 Significant positive relationship between ST depression following exercise test and coronary flow reserve observed in patients with chest pain syndrome (*n* = 32)**

It is suggested that false positive ST-segment depression may be induced by coronary microvascular dilatation disturbance.

CFR = coronary flow reserve.



**Fig. 2 Negative relationship observed between exercise-induced ST depression and coronary flow reserve in patients with coronary vasospasm (*n* = 35)**

The ST depression may not be directly related to impaired vasodilatory response of coronary microvascular beds.

Abbreviation as in Fig. 1.

CFR is shown in patients with chest pain syndrome (*n* = 32 ; **Fig. 1**) and those with coronary vasospasm (*n* = 35 ; **Fig. 2**). A significant correlation was recognized in patients with chest pain syndrome (*p* < 0.05), although CFR values between the exercise positive (*n* = 17) and negative groups (*n* = 15) were not significantly different ( $3.34 \pm 0.55$  vs  $3.76 \pm 0.89$ , respectively). However, there was no correlation in patients with coronary vasospasm. Moreover, taking all data into account, CFR of exercise ECG-positive patients (*n* = 41) did not differ from that of exercise ECG-negative

patients (*n* = 26) ( $3.50 \pm 0.77$  vs  $3.69 \pm 0.80$ , NS).

## DISCUSSION

False positive ECG ST depression has been observed in angiographically normal epicardial coronary arteries. Although the mechanism is still unclear, coronary microvascular disturbance may be partly associated with the genesis of such false positive ST depressions. This study showed relationships between CFR and exercise ECG test in patients with chest pain syndrome and coronary

vasospasm, suggesting that coronary microvascular disturbance may be associated with chest pain syndrome with false positive ST depression.

Exercise-induced ST depression was frequently found in both patients with chest pain syndrome and coronary vasospasm, who showed normal coronary angiograms (Table 3).<sup>8-10)</sup> However, we found the relationship of CFR to exercise-induced ST depression was different between these two diseases, *i.e.*, exercise-induced ST depression was correlated to CFR in chest pain syndrome, whereas no correlation was observed in patients with coronary vasospasm (Figs. 1, 2). These results suggest that the mechanism of false positive exercise-induced ST depression in patients with coronary vasospasm involves other factors such as coronary spasm during and/or following exercise, rather than impairment of coronary microvascular dilatory function. However, this possibility of epicardial coronary artery spasm during exercise remains to be verified. Moreover, some patients with coronary spasm may suffer not only regulatory impairment of epicardial coronary artery vasoactivity but also impairment of small vessel dilatory action or microvascular spasm<sup>16,17)</sup> due to exercise stress despite the absence of reduction in CFR. Hence, the papaverine-induced CFR value measured in this study is only one marker detecting impairment of small vessel vasodilatory action, and does not provide full assessment of small vessel regulatory function during exercise or exercise-induced microvascular spasm. Further study is necessary to elucidate this issue.

On the other hand, a weak but significant correlation between ST depression following exercise and CFR in patients with chest pain syndrome was observed (Fig. 1), although the values of CFR between exercise positive and negative groups were not different. These results suggest that ST depression in patients with chest pain syndrome may partly reflect coronary microvascular dysfunction. CFR values in patients with chest pain syndrome showing no angiographical coronary stenosis and exercise induced ST depression were significantly

lower than in controls,<sup>10)</sup> although no relationship between CFR values and exercise induced ST changes was detected. On the contrary, the impairment of coronary microvascular dilatory action may not be uniformly and profoundly observed in chest pain syndrome, when taking into account the present results. Therefore, as in epicardial coronary spasm, the assessment of coronary microvascular vasodilatory impairment by only CFR may not be adequate to evaluate the mechanism of exercise induced ST depression. Also, it is unclear whether microvascular spasm during exercise occurs or not in patients with chest pain syndrome.<sup>16,17)</sup> Further studies are required to clarify these issues.

### Study limitations

This study has several limitations. First, the measurement of CFR was done after coronary angiography in which ISDN was administered into each coronary artery. Coronary microvascular spasm is relieved after the ISDN injection.<sup>16)</sup> Accordingly, the ISDN injection may affect the CFR value in this study. However, this injection was performed in all patients. Second, CFR and exercise ECG test were not done simultaneously, so vasoactivity in each examination may not be the same. Third, the relationship between exercise-induced ECG ST depression and the degree of acetylcholine induced epicardial coronary spasm or flow-mediated epicardial coronary artery dilation after papaverine injection and was not investigated, so how endothelium dependent vasodilatory dysfunction, if any, contributes to ST depression in exercise remains unclear. Further studies are needed.

### CONCLUSIONS

In patients with chest pain syndrome, ST depression during the exercise ECG test may partially indicate coronary microvascular dysfunction. However, in patients with coronary vasospasm, coronary spasm or other contributing factor(s) are likely to be present during the exercise ECG test, so a careful approach is needed for the interpretation.

### 要 約

器質的冠動脈狭窄を有さない患者における運動負荷心電図試験と冠血流予備能との関係

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目 的: 冠動脈に器質的狭窄を有さない患者において, 運動負荷心電図試験陽性がしばしば認め

られる。この偽陽性ST低下については十分理解されていないが、冠微小循環機能障害に関係している可能性がある。そこで冠動脈に器質的狭窄を有さない患者において、運動負荷試験と冠血流予備能の関係を検討した。

方 法: 32例の胸痛症候群および35例の冠攣縮性狭心症について検討した。全例で薬剤を投与せずに運動負荷試験を施行し、その後日、心臓カテーテル検査により冠血流予備能を求めた。

結 果: 胸痛症候群においては、ST低下と冠血流予備能の間に有意な負の相関が認められた ( $p < 0.05$ ) が、冠攣縮性狭心症においては、そのような関係は認められなかった。

結 論: 胸痛症候群においては、運動負荷心電図試験におけるST低下は、一部、冠微小循環障害を反映している可能性がある。しかしながら、冠攣縮性狭心症においては、ST低下は必ずしも冠微小循環障害を反映しておらず、運動負荷中に冠攣縮が生じている可能性があり、その解釈には注意が必要である。

—J Cardiol 2007 Mar; 49(3): 109 - 114—

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