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Overview of the Non-Invasive Examinations in Patients with Coronary Spastic Angina

Shozo Sueda[1]*, and Hiroaki Kohno[2]

[1]*Department of Cardiology, Ehime Prefectural Niihama Hospital, Japan*
[2]*Department of Cardiology, Tsukazaki Hospital, Japan*

Abstract

Exercise test, hyperventilation test or cold pressor test was employed to reproduce ST elevation in patients with variant angina. However, cardiologists could not get the high positive frequency from these tests in patients without high disease activity. Now a days, cardiologists can easily perform coronary angiography or coronary computed tomography. Cardiologists skipped the non-invasive spasm provocation tests such as hyperventilation test or cold pressor test to diagnose patients with coronary artery spasm. Approximately a half patient with coronary spasm had pathologic responses of exercise tests. More than a third patient with coronary spasm and without fixed stenosis had ischemic findings on exercise tests, whereas more than two-third patients with coronary spasm and with organic stenosis had pathologic responses on exercise testing. We should reconsider the usefulness of exercise tests to obtain the ischemic findings due to coronary artery spasm in the clinic before performing the cardiac catheterization.

Keywords: Coronary spastic angina; Exercise test; Hyperventilation test; Cold pressor test

Introduction

Coronary artery spasm is finally diagnosed by a pharmacologic agent, such as acetylcholine or ergonovine, in the cardiac catheterization laboratory [1-3]. However, before performing the coronary angiography, it may be prefered by cardiologists to obtain ischemic findings in these patients. As a non-invasive examination treadmill exercise test, hyperventilation test and cold pressor test were employed for the induction of ischemia due to coronary artery spasm [4-13]. In patients with ischemic heart disease and obstructed coronary artery disease, treadmill/bicycle exercise tests are very useful to obtain the pathologic findings, whenever it may be difficult to obtain the ischemic findings to perform treadmill exercise tests in patients with coronary spastic angina (CSA) and non-obstructed coronary artery disease. According to the Japanese Circulation Society (JCS) guidelines [14], 24 hours to 48 hours Holter recording is classified as Class I, while the exercise test in the early morning and daytime in patients with diurnal variation in exercise tolerance is classified as Class IIa. Moreover, single exercise test in patients who are in stable condition and suspected of having CSA is classified as Class IIb. Cardiologists perform the 24 hours to 48 hours Holter monitoring in patients suspecting of CSA. However, they don't routinely perform the treadmill/bicycle exercise tests in patients who are suspected of having CSA. In this review, we investigated the usefulness of non-invasive examinations in patients with CSA.

Holter ECG

A Holter recording for 24 hours to 48 hours in cases in which CSA is strongly suspected based on subjective symptoms accompanied by syncope or palpitations without identifiable cause are classified as Class I according to the JCS guidelines. In contrast, Holter recording for 24 hours to 48 hours in cases in which it is difficult to record the ECG during attacks are defined as Class IIa. Yasue et al reported that chest pain develops in approximately a third of episodes of ischemic ST change in patients with variant angina, and the remaining two thirds events of coronary artery spasm were asymptomatic. In our 300 patients with CSA, just four patients (1.3%) had transient ST elevation (Table 1) and 18 patients (6%) with CSA had abnormal findings during 24-hour Holter examinations [15]. Before performing coronary angiography, we should try to perform the Holter recordings to obtain the ischemic ECG changes possibly due to coronary artery spasm.

Hyperventilation Test

The JCS guidelines recommend the promote vigorous hyperventilation, 25 times/minute or higher, for 6 minutes in patients suspected of having CSA with a low frequency attacks as class IIa. Positive rate by hyperventilation testing was 53.6% to 100%, as shown in Table 1 [2,3,16-18]. In patients with high disease activity who had more than 5 times spontaneous attacks per week, 84% was positive frequency, whereas moderate (less than 5 times spontaneous attacks per week) or low (less than one spontaneous attack per week) disease activity had positive results in 39% or 29%. Hyperventilation tests had limitations in patients with moderate or low disease activity to document coronary spasm. In 2005, Japanese cardiologists performed the hyperventilation tests in just 416 patients among the 208 institutions by coronary spasm questionnaire in Japan [19]. In the future, it may be difficult to become the revival of the hyperventilation tests for the induction of coronary spasm in the clinic in the world.

Treadmill Exercise Tests

In the past, some exercise tests, such as treadmill exercise test, ergometer bicycle test, upper arm exercise test and handgrip test were employed to diagnose a coronary artery spasm. In patients with variant angina or CSA, 37.8% to 67.5% of patients had positive ischemic findings as shown in Table 1. Organic stenosis was found in 14.7% to 74.6% of these patients [15,20-22]. Table 2a showed that more than a third patient with CSA and without organic stenosis had ischemic

***Corresponding author:** Shozo Sueda, The Department of Cardiology, Ehime Niihama Prefectural Hospital, Hongou 3 Choume 1-1, Niihama City, Ehime 7920042, Japan, Tel: +81897436161; Fax: +81897412900; E-mail: EZF03146@nifty.com

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	Year	Number of cases	Diagnosis	ST elevation	ST depression	Positive rate	Organic stenosis
24-hour Holter ECG							
Sueda et al. [15]	2016	300	CSA	4		4 (1.3%)	44 (14.7%)
Cold pressor test							
Waters et al. [21]	1983	34	Variant	3	2	5 (14.7%)	19 (55.9%)
Crea et al. [3]	1985	14	Variant	2	0	2 (14.3%)	10 (71.4%)
(All summed data)		48		5(10.4%)	2(4.2%)	7 (14.6%)	29 (60.4%)
Hyperventilation test							
Girotti et al. [16]	1982	10	Variant			10 (100%)	
Crea et al. [3]	1985	14	Variant	11	0	11 (78.6%)	10 (71.4%)
Kaskiet al. [17]	1986	28	Variant			15 (53.6%)	
Previtali et al. [18]	1989	30	Variant	22	3	25 (83.3%)	22 (73.3%)
Nakao et al. [2]	1997	206	CSA			127 (61.7%)	57 (27.7%)
(All summed data)		288		33	3	188 (65.3%)	89 (30.9%)
Exercise test							
De Servi et al. [20]	1981	114	Variant	40	37	77 (67.5%)	85 (74.6%)
Waters et al. [21]	1983	34	Variant	10	11	21 (61.8%)	19 (55.9%)
Castello et al. [22]	1990	91	CSA	8	37	45 (49.5%)	61 (67.0%)
Sueda et al. [15]	2016	300	CSA	15	98	113 (37.8%)	44 (14.7%)
(All summed data)		539	CSA/Variant	73(13.5%)	183(34.0%)	256 (47.5%)	209 (38.8%)

Table 1: Comparisons of non-invasive examinations in patients with coronary spasm.

	Number of cases	Diagnosis	ST elevation	ST depression	Positive rate
De Servi et al. [20]	29	Variant	9 (31.0%)	2 (6.9%)	11 (37.9%)
Waters et al. [21]	15	Variant	2 (13.3%)	5 (33.3%)	7 (46.7%)
Castello et al. [22]	30	CSA	3 (10.0%)	4 (13.3%)	7 (23.3%)
Sueda et al. [15]	256	CSA	3 (1.2%)	85 (33.2%)	88 (34.4%)
All summed data	330	CSA/Variant	17 (5.2%)	96 (29.1%)	113 (37.7%)

Table 2a: Comparisons of ischemic findings on exercise tests in coronary spastic angina patients without organic stenosis.

	Number of cases	Diagnosis	ST elevation	ST depression	Positive rate
De Servi et al. [20]	85	Variant	31 (36.5%)	35 (41.2%)	66 (77.6%)
Waters et al. [21]	19	Variant	8 (42.1%)	6 (31.6%)	14 (73.7%)
Castello et al. [22]	61	CSA	5 (8.2%)	33 (54.1%)	38 (62.3%)
Sueda et al. [15]	44	CSA	12 (27.2%)	13 (29.5%)	25 (56.8%)
All summed data	209	CSA/Variant	56 (26.8%)	87 (41.6%)	143 (68.4%)

Table 2b: Comparisons of ischemic findings on exercise tests in coronary spastic angina patients with organic stenosis.

findings on exercise tests, while more than two thirds patients with CSA with organic stenosis had ischemic findings on exercise testing as shown in Table 2b. ST elevation (26.8% vs. 5.2%, $p<0.001$) and ST depression (41.6% vs. 29.1%, $p<0.01$) in patients with CSA and organic stenosis was significantly higher than that in those without organic stenosis. The JCS guidelines defined the exercise test as class IIa when exercise test was performed in the early morning and daytime in patients with diurnal variation in exercise tolerance. In 300 patients with CSA, positive treadmill exercise tests were recognized in 113 patients (37.6%) and borderline was observed in 30 patients (10%) [15]. Therefore, approximately a half of the patients had pathologic response in treadmill exercise tests before coronary angiography. Treadmill exercise test was useful in documenting ischemia in patients with CSA. In contrast, ST segment elevation on the 24-hour Holter monitoring was observed in only four patients (1.3%) of 300 patients with CSA. Ischemic findings on treadmill exercise tests was approximately thirty fold higher than those on 24-hour Holter monitoring (37.6% vs. 1.3%, $p<0.001$). ST segment elevation on treadmill exercise tests was also significantly higher than on 24-hour Holter recording (3% vs. 1.3%, $p<0.05$).

Combined Cold Pressor and Hyperventilation Test

Cold pressor test was less effective to diagnose a coronary spasm in the clinic. Positive rate by cold pressor test was 14% to 15% of patients with variant angina, as shown in Table 1 [3,21]. Some cardiologists performed the combined cold pressor and hyperventilation test in patients with variant angina. However, positive response was not different from just hyperventilation test (82% vs. 64%, ns). We could not obtain the additive positive response by performing the combined cold pressor and hyperventilation compared with just hyperventilation test. In 2005, Japanese cardiologists performed the cold pressor tests for the induction of coronary artery spasm in just 237 patients among the 208 hospitals by the coronary spasm questionnaire in Japan [19].

Combined Accelerated Exercise just after the Hyperventilation Test

We investigated the most effective provocation test for patients with CSA, including hyperventilation plus cold pressor, hyperventilation combined with accelerated treadmill exercise test, just hyperventilation or standard treadmill exercise test. The new combined protocol, which consisted of 5 min of mild hyperventilation with a frequency of 24 breaths/min to 40 breaths/min followed by the modified treadmill exercise test accelerated every minute of Bruce's protocol, was the most useful method to obtain the positive rate [10]. In 58 patients with CSA without fixed stenosis, the positive frequency by the new combined

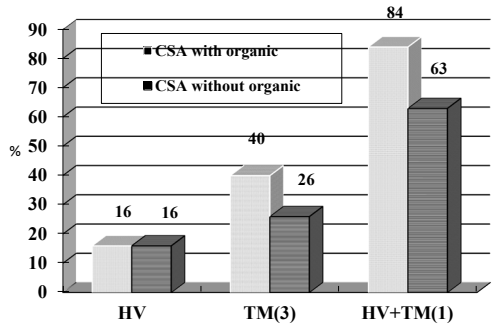
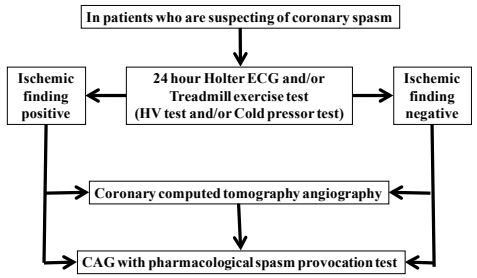


Figure 1: CSA: coronary spastic angina, HV: hyperventilation test, TM(3): standard treadmill exercise test, HV+TM(1): accelerated treadmill exercise test staged up 1 min up following hyperventilation tests.



(ECG; electrocardiogram, CAG: coronary angiography, HV: hyperventilation)

Figure 2: Schema of non-invasive and invasive spasm provocation tests in patients with coronary spasm.

protocol (63%) was significantly higher than the standard treadmill exercise test (26%) or hyperventilation test (16%), as shown in Figure 1 [12]. In contrast, we obtained the significantly higher positive response by the new combined protocol (84%) than that by standard treadmill exercise test (40%) or hyperventilation test (16%) in 40 patients with fixed stenosis and coronary artery spasm, as shown in Figure 1 [11].

Complications

Nakao et al reported that the complication during 206 hyperventilation tests was observed in 17 patients (8.3%) including 9 ventricular tachycardia, 7 atrio-ventricular blocks or one hypotension [2]. De Serve et al reported the two patients with ventricular fibrillation necessary for the cardioverter by treadmill exercise tests in 114 patients with variant angina [20], whereas Castello et al did not mention the complication by bicycle ergometer in 91 patients with CSA [22]. We enquired the two patients with complications during the accelerated exercise test following mild hyperventilation test. One complete atrio-ventricular block and one non-sustained ventricular tachycardia were observed and the administration of sublingual nitroglycerin was effective in these two patients.

Non-Invasive Spasm Provocation Test Hereafter

As a non-invasive spasm provocation test, hyperventilation test and cold pressor test are not employed to document coronary artery spasm in the clinic. Moreover, it may be difficult to get the revival for the induction of coronary spasm in these tests. Recently, we could perform coronary angiography easily and coronary computerized tomography angiography as outpatient. Now cardiologists may select to perform the coronary computerized tomography instead of non-invasive examinations as an initial examination. In diagnosing patients with CSA, we should perform firstly the non-invasive tests such as 24-hour Holter recordings and exercise tests as shown in Figure 2 for obtaining the ischemic findings, and if not satisfactory we should select to perform the coronary computed tomography angiography or coronary angiography procedures with pharmacological spasm provocation tests. We should reconsider the usefulness of non-invasive examinations for the diagnosis in patients with CSA in the clinical grounds. We hope the reconsideration of the non-invasive examinations of exercise tests and 24-hour Holter monitoring before performing coronary angiography or coronary computerized tomography angiography especially in the young generation cardiologists.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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