

Short term reproducibility of exercise testing in patients with ST segment elevation and different responses to the dipyridamole test*

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SUMMARY The short term reproducibility of exercise testing in 25 patients who had exercise induced ST segment elevation without baseline regional asynergy or a previous myocardial infarction, who had different responses to the dipyridamole test, was assessed. The patients performed a dipyridamole echocardiography test and a second exercise stress test. All underwent coronary arteriography. Seventeen patients had transient regional asynergy after dipyridamole (group 1) and either ST segment elevation (14 patients) or depression (three patients); a second group of eight had no asynergy and no electrocardiographic changes (group 2). The repeated exercise stress test was positive in 16 of the 17 patients of group 1 (11 with ST elevation and five with ST depression) and in two patients of group 2 (both had ST depression and one had coronary artery disease). The dipyridamole echocardiography test was positive in 17 of the 19 patients with coronary artery disease and was negative in all six patients without coronary artery disease. The repeated exercise stress test was positive in 17 of the 19 patients with coronary artery disease and in one patient without.

The dipyridamole echocardiography test and a repeated exercise stress test, but not a single exercise stress test, identified coronary artery disease causing exercise induced ST segment elevation.

In patients with effort induced ST segment elevation (without previous myocardial infarction) the dipyridamole echocardiography test may provide information on the underlying coronary structure and possibly the mechanism responsible for this uncommon electrocardiographic pattern on effort.¹

Dipyridamole is a selective coronary arteriolar vasodilator, and has no known vasoconstrictive effects.^{2,3} A positive dipyridamole echocardiography test with ST segment elevation is usually associated with severe coronary disease and suggests that fixed coronary lesions are responsible for the effort induced ST segment elevation.¹ Conversely, when the dipyridamole echocardiography test is negative

for both echocardiographic and electrocardiographic criteria, a functional mechanism (spasm) is most likely to be the cause of ST segment elevation during exercise.^{1,4,5}

The short term reproducibility of the exercise stress test may be another method of evaluating the underlying structure of the coronary arteries and the pathogenetic mechanism of effort induced ST segment elevation. Serial exercise stress tests in patients with angina that is predominantly caused by fixed lesions consistently demonstrate a fixed threshold,⁶ while predominantly vasospastic angina is characterised by considerable variability of the electrocardiographic findings during repeat exercise stress tests.⁷⁻⁹

The aim of this study was to evaluate the short term reproducibility of the exercise stress test in patients with effort induced ST segment elevation and different responses to the dipyridamole echocardiography test. We tested the hypothesis that

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exercise stress tests that were reproducible and had a fixed threshold indicated clinically important coronary stenosis, whereas considerable variability indicated spasm.

Patients and methods

SELECTION OF PATIENTS

Twenty five patients (23 men and two women, mean (SD) age 53 (8) years, range 39–67) with exercise induced ST segment elevation without previous myocardial infarction or baseline asynergy at echocardiography or left ventriculography were enrolled in the study. Patients performed a dipyridamole echocardiography test and a repeat exercise stress test; all underwent coronary arteriography and left ventriculography.

Fifteen patients had documented variant angina (characterised by ST segment elevation at rest or after ergometrine provocation). No patient was taking medications.

EXERCISE STRESS TEST

Patients performed two multistage bicycle ergometer tests, with an initial load of 25 W and subsequent increases of 25 W every two minutes. A 12 lead electrocardiogram and systolic and diastolic blood pressures were recorded before exercise and every minute during exercise. The end points of the test were moderately severe chest pain, a diagnostic ST segment shift, maximal age related heart rate, and limiting dyspnoea or fatigue in the absence of ischaemia.

The test was repeated in each patient at a different time the next day: once in the morning between 8 and 11 am and once in the afternoon, between 3 and 6 pm.

Electrocardiographic tracings were noted as showing myocardial ischaemia when the ST segment altered its position by > 1.00 mm 0.08 seconds after the J point occurred.

DIPYRIDAMOLE ECHOCARDIOGRAPHY TEST

Cross sectional echocardiographic and 12 lead electrocardiographic monitoring were performed during a dipyridamole infusion (0.56 mg/kg over 4 minutes).¹⁰ In patients with a negative result the test was repeated the next day with a higher dose (0.56 mg/kg over 4 minutes followed by 4 minutes of no dose and then 0.28 mg/kg (half of the previous dose) over 2 minutes); the cumulative dose was therefore 0.84 mg/kg over 10 minutes.¹¹ The test was considered positive if there was transient asynergy of contraction (hypokinesia, akinesia, or dyskinesia) that had not been present during the baseline examination.^{10 11}

Aminophylline (240 mg) was available, if needed, to reverse the effects of dipyridamole. During the

procedure, the blood pressure and the electrocardiogram were recorded each minute. The electrocardiographic criteria for ischaemia during this test were the same as those used during the exercise stress test. Cross sectional echocardiograms were continuously recorded during and up to 20 minutes after dipyridamole administration.

We used a commercially available wide angle phased array imaging system (Hewlett Packard 77020). In the baseline studies whenever it was possible we imaged all the standard echocardiographic views. During the test new areas of abnormal wall motion were identified on multiple views by rapidly moving the ultrasound transducer through various positions.

According to a generally accepted qualitative analysis, the wall motion was graded as: hyperkinetic, normal, hypokinetic, akinetic, and dyskinetic.¹⁰ Two independent observers analysed the videotapes. When there was disagreement about the results a third observer reviewed the study and decided the issue. None of the observers had access to the results of the angiographic or exercise stress tests before they graded the videotape. The dipyridamole test was repeated a second time on a different day.

ANGIOGRAPHIC STUDY

Patients underwent biplane left ventriculography and selective right and left coronary arteriography by either the Judkins' or the Sones' technique. Multiple views of each coronary artery were obtained, including craniocaudal views. Two independent observers assessed degrees of stenosis in the major coronary arteries shown by the angiograms. A vessel was considered to show significant obstruction if its diameter was narrowed by > 70%. The severity of stenosis was estimated in the projection where it appeared to be most severe.

All the observers were unaware of echocardiographic and electrocardiographic data.

STATISTICAL ANALYSIS

The statistical significance was evaluated by the χ^2 test. A p value < 0.05 was considered to be statistically significant.

Results

The table shows the results of the dipyridamole echocardiography test, of both exercise stress tests, and of coronary arteriography.

DIPYRIDAMOLE ECHOCARDIOGRAPHY TEST

In the 50 analysed tests (two for each patient), the evaluation by two observers was consistent in 46 and

Table Results of dipyridamole echocardiography test, both exercise stress tests, and coronary angiography

Patient	Age/sex	Dipyridamole test		Exercise stress tests			Coronary angiography (% stenosis)		
		ECG	Asynergy	ECG	W	RPP	LAD	LCX	RCA
1	56 M	↑V2-6	Septal-lateral	↑V2-6	75	176	90	0	50
2	66 M	↑V4-6	Septal	↑V2-6	75	179			
3	57 M	↑D3, aVF	Posterior	↑V4-6	75	165	100	0	40
4	60 M	↑D1, aVL, V2-5	Lateral-apical	↑V4	75	175			
5	63 M	↑V2-3	Septal	↑D3	100	224	0	0	90
6	54 M	↑D1, aVL, V4-6	Lateral	NC	100	214			
7	59 M	↑D3, aVF	Posterior	↑D1, aVL, V2-5	50	197	90	0	0
8	67 M	↓V4-6, D2-3, aVF	Posterior-lateral	↑D1, aVL, V2-5	50	186			
9	46 F	↓V4-6	Septal	↑V2-3	100	288	90	0	0
10	42 M	↑D1, aVL, V2-4	Lateral-apical	↑V2-3	100	274			
11	58 M	↑V2	Septal	↑V4-6	100	235	100	100	0
12	52 F	↑D2-3, aVF	Posterior	↑V4-6	125	242			
13	50 M	↑V2, aVL	Septal-apical	↑D3, aVF	75	204	90	40	100
14	49 M	↑aVL	Septal	↑D3, aVF	75	193			
15	47 M	↓V6	Apical	↑aVL	50	214	0	100	75
16	53 M	↑V4	Septal-lateral	↓D2-3, aVF, V4-6	50	211			
17	46 M	↑aVL	Septal-apical	↑V2	100	190	90	0	0
18	49 M	NC	No	↑V3-4	75	175			
19	43 M	NC	No	↑aVL, V2-6	75	280	75	0	100
20	49 M	NC	No	↑aVL, V2	50	216			
21	46 M	NC	No	↑V2	50	165	100	0	0
22	64 M	NC	No	↑V2	25	153			
23	60 M	NC	No	↑D2-3, aVF	25	170	25	90	0
24	51 M	NC	No	↑V4	50	180			
25	39 M	NC	No	↑V2	100	195	90	0	50
				↑V2	100	160			
				↑aVL	50	165	100	0	40
				↑aVL	75	198			
				↑aVL, V6	75	182	90	0	0
				↑aVL, V6	75	168			
				↑V3-5	50	150	90	0	0
				↑V2-5	50	161			
				↑aVL	25	239	100	0	0
				↑V2-5	50	248			
				↑V2-4	50	104	0	0	0
				NC	100	208			
				↑V2*	100	315	75	0	0
				NC	100	322			
				↑D1, aVL	25	103	0	90	75
				↓V4	75	224			
				↑V2-3*	75	276	50	0	0
				NC	75	280			
				↑D2-3, aVF	50	162	0	0	40
				NC	75	199			
				↑aVL	75	210	0	0	0
				NC	100	228			
				↑D1, aVL	100	163	0	25	0
				NC	100	179			
				↑V2-6	50	82	50	0	0
				↓V2-4	100	270			

*After the end of exercise.

LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; NC, no changes; RCA, right coronary artery; RPP, rate pressure product.

↓ST segment depression; ↑ST segment elevation; lateral, anterolateral wall; posterior, inferoposterior wall; septal, ventricular septum.

different in four, when the opinion of a third observer was the deciding factor.

This test identified two groups: group 1 (17 patients) with dipyridamole induced asynergy and either ST segment elevation (14 patients, figure) or depression (three patients); and group 2 (eight patients) in which dipyridamole did not induce asynergy that was detectable by either echocardiographic or electrocardiographic criteria.

The echocardiographic and electrocardiographic findings were the same in both tests. Coronary

arteriography showed clinically significant coronary artery disease in all 17 (100%) patients in group 1 and in two (25%) of the eight patients of group 2 ($p < 0.01$). The dipyridamole echocardiography test identified coronary artery disease in 92% of the patients who were positive by angiography.

EXERCISE STRESS TEST

The repeated exercise stress test showed diagnostic ST segment changes in 16 of 17 patients in group 1 (11 had ST segment elevation and five had ST

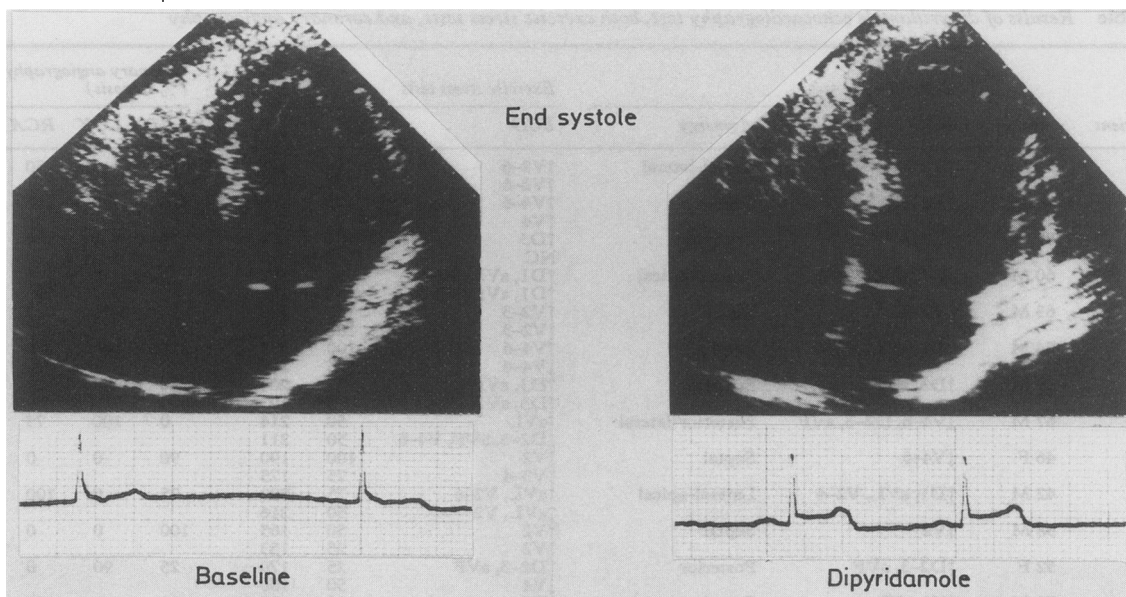


Figure Cross sectional echocardiograms recorded at rest (left) and during dipyridamole induced ischaemia (right). There was a severe basal stenosis in the left anterior descending coronary artery. Echocardiographic images were taken from the apical approach, four chamber view. They show a normally contracting apex under baseline conditions that become akinetic during dipyridamole induced ST segment elevation (V4).

segment depression) and in two out of eight patients in group 2 (both with ST depression) ($p < 0.01$). Exercise tolerance (expressed as the rate-pressure product) did not change substantially ($> 20\%$ of the mean of the two tests) in 16 of the 17 patients in group 1 and in four of the eight patients in group 2 ($p < 0.05$). The repeated exercise stress test was positive in 17/19 patients with coronary disease and in one patient without coronary disease. The repeated exercise stress test was 88% accurate in identifying coronary artery disease.

VARIANT ANGINA

We defined variant angina as angina at rest (assessed by two days of monitoring on either the coronary care unit or by Holter) or after ergometrine provocation that was associated with ST segment elevation. Ergometrine testing was performed in three patients; two of them had a positive test. Variant angina was present in eight of 17 patients in group 1 and in seven of the eight patients in group 2 (difference not statistically significant). None of the patients was in an active phase of the disease (> 5 attacks per day). In patients with angina at rest the average number of attacks per patient per day was 2.1 for group 1 and 2.5 for group 2.

Discussion

The coronary anatomy underlying effort induced ST segment elevation was identified by the dipyridamole echocardiography test and by the repeated exercise stress test but not by a single exercise stress test or a history of variant angina.

The induction of myocardial ischaemia by the dipyridamole test combined with simultaneous monitoring by 12 lead electrocardiography and cross sectional echocardiography gives useful information.^{10,11} The echocardiographic criterion of ischaemia is much more specific and probably more sensitive than electrocardiography.¹¹ Furthermore, ultrasound imaging permits the site and extent of the ischaemic zone to be identified; these are not reliably shown by the electrocardiogram.¹¹ But dipyridamole induced ST segment elevation is a more specific marker of ischaemia than ST segment depression,¹ and in the highly selected population in this study we found that it was as good as echocardiography in identifying patients with clinically important coronary artery disease.

COMPARISON WITH PREVIOUS STUDIES

There is debate about the short term reproducibility

of the exercise stress test in patients with effort induced ST segment elevation. De Servi *et al* and Brunelli *et al* showed a variable exercise threshold and multiple electrocardiographic patterns in patients with documented vasospastic angina undergoing repeat exercise stress testing.^{8,9} Yasue *et al* in a study of 13 patients with variant angina, also found poor reproducibility for ST segment elevation on effort in 11 patients (five of them had < 70% coronary stenosis).⁷

In contrast, Specchia *et al* found reproducible ST segment elevation in four patients with variant angina. Coronary arteriography showed insignificant (< 70%) coronary lesions in three of them and a 75% stenosis in the other patients.¹² Waters *et al* also reported reproducible ST segment elevation in patients with variant angina and absent or mild (< 50%) coronary artery disease.¹³ These "discrepancies" may not be real because the reproducibility of a test is mainly a function of the activity of the vasospastic disease (with vasospasm being more easily elicited on effort if patients are in a more active phase of the disease).¹⁴ Variant angina is cyclical and clinical observations and laboratory findings depend on the phase in the disease process and on treatment.¹³ All four patients studied by Specchia *et al*¹² had multiple spontaneous episodes of ST segment elevation at rest; five of the seven patients studied by Waters *et al*¹⁴ had a spontaneous attack during the coronary angiography, without any provocative stimulus, indicating that they were in an active phase of the disease.

Though we agree that the cyclical nature of the disease must influence the results of screening it cannot explain the findings of our own study. Patients with dipyridamole induced ST segment elevation had more reproducible findings in the repeated exercise stress test, though they were in a less active phase of the disease than patients with negative dipyridamole echocardiography test—the average number of attacks per patient per day was lower in this group. These data draw attention to another fundamental factor that determines the short term reproducibility of the exercise stress test—the underlying organic coronary disease. Active coronary vasospasm is not the only pathogenetic mechanism of exercise induced ST segment elevation, and a severe stenosis can cause ST segment elevation on effort¹⁵ or after dipyridamole¹ through a purely haemodynamic (non-vasospastic) effect.¹⁶ In this event, because effort induced ST segment elevation is caused by organic factors it is not surprising that the electrocardiographic pattern is consistent in repeated exercise stress tests.

In patients in group 2, effort induced ST segment elevation was probably caused by vasospasm—the

second exercise stress test was almost always the least abnormal. This is probably because of the inclusion/exclusion criteria of this study. All patients had ST segment elevation in the first exercise stress test and none had more than five anginal attacks per day. Under these conditions the second exercise stress test is more likely to give better results than the first one; also patients will be less anxious (a possible contributing factor to spasm) about a repeat test.

CLINICAL IMPLICATIONS

In the absence of previous myocardial infarction, elevation of the ST segment with exercise is considered to be specific for coronary spasm by some^{4,5} and a reliable marker of very severe fixed coronary artery disease by others.^{15,17,18} Both these views may need to be amended in the light of our findings. A negative repeated exercise stress test with a negative high dose dipyridamole echocardiography test strongly suggest that no haemodynamically significant stenosis is present,^{11,19} even if superimposed functional factors may transiently impair the exercise capacity.²⁰ Conversely, a dipyridamole induced ST segment elevation must imply the presence of physiologically, as well as anatomically, severe coronary stenosis, which probably also limits exercise capacity.

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