Influence of R wave analysis upon diagnostic accuracy of exercise testing in women

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SUMMARY Exercise electrocardiography in women with chest pain is associated with a high incidence of false positive ST segment depression. The recent observation that changes in R wave amplitude during exercise can also be used diagnostically may improve the value of stress testing in women. The results of 12 lead treadmill exercise and coronary angiography were reviewed in 62 women, mean age 51 years, presenting with "angina" without previous myocardial infarction. These were compared with exercise results in 14 healthy asymptomatic volunteers with a mean age of 26 years. In addition to conventional ST analysis, R wave amplitude changes during exercise, measured in leads II, III, aVF, and V4 to 6, were examined. While the sensitivity and specificity of ST and R wave changes were similar at about 67%, their combined interpretation was helpful. If both ST and R wave criteria were negative the predictive accuracy for normal coronary angiography was 94% (17/18). Alternatively, in tests showing both ST depression and an abnormal R wave response, coronary angiography was always abnormal (13/13). None of the normal volunteers developed ST segment depression and 93% (13/14) had a normal R wave response. If both were positive, however, coronary angiography was always abnormal (13/13).

Although stress test interpretation in women is difficult, R wave analysis is a useful adjunct to ST change and can improve the predictive accuracy of the test in a significant number of patients.

Conventional interpretation of an exercise electrocardiogram using ST segment analysis in women with chest pain may show many falsely positive tests when judged by the results of coronary angiography.¹⁻⁷ Women have a lower prevalence of occlusive disease, however,^{8, 9} and the use of coronary artery stenosis as the ultimate standard for comparison may be inappropriate. Small vessel disease, reduced coronary dilatory capacity, coronary spasm, inadequate arterial size, cardiomyopathy, abnormal oxygen dissociation, psychosomatic aetiology, and angiographic misinterpretation have been put forward to explain the association of angina-like chest pain and "normal" coronary arteries in women.^{1-7 10 11} Even though the prognosis of the syndrome is good,¹⁰ many women undergo coronary angiography, with the attendant risk of morbidity, to exclude coronary artery stenosis. There remains a requirement for improved non-invasive diagnosis in this difficult group of patients.

R wave amplitude decreases during the course of a

normal exercise test¹²⁻¹⁵ and it seemed possible that adding R wave analysis to conventional ST analysis would increase the diagnostic accuracy of stress testing in women. The object of this study was to examine the influence of R wave amplitude change on the interpretation of 12 lead treadmill exercise electrocardiograms in women admitted to the National Heart Hospital for coronary angiography during investigation for chest pain. All women having both exercise tests and angiography, without electrocardiographic evidence of previous myocardial infarction, were reviewed irrespective of their exercise performance to provide an evaluation of both the diagnostic criteria and the exercise test. The results were compared with those in a small group of healthy asymptomatic young women.

Subjects and methods

Since 1978, 275 women have undergone diagnostic 12 lead exercise testing at the National Heart Hospital. All women who had had cardiac catheterisation in addition were eligible for this study. We excluded

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Table 1 Exercise test results in 14 normal volunteers

Subject	Age (y)	Duration of exercise (min)	ΣR (rest)	ΣR (peak)	% ΔR	Peak heart rate
1	29	18	10.95	8.25	-25	188
2	23	15	7.8	4.65	-40	182
3	23	15	10.90	9.90	-9	150
4	25	14	3.75	4.60	+23*	188
5	21	12	9.40	7.80	-17	180
6	30	13	8.90	6.95	-22	160
7	23	12	3.10	1.20	-61	184
8	28	15	6.8	4.50	-34	164
9	27	17	8.25	7.80	-5	168
10	30	15	8.20	7.40	-10	122
11	21	14	10.80	8.35	-23	178
12	20	15	7.70	6.25	-19	172
13	24	15	5.20	3.90	-25	180
14	35	15	3.30	1.70	-48	180
Mean	26	14	7.50	5.95	-23	171
(SEM)	1	0.4	0.7	0.7	5	5

ΣR (rest)=six lead R wave sum (leads II, III, aVF, V4 to 6), recorded at rest in the erect position and expressed in mV.

ΣR (peak)=six lead R wave sum in the same leads at peak exercise.

% ΔR =(ΣR (rest)- ΣR (peak)) as percentage change from ΣR (rest).

*=Abnormal R wave response to exercise.

Table 2 Distribution of clinical findings related to presence or absence of coronary artery stenosis

Coronary artery disease (n=27)		No fixed coronary stenosis (n=35)
25 (93%)	Angina	23 (66%)
22 (81%)	Beta blockade	13 (37%)
13 (48%)	Normal electrocardiogram (at rest)	21 (60%)

those who had electrocardiographic evidence of prior myocardial infarction, conduction defects such as bundle-branch block or atrial fibrillation, and those taking digoxin, or with associated rheumatic or congenital heart disease, or hypertrophic cardiomyopathy.

Sixty two women, aged 29 to 64 (mean age 51 years), fulfilled the study criteria. They all presented with chest pain. Thirty four (55%) had a normal resting electrocardiogram, with the remainder showing only repolarisation changes. Forty eight (77%) were thought to have classical angina pectoris with the rest classified by the admitting physician as either probable or atypical angina. Thirty five (56%) had taken a beta blocking drug within 48 hours of the exercise test. The results were compared with the findings in 14 healthy asymptomatic female volunteers aged 21 to 35 (mean 27) years who were not taking drugs and in whom cardiovascular examination was normal.

EXERCISE TESTING AND INTERPRETATION

The 12 leads chosen were the same as for a standard electrocardiogram with the limb leads attached to the

trunk close to the limb in question. Recordings were made in the erect position at rest and at three minute intervals during exercise, at peak exercise, and every one to two minutes during recovery. The Bruce protocol was used, modified by the addition of a warm-up stage of 1 mph at 5% grade.¹⁶ Each electrocardiogram was recorded on a fully automated three channel recorder (either Cambridge Instruments model 3038 or Hewlett Packard model 1517). The recording equipment and exercise procedures complied with American Heart Association standards.^{17 18}

Each exercise test was examined without knowledge of the results of cardiac catheterisation. ST segment and R wave amplitude changes were analysed. ST change was considered positive if there was at least 0.1 mV horizontal or downsloping depression, from rest, for at least 80 ms after the J point. R wave amplitude was measured in six leads (II, III, aVF, V4 to 6) in each electrocardiogram and considered abnormal if the peak exercise six lead sum failed to show a 5% decrease when compared with the resting value. A fall in systolic blood pressure of 10 mmHg or more from the resting level during exercise was also regarded as a positive indicator of disease even without additional electrocardiographic abnormalities.

ANGIOGRAPHY

Left ventricular and coronary angiography were performed by the Sones technique. Stenosis of a major coronary artery was considered significant if there was greater than 50% narrowing of the diameter.

Results are expressed, where necessary, as mean ($\pm$ SEM) and analysis performed using χ^2 or Student's t test for paired and unpaired samples.

Table 3 Exercise test results using ST segment depression or R wave amplitude change alone or in combination

	True positive	False negative	True negative	False positive	Sensitivity	Specificity	Predictive accuracy Positive	Negative
ST depression	18	9	26	9	67%	74%	67%	74%
R wave change	18	9	23	12	67%	65%	60%	72%
ST -ve and R wave -ve		1*	17			49%		94%
ST +ve and R wave +ve	11			2†	41%		85%	

*Patient with non-dominant right coronary disease.

†Both patients with unprovoked coronary spasm during coronary angiography.

Table 4 Findings in 18 women showing both no ST segment depression and decreased R wave amplitude at peak exercise

Patient	Age (y)	Duration of exercise (min)	HRmax	ΣR (rest)	ΣR (peak)	% ΔR	ST	Angio
15	54	8	168	6.0	4.4	-27	—	N
16	50	12	190	7.45	5.55	-26	—	N
17	42	10.5	156	11.00	9.50	-14	—	N
18	52	12	155	7.25	6.40	-12	—	N
19	39	12.5	160	6.70	5.45	-19	—	N
20	51	7	156	4.65	3.45	-26	—	N
21	35	12	180	6.35	6.00	-6	—	N
22	29	10	132	10.10	9.50	-6	—	N
23	39	12	150	7.45	6.80	-11	—	N
24	43	11.5	152	7.70	6.15	-20	—	N
25	47	12	160	10.40	8.00	-23	—	N
26	54	11.5	160	2.10	1.75	-17	—	N
27	51	12	132	6.60	5.70	-14	—	N
28	33	6	85	4.20	3.90	-7	—	N
29	48	12	100	6.30	6.00	-5	—	N
30	43	12	160	7.50	6.80	-9	—	N
31	46	13	170	7.55	6.65	-12	—	N
32	57	10	120	6.50	6.10	-6	—	IVD
Mean (SEM)	45	10.9	149	6.99	6.01	-14		
	2	0.5	6	0.5	0.5	2		

HRmax = peak heart rate attained during exercise.

 ΣR (rest) = six lead R wave sum (leads II, III, aVF, V4 to 6), recorded at rest in the erect position and expressed in mV. ΣR (peak) = six lead R wave sum in the same leads at peak exercise.% ΔR = (ΣR (rest) - ΣR (peak)) as percentage change from ΣR (rest).

*Abnormal R wave response to exercise.

**Systolic hypotension at the end-point of exercise.

ST = Results of ST segment analysis at peak exercise.

— = Negative test.

A = Positive anterior (V2 to 4) ST depression.

L = Positive lateral (I, aVL, V5, V6) depression.

I = Positive inferior (II, III, aVF) depression.

Angio = Results of coronary angiography in each patient.

N = Normal.

1VD = Single vessel disease.

2VD = Double vessel disease.

3VD = Triple vessel disease.

AbLV = Abnormal ventriculogram, normal coronary angiography.

APT = Abnormal atrial pacing test.

PMV = Prolapse of mitral valve.

Spasm = Unprovoked variation of coronary calibre without demonstrable coronary stenosis.

Results

NORMAL VOLUNTEERS

These 14 normal women achieved a peak heart rate of 171 ± 5 bpm, with no evidence of ST segment depression. The average exercise duration was 14.6 ± 0.4 minutes. R wave amplitude decreased from 7.50 ± 0.7 mV at rest to 5.95 ± 0.7 mV at peak exercise ($t = 5.7$, $p < 0.001$). This mean decrease of the resting value

was 23%. All but one of the women showed decreased R wave height, ranging from 5 to 61% of the resting amplitude (Table 1).

PATIENTS

Twenty seven women had coronary artery stenosis (10 single vessel, eight double vessel, and nine triple vessel disease). Thirty five women had no evidence of fixed coronary artery stenosis on angiography, though

Table 5A Findings in 15 women without angiographic evidence of coronary stenosis having exercise test result showing either ST depression or abnormal R wave response

Patient	Age (y)	Duration of exercise (min)	HRmax	ΣR (rest)	ΣR (peak)	% ΔR	ST	Angio
33	57	7.5	146	6.00	6.10	0 *	—	N
34	43	9.0	176	3.10	3.10	0 *	—	N
35	54	12.5	160	5.90	5.90	0 *	—	N
36	53	7.0	74	9.10	8.30	- 9	I	N
37	43	15.0	142	6.40	5.20	-19	I	N
38	54	9.0	170	7.00	6.15	-12	I	N
39	59	9.0	130	4.45	5.00	+12 *	—	N
40	58	3.0	80	4.25	5.05	+19 *	—	N
41	59	1.5	130	5.90	6.20	+ 5 *	—	N
42	48	4.0	126	6.55	7.50	+15 *	—	N
43	58	8.0	100	5.95	6.30	+ 6 *	—	AbLV
44	47	12.0	85	3.60	3.30	- 8	L	APT
45	56	9.5	156	5.00	5.40	+ 8 *	—	APT
46	48	9.5	130	11.70	9.30	-21	I	APT
47	51	12.0	145	10.50	9.60	-10	IL	PMV
Mean (SEM)	53 6	9.5 0.9	130 8	6.36 0.6	6.16 0.5	- 1 3		

HRmax = peak heart rate attained during exercise.

ΣR (rest) = six lead R wave sum (leads II, III, aVF, V4 to 6), recorded at rest in the erect position and expressed in mV.

ΣR (peak) = six lead R wave sum in the same leads at peak exercise.

% ΔR = (ΣR (rest) - ΣR (peak)) as percentage change from ΣR (rest).

*Abnormal R wave response to exercise.

**Systolic hypotension at the end-point of exercise.

ST = Results of ST segment analysis at peak exercise.

- = Negative test.

A = Positive anterior (V2 to 4) ST depression.

L = Positive lateral (I, aVL, V5, V6) depression.

I = Positive inferior (II, III, aVF) depression.

Angio = Results of coronary angiography in each patient.

N = Normal.

1VD = Single vessel disease.

2VD = Double vessel disease.

3VD = Triple vessel disease.

AbLV = Abnormal ventriculogram, normal coronary angiography.

APT = Abnormal atrial pacing test.

PMV = Prolapse of mitral valve.

Spasm = Unprovoked variation of coronary calibre without demonstrable coronary stenosis.

Table 5B Findings in 16 women with proven coronary stenosis and exercise test showing either ST depression or abnormal R wave response

Patient	Age (y)	Duration of exercise (min)	HRmax	ΣR (rest)	ΣR (peak)	% ΔR	ST	Angio
48	47	10	100	8.30	7.40	-11	IL	1VD
49	48	6	75	6.70	6.50	- 3 *	—	1VD
50	46	8	150	7.35	7.35	0 *	—	1VD
51	44	7	155	5.60	5.20	- 7	I	1VD
52	50	13.5	145	3.65	2.90	-21	IL	1VD
53	57	6	92	6.70	8.40	+25 *	—	1VD
54	50	6	96	11.55	11.65	0 *	—	1VD
55	58	7	98	8.15	6.50	-20	IL	2VD
56	58	5.5	145	2.70	1.70	-37	L	2VD
57	58	10	132	7.10	5.40	-24	IL	2VD
58	38	15	122	6.20	5.70	- 8	IL	2VD
59	59	5	60	7.35	7.35	0 **	—	2VD
60	63	9	90	10.10	10.60	+ 5 *	—	2VD
61	56	6	78	2.45	1.85	-24	I	3VD
62	63	10	90	5.30	5.90	+11 *	—	3VD
63	55	4	80	7.65	7.65	0 **	—	3VD
Mean (SEM)	53 7	8 0.8	107 8	6.68 0.60	6.38 0.70	- 7 4		

For explanation to abbreviations see footnote to Table 5A.

seven (20%) showed other abnormalities comprising severe coronary spasm in two, abnormal left ventriculography in one, mitral prolapse without regurgitation in one, and an abnormal pacing stress test (ST depression and chest pain or raised left ventricular end-diastolic pressure) in three patients (of four who had an atrial pacing test). The distribution of clinical findings related to the results of angiography is shown in Table 2.

EXERCISE TEST

The sensitivity and specificity of ST or R wave changes were lower than we would expect from exercise testing of our typical hospital population,¹⁹ and the predictive values of 60 to 70% are not clinically useful (Table 3). When both criteria were employed, that is with both negative ST and reduced R wave amplitude in the same test, there was a 94% predictive accuracy for normal coronaries though specificity was only 49%. Likewise, the doubly positive test had a low sensitivity but a high predictive accuracy (Table 3).

Individual results for all the patients are shown in Tables 4, 5, and 6, arranged according to the findings

of the exercise test. Of the 18 test results fulfilling both negative criteria, 17 had normal coronary angiography, with the remaining patient having non-dominant right coronary disease (Table 4). The results in this group are similar to those in the normal volunteers (Table 1) with the significantly lower exercise duration (10.9 ± 0.5 versus 14.6 ± 0.4 min, $p < 0.001$) and maximum heart rate (149 ± 6 versus 171 ± 5 , $p < 0.01$) reflecting the difference in age between the two groups.

In contrast, the remaining patients shown to have no coronary stenosis had either an abnormal R wave response (in nine) or "false" ST segment depression (in six women) (Table 5a). Five patients in this subgroup had abnormalities other than coronary stenosis. The abnormal R wave response was not the result of a poor chronotropic response as the mean peak heart rate in those nine patients was 134 ± 10 which is $86\% \pm 6\%$ of the predicted age related maximum.

Sixteen (59%) of those with coronary disease had either ST depression or an abnormal R wave response to exercise (Table 5b). Comparison of Tables 5a and 5b shows significant difference only with respect to

Table 6 Findings in 13 women with exercise tests showing both ST depression and abnormal R wave amplitude change

Patient	Age (y)	Duration of exercise (min)	HRmax	ΣR (rest)	ΣR (peak)	% ΔR	ST	Angio
64	55	10.0	82	5.30	5.20	- 2 *	IL	Spasm
65	52	7.5	122	10.50	10.40	- 1 *	IL	Spasm
66	59	6.0	110	4.70	5.00	+ 6 *	IL	1VD
67	64	8.0	78	11.60	12.10	+ 4 *	L	1VD
68	48	7.0	135	4.55	6.05	+33 *	AIL	1VD
69	63	12.0	70	10.35	10.05	- 3 *	L	2VD
70	53	8.5	166	5.85	5.90	+ 1 *	L	2VD
71	56	9.5	104	4.80	6.05	+26 *	L	3VD
72	49	8.0	112	8.80	9.05	+ 3 *	L	3VD
73	56	10.0	135	3.65	4.70	+29 *	IL	3VD
74	54	12.0	110	4.50	7.20	+60 *	IL	3VD
75	53	5.0	118	1.40	1.65	+18 *	AIL	3VD
76	63	9.0	82	5.70	5.60	- 2 *	AIL	3VD
Mean (SEM)	56 (5)	8.7 (0.6)	110 (8)	6.28 (0.80)	6.84 (0.80)	+13 (5)		

For explanation to abbreviations see footnote to Table 5A.

Table 7 Results of conventional ST analysis in this study compared to previous published reports

Reference	Ex	Electrocardiogram	ST	N	Sensitivity	Specificity	Predictive accuracy Positive	Predictive accuracy Negative
This study	T	12L	0.1	62	67%	74%	67%	74%
Weiner <i>et al.</i> ⁹	T	12L	0.1	526	76%	61%	49%	86%
Barolsky <i>et al.</i> ⁷	T	Orth	0.1	66	55%	95%	45%	77%
Detry <i>et al.</i> ⁴	B	12L	0.1	53	88%	81%	68%	94%
			0.2	53	23%	97%	80%	73%
Reuben <i>et al.</i> ⁶	T	CM5	0.1	253	47%	62%	41%	64%
Sketch <i>et al.</i> ²	T	12L	0.1	56	45%	78%	33%	85%
Linhardt <i>et al.</i> ¹	T	12L	0.1	98	71%	78%	52%	89%

Ex = Exercise test used: T, treadmill; B, bicycle.

Electrocardiogram = Electrocardiograph lead system (12L=12 lead, orth=X, Y, Z leads).

ST = Degree of ST depression used in the study in mV.

the maximum heart rate (130 ± 8 versus 107 ± 8 , $p < 0.05$). Two women showed exercise-induced hypotension without ST change during exercise and both had severe coronary disease. Five of the six women with coronary disease and no ST depression had a low peak heart rate which may, in some, account for the "abnormal" R wave response.

All 13 patients showing both ST and R wave abnormal tests had abnormalities shown on angiography, though only 11 (85%) had significant coronary stenosis (Table 6). Two showed severe unprovoked coronary spasm.

Discussion

The diagnosis of coronary artery disease in women with chest pain is difficult as even classical angina may not be diagnostic.⁹ Though the poor predictive accuracy of tests in women may reflect a lower prevalence of coronary disease^{8 9 20} a "positive" exercise test is associated with an increased risk for future sudden death or myocardial infarction, albeit less than that for such a result in men.²¹ Previous authors have underlined the limitations of ST segment interpretation in women (Table 7). Normal angiography at rest does not necessarily relate to cardiac function at peak exercise and many patients remain symptomatic despite reassurance that all is "normal".²²

The results of standard ST segment interpretation in this study are similar to previous work showing a test sensitivity and specificity of about 70% (Table 7). R wave analysis usefully increased predictive accuracy in many women though the results were insufficient to provide correct interpretation in all. The overall effect of combined ST and R wave analysis is to identify reliably two subgroups of women. Firstly those with a doubly negative test (no ST depression and reduced R wave amplitude at peak exercise) are most unlikely to have coronary artery disease. The only patient with such a result and abnormal coronary angiography had non-dominant right coronary disease of little clinical significance (Tables 1 and 4). Secondly the doubly positive test is highly likely to occur with coronary disease (Table 6). These two subgroups accounted for half the subjects studied.

The decrease in R wave amplitude during exercise in normal subjects has been widely reported and the phenomenon confirmed using several different electrocardiographic lead systems. The R wave decreases as heart rate increases, though the absolute change is not predictable in an individual. Of our 14 normal volunteers, 13 showed a 5% to 94% decrease from rest to peak exercise. The mechanism for R wave change is both complex and controversial and a definitive explanation has yet to be proposed, though changes in cardiac volume have been related both in theory and

practice.²³⁻²⁵ There is therefore a good basis for accepting reduced R wave amplitude on exercise, certainly treadmill exercise,¹²⁻¹⁵ as a criterion for a normal test.

Increased or unchanged R wave amplitude at peak exercise is less well recognised as an index of abnormality,²⁶⁻²⁸ though other workers have found it extremely predictive of coronary disease in men.¹²⁻¹⁵ In this study it was only highly predictive of coronary disease if it was associated with ST segment depression (Table 6). Ischaemia may alter the QRS wave directly or produce a secondary change with increased intracardiac volume and the resultant effect in an individual will depend upon the resting electrocardiographic pattern and relative interplay of these two mechanisms. This may explain why some patients with pronounced ST depression show reduced R wave amplitude and vice versa.

Changing the percentage R wave decrease necessary to denote abnormality would alter specificity with reciprocal effect on sensitivity just as it would for ST segment change. Patients with a low heart rate response (Table 5b) often showed an unexpected increase in amplitude, perhaps reflecting increased left ventricular volume. Even if these patients are not "ischaemic" at the end of exercise the absence of a satisfactory chronotropic response represents a significant difference from the normal population.⁷ Beta blockade will reduce the peak heart rate attained during an exercise test but does not of itself cause a change in the rate-R wave relation.

For women with either ST or R wave positive tests there was no reliable predictive accuracy for the presence of coronary stenosis (Tables 5a and b). Within this subgroup many showed abnormalities other than coronary disease but we stress that in this retrospective review no systematic additional studies (for example atrial pacing test) had been performed. Ergometrine was not administered to any of these women. Ellestad and colleagues³ found only 13% of a selected group of 95 men and women with "false positive" tests to be entirely normal. In our patients seven (41%) of the 17 with "false positive" tests had abnormalities other than coronary stenosis: three had an abnormal atrial pacing test (ST depression with associated chest pain and elevation of left ventricular end-diastolic pressure), one had an abnormal left ventriculogram, one had significant mitral prolapse without regurgitation, and two had severe unprovoked coronary artery spasm unrelated to either the catheter tip or identifiable coronary disease. These abnormalities may be the underlying cause of the chest pain in the patients concerned. Indeed, by implication, patients with either abnormal ST or R wave amplitude responses and "normal" coronary arteries are more likely to have an underlying abnormal-

malities other than coronary artery stenosis. An exercise test may therefore be as accurate a diagnostic test as a coronary angiogram in women presenting with chest pain.

Of all those undergoing angiography for chest pain, 10 to 30% have ostensibly normal coronary arteries. In women, especially young women, however, as few as one-quarter have demonstrable stenoses.⁸ As this study indicates that a double negative (normal ST segment and reduced R wave at peak exercise) treadmill exercise test is a good predictor for normal coronaries many women presenting with chest pain can be reassured without recourse to coronary angiography. Women with abnormal exercise tests and yet "normal" coronary angiography are a heterogeneous group, with several possible underlying aetiologies. It is this subgroup of women, in our consecutive series being about one-quarter of those investigated, that requires careful follow-up and future study if the chest pain persists.

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