Heart 1996;**76**:156–160

Women with chest pain: is exercise testing worthwhile?

Nicholas Curzen, Deven Patel, Debbie Clarke, Christine Wright, David Mulcahy, Ann Sullivan, Diana Holdright, Kim Fox

Abstract

***Objective*—To determine the diagnostic value of the exercise tolerance test (ETT) in women presenting with chest pain.**

***Design*—Prospective study of all women presenting to a centre with chest pain between 1987 and 1993 who were assessed by an ETT and coronary angiography.**

***Setting*—The outpatient clinic of one consultant cardiologist in a tertiary referral centre.**

***Patients*—All women referred to this outpatient clinic with chest pain were screened. For inclusion, patients had to perform ETT and undergo coronary angiography. Of the 347 referred during this period, 142 were excluded because they were unable to perform ETT or because of Q waves or other abnormalities on their resting electrocardiogram.**

***Results*—Overall the sensitivity of the ETT was 68% and the specificity was 61%, with a positive predictive value of 0·61 and a negative predictive value of 0·68. There were 42 false positive and 31 false negative ETT results (36% of the study group). The predictive value of a negative test was higher in younger women (< 52 years) than in the older group (≥ 52 years) (P = 0·004), but the positive predictive value in the two groups was not significantly different. The predictive value of a negative test was also higher in those with two or fewer risk factors than in those with three or more risk factors (P = 0·001). The negative predictive value for those women above 52 years with three or more risk factors (24% of the study group) was only 0·25. Lack of chest pain during ETT was associated with a higher negative predictive value in the younger group than in the older women (P = 0·006).**

***Conclusions*—In women with chest pain use of the ETT was a misleading predictor of the presence or absence of coronary disease in 36% of these patients. In particular, a negative test in older women with three or more risk factors had a very low predictive value. The inclusion of risk factors and division by age can, however, be used to identify a population at intermediate risk for coronary artery disease in whom the ETT result has the highest diagnostic utility.**

(*Heart* 1996;**76**:156–160)

Keywords: exercise test; women; chest pain; coronary angiography.

Department of Cardiology, Royal Brompton Hospital, Sydney Street, London
N Curzen
D Patel
D Clarke
C Wright
D Mulcahy
A Sullivan
D Holdright
K Fox

Correspondence to:
Dr N Curzen, Department of Cardiology, Royal Brompton Hospital, Sydney Street, London SW3 6NP.

Accepted for publication 24 January 1996

Coronary disease is a common cause of morbidity and mortality in women, and is the commonest cause of death in those over the age of 65 years.[1] According to the Framingham study[2] the prevalence of coronary artery disease in younger women is lower than in men, but the death rates of the two sexes converge in late middle age. Women with chest pain account for a considerable proportion of cardiological referrals.[3]

Exercise testing has been a widely used screening procedure for the assessment of cardiac status for over 30 years. None the less, the value of this procedure in the screening of women to predict the presence of obstructive coronary disease has been the subject of considerable controversy.[4-8] The usual electrocardiographic criteria applied in exercise testing seem less valuable in women than in men.[4-7] In symptom free women "significant" ST segment changes are up to three times more common than in men.[9] In addition, symptomatic women with a positive exercise tolerance test (ETT) have a lower prevalence of coronary artery disease and fewer coronary events than men.[10,11] We have previously shown that a diagnosis of normal coronary arteries was five times more likely in women referred with chest pain than in a matched population of men.[12] To a great extent, the apparent differences in predictive accuracy between men and women reflect not much more than a clinical proof of Bayes theorem, whereby the predictive accuracy of a test is dependent on the prevalence of the disease in the population being studied. It has also been suggested, however, that in patients with chest pain the higher positive predictive value of exercise testing in men compared with women cannot be fully explained by a difference in disease prevalence.[8] In current clinical practice the ETT result is a key factor in the decision to perform an invasive investigation and unless coronary angiography were without significant risk or cost it could not become the primary diagnostic test for patients with chest pain.

The aim of this study was to describe the results of exercise testing as a diagnostic test for the presence or absence of coronary disease in women. We aimed to identify subgroups of women in whom ETT was especially useful or particularly misleading.

Patients and methods

We screened all women referred to one cardiologist's outpatient clinic with chest pain who underwent coronary angiography over the

period 1987–1993. All women included in the study had both an ETT and coronary angiography. Exclusion criteria included pathological Q waves or left or right bundle branch block on the electrocardiogram at presentation; organic valvar or congenital heart disease; previous angiographically documented coronary artery disease; and inability to perform ETT, either because of disability or symptoms. The presence of recognised risk factors for coronary disease, including a family history (first degree relative with coronary artery disease), diabetes mellitus (diet or drug controlled), hypertension, raised cholesterol (random total cholesterol $\geqslant$ 6·5 mmol/l, or taking lipid lowering medication), or smoking (at the time of referral) was documented for all patients. When risk factor profiles were incomplete, follow up was undertaken using notes from other hospitals and GPs or by asking the patients. We analysed electrocardiograms (ECG) obtained at the original referral or at the first consultation at this centre. All exercise ECGs were analysed in this department, and were regarded as positive when they showed horizontal or downsloping ST segment depression of 1 mm from the baseline 80 ms after the J point. Coronary angiograms were analysed by the same consultant cardiologist throughout, and coronary artery disease was diagnosed when there was luminal stenosis greater than 50% of any epicardial coronary artery.

ANALYSES

The following formulae were applied to the test results:

Sensitivity = true positives/(CAD+)
Specificity = true negatives/(CAD−)
Positive predictive value = true positives/(ETT+)
Negative predictive value = true negatives/(ETT−)

where (CAD+) is the number of patients with coronary disease, (CAD−) is the number of patients with normal coronary arteries, (ETT+) is the number of patients with a positive ETT, and (ETT−) is the number of patients with a negative ETT.

The predictive value of a test represents the frequency with which the test result matches that of the disease state.

For more detailed analysis, women were divided into two age groups: less than 52 years and 52 years and above. This division is arbitrary, but takes account of data from the Nurses' Health Study[13] of 121 700 women, in whom the median age for the menopause ranged from 52·4 years in non-smokers to 50·4 years in heavy smokers. Women were also subdivided according to how many of the five risk factors they had, as well as by the presence of chest pain at ETT.

Statistical analysis was undertaken using the χ^2 test, with Fisher's exact test for groups with sample numbers of five or less.

Results

ALL WOMEN

Three hundred and forty seven women were referred for coronary angiography between 1987 and 1993, representing 23% of all patients with stable symptoms undergoing diagnostic angiography during this period. A total of 142 of these women were excluded (92 had no ETT, 35 had pathological Q waves, 15 had incomplete risk factor profiles). Thus 205 women were included in the study (table 1), of whom 96 had coronary artery disease (47%) and 107 (52%) had a positive ETT. A hundred and twenty six (61%) ETTs were performed according to the standard Bruce protocol and the remaining 79 were modified Bruce. The specificity and sensitivity of exercise testing in all women were 61% and 68% respectively. The positive predictive value was 0·61, and negative predictive value was 0·68 (table 2).

When the 205 women were subclassified according to risk factors (figure), the predictive values for the test were different (table 2). While the positive predictive values for women with less than three risk factors, and those with three or more risk factors were not significantly different (0·56 *v* 0·67), the negative

Table 1 Details of study population

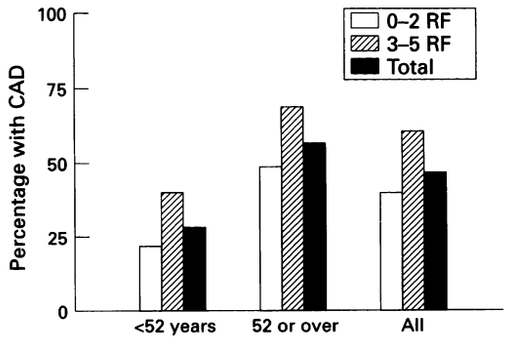
Total	205
Mean age at cardiac catheter (yr)	56·6 (range 25-93)
CAD:	
One vessel	35
Two vessel	31
Three vessel	30
Risk factors:	
Family history	123 (60%)
Hypertension	83 (40%)
Raised cholesterol	114 (56%)
Smoker	75 (37%)
Diabetes	15 (7%)
None	21 (10%)
1RF	47 (23%)
2RF	65 (32%)
3RF	46 (22%)
4RF	10 (10%)
5RF	3 (1%)

Percentage figures given in brackets are for the whole study group.

Table 2 Exercise test results in all women (n = 205)

	No. of risk factors		
	All (n = 205)	*0–2 (n = 136)*	*$\geqslant$ 3 (n = 69)*
Specificity (%)	61	63	56
Sensitivity (%)	68	76	57
Pos PV	0·61	0·56	0·67
Neg PV	0·68	0·80	0·45**

**P = 0·001 for 0–2 *v* $\geqslant$ 3 RF groups.
PV, predictive value; pos, positive; neg, negative.



Percentage of women with coronary artery disease according to risk factors (RF) and age.

Table 3 Exercise test results in all women according to presence or absence of pain during test

	Chest pain (n = 80)	*No chest pain (n = 125)*
Specificity (%)	64	60
Sensitivity (%)	86	56
Pos PV	0·71*	0·53*
Neg PV	0·78	0·64

*P = 0·08.
PV, predictive value; pos, positive; neg, negative.

predictive value was 0·80 in the lower risk factor group and only 0·45 in the others (P = 0·001). Eighty women had chest pain during the ETT, of whom 48 (60%) had significant ST segment depression (table 3). Fifty nine (47%) of the 125 patients who were pain free had a positive test. The specificity for the exercise test in those with chest pain was 64% and the sensitivity was 86%, compared with 60% and 56% respectively in the pain-free group. The positive predictive value was higher in those with chest pain compared with those with no pain (0·71 *v* 0·53 respectively), although this did not reach statistical significance (P = 0·08). There was also a trend of higher negative predictive value in the pain group (0·78) than in the pain-free patients (0·64).

YOUNGER WOMEN (< 52 YEARS)
There were 69 women in this group (table 4) of whom only 28% (19) had coronary disease. The positive predictive value was 0·46, and the negative predictive value 0·85. Predictive values in the two risk groups were not significantly different.

Twenty eight of these women (41%) had chest pain at exercise and the remaining 41 (59%) did not (table 5). In those with chest pain, 10 had positive ETT and nine had coronary artery disease, so that the positive predictive value was 0·6, with a negative predictive value of 0·83. In those with no pain 18 (44%) had positive tests and 10 had coronary disease. The positive predictive value was only 0·39 and the negative predictive value was 0·87. Again these results were not significantly different.

OLDER WOMEN (⩾ 52 YEARS)
Seventy seven (57%) of the 136 women in this group had coronary artery disease. This was significantly higher than in the younger group (P < 0·001). The positive predictive value was 0·66 and negative predictive value 0·56 (table 4). This negative predictive value was significantly lower than for the younger women (P = 0·004). The negative predictive value was very low for those with three or more risk factors (0·25) compared with those with two or fewer (P = 0·001). The positive predictive value was, however, the same for both risk factors groups.

Fifty two of this group had chest pain (38%) during the test and 84 did not (table 5). The positive predictive value for those with pain was 0·74 and the negative predictive value was 0·71. In the pain-free subgroup the values were 0·59 and 0·51 respectively. The negative predictive value in those with no chest pain was significantly lower than for the same subgroup in the younger women (0·51 *v* 0·87, P = 0·006).

Table 4 Exercise results in women divided according to age and number of risk factors

	Less than 52 years (n = 69)			*52 years or older (n = 136)*		
	No risk factors					
	All	*0–2 (n = 49)*	*⩾ 3 (n = 20)*	*All*	*0–2 (n = 87)*	*⩾ 3 (n = 49)*
ETT+	28	21	7	79	50	29
ETT−	41	28	13	57	37	20
CAD+	19	11	8	77	43	34
CAD−	50	38	12	59	44	15
Specificity (%)	70	66	83	54	61	33
Sensitivity (%)	68	73	63	68	77	56
Pos PV	0·46	0·38	0·71	0·66	0·66	0·66
Neg PV	0·85*	0·89	0·77†	0·56*	0·73‡	0·25†‡

*P = 0·004.
†P = 0·008.
‡P = 0·001.

Table 5 Exercise test results in women divided according to age and chest pain at exercise

	Younger (< 52 yr)		*Older (⩾ 52 yr)*	
	Chest pain (n = 28)	*No chest pain (n = 41)*	*Chest pain (n = 52)*	*No chest pain (n = 84)*
Specificity (%)	79	65	50	56
Sensitivity (%)	67	70	88	53
Pos PV	0·60	0·39	0·74	0·59
Neg PV	0·83	0·87*	0·71	0·51*

*P = 0·006.

Discussion

Although coronary artery disease is common in women, presentation with chest pain is much more common. Identifying those with coronary artery disease among women with chest pain is a common clinical problem. The ETT has become one of the main methods used to evaluate women with chest pain, and to decide who should undergo further investigation. It is simple to perform, widely available, and the mortality is low.[14 15] However, if conventional ECG criteria alone are used women have a high false positive rate.[4 8] So although the sensitivity of the ETT is generally shown to be as good as in men,[5 12 16 17] the specificity is lower. Another disadvantage as a screening procedure is that a significant proportion of patients will not be suitable for the test and this was well illustrated by our study in which 27% (92 of 347) of patients did not have a test. These problems may contribute to the selection bias that exists against women when referral for coronary angiography is being considered.[18 19] Unfortunately, practical and financial considerations prevent the use of tests such as nuclear imaging, which has greater sensitivity and specificity,[16 17 20] as the universal method for investigating these patients.

This study set out to identify which subgroups of women referred to a tertiary referral centre for assessment of their chest pain benefit most from exercise testing as a means of deciding who should undergo coronary angiography. One limitation of the study is that it is based on a "selected" population, because we are unable to take into account

those women who had ETT and were not referred to our centre.

Overall, the sensitivity of exercise testing (68%) compares favourably with our previous results in women[12] although the specificity of the test was even lower (61%) than in our previous observations (71%). From the 205 women there were 42 false positive ETT results and 31 false negative results, which means that management decisions based on this test alone would have been inappropriate in 36% (73 of 205) of the patients.

Further analysis was therefore aimed at identifying subgroups of patients in whom the exercise data were either especially useful at predicting the presence of coronary disease or in whom they were particularly poor. Comparisons of predictive values were deemed the most appropriate, because this value represents the frequency with which the test result matches the disease prevalence. It is well established that risk factors, including hypercholesterolaemia,[21] hypertension,[22] diabetes mellitus,[23] smoking[24] and family history[25] are associated with increased incidence of coronary disease. We therefore divided the patients into two risk factor groups. This division was arbitrary, but its suitability was demonstrated by the finding that for the whole population, the predictive value for a negative test in women with fewer risk factors was significantly different from that of patients with a higher risk factor load (0·80 *v* 0·45, P = 0·001), and in all our groups a cumulative increase in risk factor load correlated with the risk of coronary disease (figure). Likewise, the classification of the women by age (coinciding with the national mean age for the menopause) confirmed that the prevalence of coronary disease was significantly higher in the older women. In addition, the predictive value of a negative exercise test was much higher in the younger women than in the older age group (0·85 *v* 0·56, P = 0·004). This confirms Bayesian principles, but emphasises the low clinical value of a negative test in the older group. Furthermore, in the older cohort of patients, the negative predictive value was so low in the group with at least three risk factors (0·25) that it should not deter referral for further investigation. This is an important finding, applying as it does to 24% (49 of 205) of our total population. By contrast, the negative predictive value in the older, low risk factor group was as high as in all the women put together. The difference between the predictive value of a negative ETT in older women with less than three risk factors is significant compared with the higher risk factor group (P = 0·001), and referral for invasive assessment should therefore be altered appropriately. In younger women, the predictive value of a negative exercise test was not significantly affected by risk factor load.

The positive predictive value was not significantly different in any group. In fact, as would be predicted by Bayes theorem, in the younger women with fewer risk factors the positive predictive value (0·38) was lower than in the remaining younger patients (0·71), but this difference did not reach statistical significance (P = 0·27). The number of patients in this group is small (49), but the positive predictive value is so low that it may be appropriate to offer them further non-invasive assessment before angiography or not to embark on exercise tests at all.

Overall, the presence of chest pain at exercise did result in a higher positive predictive value (P = 0·08 for pain group *v* no pain), and the same trend was maintained after division by age; but these differences did not reach significance. Our study was therefore unable to confirm the clinical suspicion that the presence of chest pain during a positive exercise test improves its predictive power, although a much larger study could answer this question with greater confidence. The absence of pain in a negative test, however, was associated with a much higher negative predictive value in the younger women than in the older group (0·87 *v* 0·51, P = 0·006). The confidence with which a negative test can be used to predict absence of coronary disease would therefore be much higher in younger women with no pain than in the equivalent older group.

This study confirms that the use of the exercise test as a diagnostic procedure for women with chest pain is flawed in two fundamental respects. Firstly, many women (27%) were unsuitable for conventional exercise testing. Secondly, in 36% of the group who underwent ETT, simple ECG criteria would have lead to inappropriate management if this had been the sole element in decision-making. Our study has highlighted that the negative test result is a good predictor of the absence of coronary disease in younger women, but a poor predictor in the older group. The value of a negative test in the older women with a high risk factor load is so low that the test is not worthwhile as a predictive tool. In addition, the predictive value of a positive ETT in younger women with few risk factors is very low, possibly even to the point where this test may not be appropriate.

The exercise test remains a worthwhile tool in many women with chest pain, but its value is dependent on stratification of the population. A larger study is now needed to provide sufficient statistical power for an analysis matching individual risk factors and the exercise test result. Such a study would be of widespread clinical value.

NC is a Medical Research Council Training Fellow.

1 Office of population censuses and surveys monitor 1992, DH2 92/2.
2 Lerner DJ, Kannel WB. Patterns in coronary heart disease—morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. *Am Heart J* 1986; **111**:383–90.
3 Coronary Prevention Group, British Heart Foundation Statistics Database. *Coronary heart disease statistics 1991*. London: Coronary Prevention Group, 1991:30.
4 Sketch MH, Mohiuddin SM, Lynch JD, Zencka AE, Runco V. Significant sex differences in the correlation of electrocardiographic exercise testing and coronary arteriograms. *Am J Cardiol* 1975;**36**:169–73.
5 Detry J-MR, Kapita BM, Cosyns J, Sottiaux B, Brasseur LA, Rousseau MF. Diagnostic value of history and maximal exercise electrocardiography in men and women suspected of coronary heart disease. *Circulation* 1977;**56**: 756–61.
6 Val PG, Chaitman BR, Waters DD, Bourassa MG, Scholl

J-M, Ferguson RJ, Wagniart P. Diagnostic accuracy of exercise ECG lead systems in clinical subsets of women. *Circulation* 1982;**65**:1465–74.
7 Kuhn FE, Rackley CE. Coronary artery disease in women: risk factors, evaluation, treatment, and prevention. *Arch Intern Med* 1993;**153**:2626–36.
8 Barolsky SM, Gilbert CA, Faruqui A, Nutter DO, Schlant RC. Differences in electrocardiographic response to exercise of women and men: a non-Bayesian factor. *Circulation* 1979;**60**:1021–7.
9 Koppes G, Mckiernan T, Bassan M, Froelicher VF. Treadmill exercise testing, part II. *Current Probl Cardiol* 1977;7:1–45.
10 Manca C, Dei Cas L, Albertini D, Baldi G, Visioli O. Different prognostic value of exercise electrocardiogram in men and women. *Cardiology* 1978;**63**:312.
11 Allen WH, Aronow WS, Goodman P, Stinson P. Five-year follow-up of maximal treadmill stress test in asymptomatic men and women. *Circulation* 1980;**62**:522.
12 Sullivan AK, Holdright DR, Wright CA, Sparrow JL, Cunningham D, Fox KM. Chest pain in women: clinical, investigative, and prognostic features. *BMJ* 1994;**308**: 883–6.
13 Willett W, Stampfer MJ, Bain C, Lipnick R, Speizer FE, Rosner B, *et al.* Cigarette smoking, relative weight, and menopause. *Am J Epidemiol* 1983;**117**:651–8.
14 Rochmis P, Blackburn H. Exercise tests: a survey of procedures, safety, and litigation experience in aproximately 170,000 tests. *JAMA* 1971;**217**:1061–6.
15 Stuart RJ, Ellestad MH. National survey of exercise stress testing facilities. *Chest* 1980;**77**:94–7.
16 Hung J, Chaitman BR, Lam J, *et al.* Noninvasive diagnostic test choices for the evaluation of coronary artery disease in women: a multivariate comparison of cardiac fluoroscopy, exercise electrocardiography and exercise thallium myocardial perfusion scintigraphy. *J Am Coll Cardiol* 1984;**4**:8–16.
17 Melin JA, Wijns W, Vanbutsele RJ, Robert A, De Coster, Brasseur LA, *et al.* Alternative diagnostic strategies for coronary artery disease in women: demonstration of the usefulness and efficiency of probability analysis. *Circulation* 1985;**71**:535–42.
18 Steingart RM, Packer M, Hamm P, Coglianese ME, Gersh B, Geltman EM, *et al.* Sex differences in the management of coronary artery disease. *N Engl J Med* 1991;**325**:226–30.
19 Jackson G. Coronary artery disease in women. *BMJ* 1994; **309**:555–6.
20 Tavel ME. Specificity of electrocardiographic stress test in women versus men. *Am J Cardiol* 1992;**70**:545–547.
21 Kannel WB. Metabolic risk factors for coronary heart disease in women: perspectives from the Framingham study. *Am Heart J* 1987;**114**:413–19.
22 Stokes AJ, Kannel WB, Wolf PA, Cupples LA, D'Agostino RB. The relative importance of selective risk factors for various manifestations of cardiovascular disease among men and women from 35 to 64 years old: 30 years of follow up in the Framingham study. *Circulation* 1987;**75** (suppl):65–73.
23 Kannel WB, McGee DL. Diabetes and cardiovascular disease. *JAMA* 1979;**241**:2035–2038.
24 Willett WC, Green A, Stampfer MJ, Speizer FE, Colditz GA, Rosner B, *et al.* Relative and absolute risks of coronary heart disease among women who smoke cigarettes. *N Engl J Med* 1987;**317**:1303–09.
25 Colditz GA, Stampfer MJ, Willett WC, Rosner B, Speizer FE, Hennekens CH. A prospective study of parental history of myocardial infarction and coronary heart disease in women. *Am J Epidemiol* 1986;**123**:48–58.