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Female False Positive Exercise Stress ECG Testing – Fact Verses Fiction

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Background Exercise stress testing is a well validated cardiovascular investigation. Accuracy for treadmill stress electrocardiograph (ECG) testing has been documented at 60%. False positive stress ECGs (exercise ECG changes with non-obstructive disease on anatomical testing) are common, especially in women, limiting the effectiveness of the test. This study investigates the incidence and predictors of false positive stress ECG findings, referenced against stress echocardiography (SE) as a standard.

Methods Stress echocardiography was performed using the Bruce treadmill protocol. False positive stress ECG tests were defined as greater than 1 mm of ST depression on ECG during exertion, without pain, with a normal SE. Potential causes for false positive tests were recorded before the test.

Results 3000 consecutive negative stress echocardiograms (1036 females, 34.5%) were analysed (age 59+/-14 years. False positive (F+) stress ECGs were documented in 565/3000 tests (18.8%). F+ stress ECGs were equally prevalent in females (194/1036, 18.7%) and males (371/1964, 18.9%, p = 0.85 for the difference). Potential causes (hypertension, left ventricular hypertrophy, known coronary disease, arrhythmia, diabetes mellitus, valvular heart disease) were recorded in 36/194 (18.6%) of the female F+ ECG tests and 249/371 (68.2%) of the male F+ ECG tests ($p < 0.0001$ for the difference).

Conclusions These data suggest that F+ stress ECG tests are frequent and equally common in women and men. However, most F+ stress ECGs in men can be predicted before the test, while most in women cannot. Being female may be a risk factor in itself. These data reinforce the value of stress imaging, particularly in women.

Keywords Stress testing • Stress echocardiography • Female • False positive • Predictors

Introduction

Stress electrocardiographic (ECG) testing is a well validated method for assessing cardiovascular status and to investigate for a variety of cardiovascular conditions, including myocardial ischaemia. Diagnostic accuracy for the detection of inducible coronary ischaemia has been previously documented at only 60% [1–5]. This has been largely driven by false positive ECG

Abbreviations: AS, aortic stenosis; BMI, body mass index; CT, computerised tomography; ECG, electrocardiograph; ETT, exercise treadmill test; F+, false positive; FRS, Framingham risk score; HT, hypertension; LVH, left ventricular hypertrophy; METs, metabolic equivalents; SE, stress echocardiogram

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changes (see Figure 1) which have subsequently been shown to have non-obstructive disease on anatomical testing [2,3,5–7].

Imaging stress testing has been shown to be more specific for the detection of obstructive coronary artery disease, perhaps because systolic dysfunction (and regional wall motion changes) should occur before ECG changes on the ischaemic cascade [2,3,5,8–10]. Thus, patients with ECG changes but normal cardiac imaging can be said to have a false positive stress ECG. Confirming the results of stress echocardiography with invasive coronary angiography in these types of patients has supported this concept [2,3,5,8,9,11,12].

Previous research has reported that females have a higher incidence of false positive ECG tests than males, limiting the effectiveness of stress ECG tests in women [13–16]. This study investigates this proposition in a large, prospective cohort and in a contemporary setting.

Material and Methods

Consecutive patients referred to HeartCare Partners clinical testing facilities for stress echocardiography were studied prospectively. Standard Bruce protocol treadmill testing with digital gated echocardiography before and after exercise was performed. Positive stress echocardiograms (concordant ECG and imaging abnormalities), patients requiring dobutamine stress echocardiography, patients with resting left bundle branch block and those with a paced rhythm were excluded. False positive stress ECGs were defined as having ST depression during exertion, (see Figure A1) without pain and with the stress echocardiogram not suggesting myocardial ischaemia. Potential and predictable causes for a false positive ECG stress test were recorded before the test (see Table 1) [1,2,4,17,18]. Anatomical tests (invasive coronary angiograms or computed tomography (CT) coronary angiograms) were not routinely conducted if the stress echocardiogram result was negative for ischaemia.

General Electric medical grade treadmills using Case systems were used to replicate and estimate exercise. Standard Bruce protocols were used to produce exercise stress in a controlled environment, and in a reproducible manner. Imaging was performed using high end echocardiography machines including the General Electric Vivid e9 and Vivid 7,

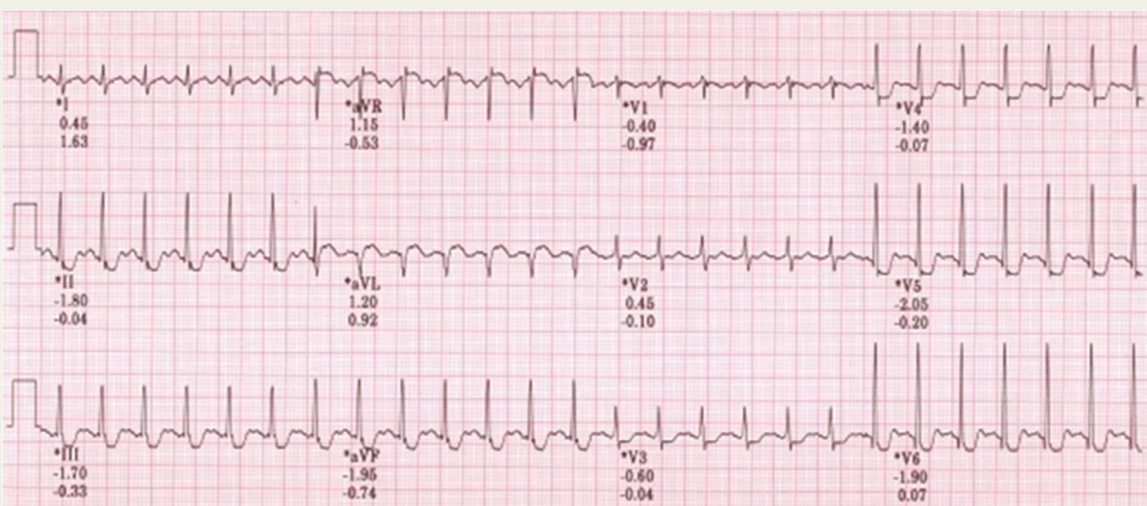

Figure 1 ECG with significant ST depression.

Table 1 List of predetermined predisposing factors for false positive stress ECGs.

Cause	Percentage of whole population	Females	Males	Comparison of males and females
Hypertension	38.1%	83%	74%	p = 0.0001
LVH by ECG	36.1%	61%	73%	p < 0.0001
Known coronary artery disease	25.3%	25%	47%	p < 0.0001
LVH by echocardiography	9.9%	11%	21%	p < 0.0001
Arrhythmia (any)	4.6%	11%	8.8%	p = 0.3069
Diabetes Mellitus	2.8%	5.6%	5.6%	p = 0.0073
Valvular heart disease (any – mostly AS)	1.4%	2.8%	3%	p = 0.2345
Heart failure (systolic)	0.5%	0%	3%	p = 0.0098

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Siemens SC2000 and SC2000 Prime and the Phillips ie33 Q4 scanners.

A positive stress ECG result was designated as greater than 1 mm at 60 ms after the J-point in three simultaneous beats in two contiguous leads, during exercise or recovery. A positive stress echocardiographic result was defined as worsening regional wall function in two contiguous segments (typically normal to hypokinetic segmental function), or normal contractility to global dysfunction with cavity dilatation. All stress imaging was completed by 60 seconds after cessation of exercise.

All tests were supervised and read by cardiologists with subspecialty training in stress echocardiography, and an exercise physiologist. The echocardiogram was performed by cardiac sonographers with extensive subspecialty training in stress echocardiography. Results were then over-read and standardised by a stress echocardiography specialised cardiologist. If angiography was subsequently performed, these results were only made available after the stress echocardiogram result was over-read and results recorded into the database. These were only performed subsequently if clinically requested by the referring cardiologist.

The data were collected and the statistical analysis was Q5 completed using the GraphPad Prism 6 software. Unpaired t-tests were used for cohort analysis of continuous data where appropriate. Categorical variables were expressed as proportions and were assessed using Pearson's chi-square test. Data expression was presented as the mean plus or minus the standard deviation.

Results

A total of 3000 consecutive negative stress echocardiograms were analysed. There were 1036 females (34.5%) and 1964 males (65.5%). Mean age was 59 +/- 14.3 years (similar in both groups). The baseline characteristics of the patients are recorded in Table 2. This was an intermediate risk group based on Framingham risk scoring (FRS) pre-test (mean score 15.7+/-12/1). Female and male FRS were both in the intermediate risk range pre-test, but female risk was statistically lower then male risk. Females had statistically lower body mass indexes (BMIs), had lower systolic blood pressures, lower FRS and had lower exercise capacity compared to the men. Maximum achieved heart rates were similar in the two groups (see Table 2).

False positive stress ECGs were recorded in 565 tests (18.8%). There were 194 female false positive stress ECGs recorded (18.7%). False positive stress ECGs were found in 371 male tests (18.9%, not statistically different to the women, p = 0.85 for the difference). The distribution of ECG changes was similar in both females and males. Potential causes for false positive stress ECG tests were recorded before the stress echocardiogram in 36 (18.6%) of the female false positive stress ECG tests and 249 (68.2%) of the male false positive stress ECG tests ($p < 0.0001$ for the difference, see Figures 2 and 3). Potential causes and their incidence for false positive stress ECG tests are listed in Table 1. The most common predisposing causes were hypertension, known coronary artery disease, and left ventricular hypertrophy. The ranking was similar in females and males, but the percentage of females with each of the predicting factors was different compared to the males for many of the causes (see Table 1 and Figures 2 and 3). Of those that had risk factors, males were more likely to manifest these risk factors as an actual false positive test.

A total of 161 out of the 3000 stress tests (5.4%) were corroborated with either a CT coronary angiogram or invasive coronary angiography (tests were done based on clinical requirements, not as part of the study protocol). Of these, 151 of the 161 stress tests were confirmed as false positive stress ECGs (no significant coronary artery disease, negative stress echocardiographic imaging and angiographically graded lesions with less than 50% stenosis). There were 10 of the 161 tests which did show obstructive plaque (false negative stress echocardiogram). This would suggest a specificity of 93.8% on a very small sample of the total group. While the numbers are very small, it suggests a high overall specificity for the stress echocardiography performed in this study.

Of the 565 false positive stress tests, 20 had an anatomical test performed (3.5%). In this group, 19 were confirmed

Table 2 **Baseline characteristics – All patients.**

	All Patients (n = 3000)	Female (n = 1036)	Male (n = 1964)	
False positive tests	565/3000	194/1036	371/1964	
F+ %	18.8%	18.7%	18.9%	p = 0.85
Mean age	58.6 years	58.0	58.8	p = 0.76
Mean BMI	28.2	27.2	29.0	p < 0.0003
Mean resting BP	125/77 mmHg	123/75	128/76	p = 0.0016
Mean MPHR %	94.6%	95.7	94.2	p = 0.0781
Mean pre-test Framingham risk score	15.71	10.2	17.6	p = 0.015
Mean exercise capacity (in METs)	10.8	9.9	11.7	p < 0.0001

Q6 **Abbreviations:** BP, blood pressure; BMI, body mass index; MPHR,; METS, metabolic equivalents.

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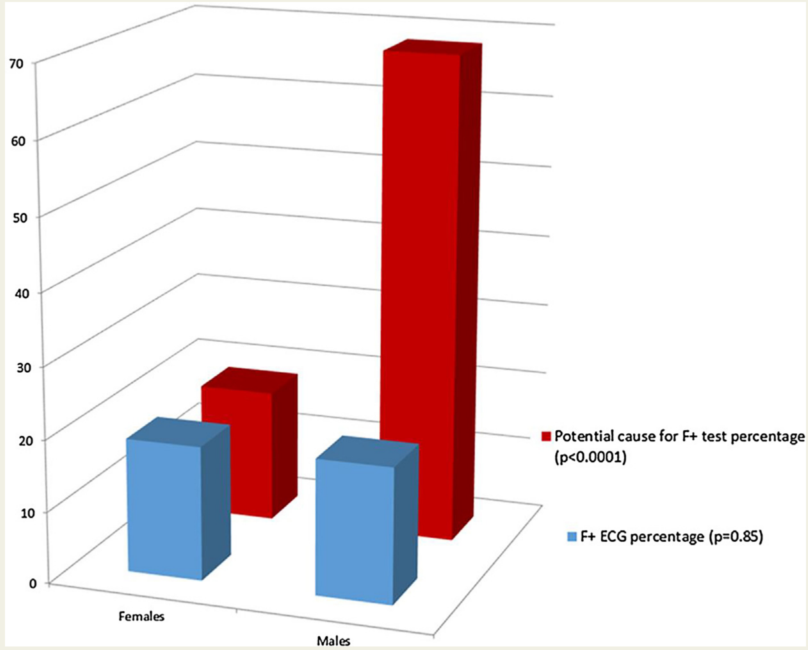

Figure 2 Graph of false positive females in females and males.

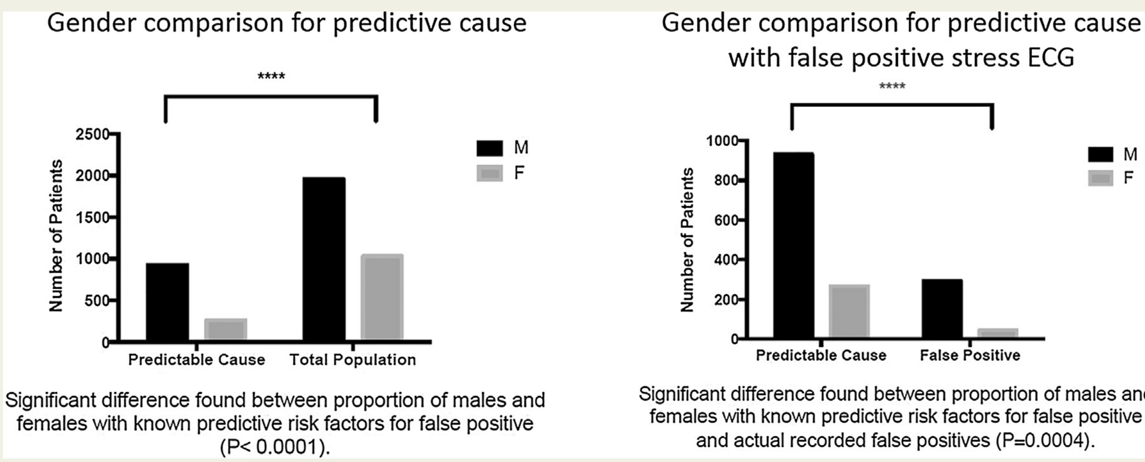

Figure 3 Statistical comparison of predictive causes of false positive stress ECGs.

as true negatives, with only one (1) coronary angiogram showing significant disease. This suggests a sensitivity of 95%, again on a very small sample, similar to the overall group. It supports the assumption that ECG changes in the setting of a normal stress echocardiogram are false positive changes.

Discussion

Exercise stress testing investigates the haemodynamic effects of physical effort on the cardiovascular system. It allows clinicians to quantitate a patient's exercise tolerance, and the heart rate and blood pressure response to exertion [3,19]. The test permits a non-invasive assessment of cardiac diseases including myocardial ischaemia [1–4]. Exercise results in an increase in heart rate and blood pressure, producing an increase in cardiac output with a resultant increased myocardial oxygen demand. Flow limiting coronary artery lesions should produce an inadequate blood supply, limiting delivery of oxygen, resulting in myocardial ischaemia. The ischaemic cascade suggests that abnormalities occur first in diastolic dysfunction, followed by systolic dysfunction, then electrocardiographic (ECG) abnormalities (ST segment changes) and lastly, chest pain [1,2,20,21].

Exercise stress ECG is a valuable, non-invasive method for assessing the risk of underlying coronary artery disease ubiquitously employed as entry-level testing. Using standardised protocols, patients' exercise capacity and physical responses can be assessed [1,2,5,19]. The development of ECG changes and/or chest pain may suggest myocardial ischaemia. A positive ECG response is defined as planar or downsloping ST segment depression [1,2,22] (designated as greater than 1 mm at 60 ms after the J-point in three simultaneous beats in two contiguous leads in this study). A false positive exercise stress test is defined as a test meeting these criteria in an individual without obstructive coronary artery disease [1–3,5]. The specificity of stress ECG testing has been reported to be reduced by valvular heart disease, left ventricular hypertrophy (LVH), resting ST segment depression, and medical therapy (e.g. digitalis). Non-coronary causes of ST segment depression include severe aortic stenosis (AS), severe hypertension (HT), cardiomyopathy, anaemia, hypokalaemia, sudden excessive exercise, left ventricular hypertrophy, mitral valve prolapse, bundle branch block, pre-excitation syndrome, severe aortic or mitral regurgitation or arrhythmias [1,2,4,17,18].

The gold reference standard against which all stress testing have been assessed is invasive coronary angiography with at least 50–70% obstruction [1–4]. Imaging stress testing (e.g. stress echocardiography or myocardial perfusion scanning), results in significantly increased sensitivity and specificity over stress ECGs, by assessing more subtle and possibly earlier manifestations of induced ischaemia, including induced regional wall motion abnormalities or reversible perfusion defects [1–5,10,23]. In much smaller subsets, patients with abnormal exercise ECGs but normal stress echocardiograms have been assessed [11,12,24,25]. The superior sensitivity and specificity of stress echocardiography have been demonstrated and confirmed with subsequent invasive coronary angiography. These studies have confirmed that an ischaemic stress ECG with normal regional wall motion response is usually a false positive ECG result [11,12,25]. Imaging stress tests have been broadly adopted because of these reasons.

Previous research, expert opinion and common clinical experience have held that females have a high incidence of false positive tests, with the presumption that this is more frequent than in males [13–15]. A variety of explanations have been proposed for the higher rate of false positive stress ECG tests in women. The standard stress ECG has been reported to have a lower overall test accuracy in women compared to men. Lower accuracy appears to be due to a lower sensitivity and specificity for women compared to men (often due to different pre-test probabilities) [1,2,13,14]. Endogenous and exogenous oestrogens have been implicated in ST depression in healthy females [1,2,13,14]. A lower exercise capacity has also been suggested [1,2,13,14]. The females in this study did have a lower exercise capacity, as estimated by metabolic equivalents (METs) – see Table 2. Differing heart rate recovery and blood pressure responses between males and females may also play a role [13,14].

The data presented in this study run counter to the current belief of a higher incidence of false positive stress ECGs in females. The incidence reported here was not statistically different between the genders. This raises the question of how this result has occurred. Was this cohort of women different to previous groups? One possibility is that this was an older group of women. The average age of 58 years suggests that many of the females were post-menopausal, meaning that the effects of oestrogen could be less (one of the purported reasons for the difference between males and females). The largest cohort of females tested previously had an average age of 60 years, however [12]. Women had an intermediate pre-test probability for coronary disease ("ideal" for stress testing), but women had statistically lower risk than the males in this study. Generally this would occur in most cohorts, as being female reduces pre-test risk compared to being male. It is possible that there were other relevant factors that have not been accounted for. This is the largest group of females tested in this manner. Most of the early tests looking at stress testing were almost entirely male [14]. It has been suggested that historically, " . . . the representation of females in published studies was too small to determine gender differences in test accuracy" [14].

The difference between men and women was that the majority of male false positive tests can be predicted by history and demographics. In women, exercise induced ST depression is mostly unpredictable. Further, of those that have risk factors, males are more likely again to manifest these risk factors as an actual false positive (see Figure 3). The surprising finding that false positive stress ECGs occur equally in males and females raises the possibility that being female is an independent risk factor for having a false positive stress ECG. These data are supportive of this theory (see Table 3).

This study confirms that false positive stress ECG tests are common. Previously described conditions are associated with ST depression on stress ECG testing [1,2,4,17,18], and many of these were shown to be common in this study (see Tables 1 and 3). For these patients, a more efficient approach to assessment could be to proceed directly to an imaging stress test. In men who do not have predictors of a false

Table 3 List of predisposing factors as a percentage of all false positive stress ECGs.

Hypertension	215 of 565	38.1%
LVH by ECG	204	36.1%
Female sex	194	34.3%
Known coronary disease	143	25.3%
LVH by echocardiography	56	9.9%
Arrhythmia (any)	26	4.6%
Diabetes mellitus	16	2.8%
Valvular heart disease (any – mostly AS)	8	1.4%
Heart failure (systolic)	3	0.5%

Abbreviations: LVH, left ventricular hypertrophy; ECG, electrocardiograph; AS, aortic stenosis.

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positive test, a stress ECG could be a reasonable and more economical first step. For women, an argument can be made for proceeding directly to imaging stress tests, due to a high false positive rate that is difficult to predetermine.

There are a number of limitations to this study. By design, the use of cardiac imaging as the standard to determine the accuracy of stress ECG is less optimal than using an anatomical test. Ideally this study would be conducted with patients undergoing an anatomical test to confirm the diagnosis, blindly after the stress test. From a practical and clinical viewpoint, this is not feasible, as it would negate the non-invasive attribute of stress echocardiography. In the real world, this is how imaging stress testing is used. Previous studies have suggested that this is a valid model [11,12,24]. There would also be ethical implications for intermediate risk patients [2,3,5,8,9]. In most clinical scenarios, non-invasive testing is used to attempt to avoid an invasive test. Only a very small number of patients in this study had a clinical reason to evaluate the anatomy, making it difficult to draw scientific conclusions. However, in that small group of patients, the effective role of imaging in this setting was supported. This was a single centre experience. The criteria used to describe a false positive ETT in this study limits and defines the sensitivity and specificity of the results reported here.

It is possible that, in conducting the stress imaging once exercise had completed, that ischaemic alterations detected by imaging may restore too quickly after the ischaemic provocation. In this scenario, the ECG changes would be true positives and the normal imaging a false negative finding. However, there is evidence that ischaemia persists for at least 60 to 90 seconds after ischaemic stress [26–29]. Additionally, comparisons between imaging immediately after treadmill exercise and continuous imaging during supine bicycle exercise have shown similar accuracy for the detection of myocardial ischaemia [3,28,30]. As a consequence, this method of imaging post exercise is regarded as valid, with the imaging protocol regarded as being more accurate than the ECG findings [3,11,12]. Within this sample, there were significantly less women than men (a common problem in cardiac research). This does reflect real world experiences. However, this is the largest cohort of women investigated in this manner. Symptoms and previous history were self-reported, which may underestimate these values. The reviewing cardiologist was not blinded to the results of the stress test.

Conclusions

These data suggest that false positive stress ECG tests are equally common in women and men, occurring in almost one in five cases. Most false positive stress ECG tests in men can be predicted by patient history and demographic features, while most in women cannot. As such, being female may be an independent risk factor for a false positive stress ECG. These data reinforce the incremental accuracy and specificity of stress echocardiography, particularly in women.

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Conflict of Interest

None declared

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