The Effect of Estrogen Compared to Estrogen Plus Progesterone on the Exercise Electrocardiogram

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OBJECTIVES	The objective of this study was to evaluate the effect of estrogen compared to estrogen plus progesterone on the stress electrocardiogram (ECG) in relationship to stress-gated myocardial perfusion imaging (MPI) in postmenopausal women.
BACKGROUND	It is generally recognized that estrogen may cause false positive ST depressions on the stress ECG. The effects of estrogen plus progesterone are not known. This study was performed to define the effects of these agents on the stress ECG correlated with results from MPI.
METHODS	We evaluated 140 postmenopausal women—31 not taking any hormone replacement therapy (HRT); 75 taking estrogen alone; and 34 taking estrogen plus progesterone. Women with a history of coronary artery disease (CAD), cardiomyopathy, or an abnormal resting ECG were excluded. All women underwent a symptom-limited treadmill test and MPI.
RESULTS	The overall sensitivity and specificity of the stress ECG compared to MPI in women not taking HRT was 54% and 78%, respectively. In women taking estrogen or estrogen plus progesterone, the sensitivity was unchanged. The power to detect clinically meaningful sensitivity difference (10%) was poor (p = 0.09). The specificity was reduced to 46% (p < 0.01) in women on estrogen therapy. In women taking estrogen plus progesterone, specificity was 80%.
CONCLUSIONS	Our results suggest that estrogen increases the false positive rate of the stress ECG. This decreased specificity is countered by co-administration of progesterone. Nonetheless, because the sensitivity of the stress ECG is only 50% to 57% in postmenopausal women, women at risk should have imaging in conjunction with stress for the optimal detection of CAD. (J Am Coll Cardiol 2002;40:1092–6) © 2002 by the American College of Cardiology Foundation

In Western societies, coronary artery disease (CAD) has now become the leading cause of death in women (1). Although the prevalence of CAD in women is lower than in men during the third through fifth decade, the incidence increases thereafter, and by the time women reach the eighth decade, the prevalence of CAD actually exceeds that of men (2). In addition, women have poor outcomes when they do manifest CAD compared to men (3,4).

Despite this high prevalence and poor outcome, the diagnosis of CAD in women is more complex because women present with more atypical than typical anginal features. Although stress electrocardiography (ECG) is widely available and is relatively inexpensive, the sensitivity and especially the specificity rates of the stress ECG are lower in women than in men (5–7). This is believed to be related both to the lower work loads achieved by women when corrected for age, and the putative effect of estrogen on the stress ECG (8,9). Thus, women are 5 to 20 times more likely to have a false positive stress ECG than men (8). As a result of this lower specificity, the best diagnostic strategy for the detection of CAD in women remains controversial. Although the high prevalence of false positive findings on the exercise ECG has been attributed to the presence of higher estrogen levels (9), the exact cause of the lower specificity in women is not clear. In addition, estrogen

levels decrease after menopause, but the specificity of the ECG still is low. Thus, the effects of estrogen in combination with progesterone on the exercise ECG are not well known (10).

Accordingly, we evaluated the effect of estrogen with or without progesterone on the exercise ECG in postmenopausal women presenting to the stress laboratory for symptoms believed to relate to CAD, and to correlate changes with results of myocardial perfusion imaging (MPI).

METHODS

Subjects. We performed a retrospective study on 140 consecutive postmenopausal women referred for the diagnosis of chest pain or dyspnea on exertion by either their primary care physician or cardiologist. Postmenopausal status was defined as age more than 50 years with cessation of menses for at least six months before the test period. Patients with classic angina or documented CAD, cardiomyopathy, and those with abnormal ECGs (left bundle branch block, paced rhythm, ECG criteria of left ventricular hypertrophy, delta waves suggestive of Wolff-Parkinson-White syndrome, patients on digitalis, or patients with resting ST-T wave changes) were excluded. Patients who could not achieve 85% of age-adjusted predicted maximum heart rate (calculated as 220 − age) during exercise stress testing and those who did not achieve age-corrected Bruce protocol exercise times were also excluded.

Patients were divided into three groups: those receiving

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Abbreviations and Acronyms
CAD    = coronary artery disease
ECG    = electrocardiogram/electrocardiography
EPRT   = estrogen plus progesterone replacement
           therapy
ERT    = estrogen replacement therapy
HRT    = hormone replacement therapy
MPI    = myocardial perfusion imaging
MVD    = multivessel disease
SPECT  = single-photon emission computed
           tomographic imaging
SVD    = single-vessel disease
Tl-201 = thallium-201
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no hormone replacement therapy (HRT); those receiving estrogen replacement therapy (ERT) alone; and those receiving estrogen plus progesterone replacement therapy (EPRT). Patients in the no-HRT group ranged in age from 52 to 76 years (mean 64 ± 7 years). Those in the ERT group ranged in age from 51 to 74 years (mean 61 ± 8 years) and were taking 0.625 mg of conjugated estrogen daily by mouth. Patients in the EPRT group ranged in age from 53 to 78 years (mean 63 ± 7 years) and were taking 0.625 mg of conjugated estrogen plus 2.5 or 5.0 mg of medroxyprogesterone daily by mouth. Patients in the ERT and EPRT groups had been taking their medication for at least six months prior to the exercise test. No statistically significant difference existed between the groups on the basis of risk factors (Table 1).

Study protocol. All patients underwent symptom-limited treadmill exercise testing with the Bruce protocol. Medications were withheld for at least 12 h prior to the test. All patients had gated single-photon emission computed tomographic (SPECT) MPI performed in conjunction with stress testing.

Stress ECG. During stress testing, each patient had ECGs recorded with 12-limb and left precordial ECG leads. The skin was cleansed vigorously with alcohol, and ECG leads

were placed. Treadmill testing was performed on Marquette ECG machines (model Case 15, Marquette Electronics, Milwaukee, Wisconsin). ECGs were recorded continuously before and during stress testing and for up to 10 min during the recovery period. Raw and averaged ECGs were then analzed separately by two physicians with extensive stress-testing experience and who were blinded to HRT status.

The ST-segment changes during stress were considered positive if there was horizontal or downsloping ST-segment depression of at least 1 mm at 80 ms after the J point compared with the baseline ECG, or an upsloping ST-segment depression of at least 1.5 mm at 80 ms after the J point compared with the baseline ECG. The line between two PR segments was used as a baseline. Changes needed to be observed in two contiguous leads to be considered positive. Equivocal changes not meeting the above criteria for ischemia were reported as such to the patients' referring physicians, but they were included in the normal ECG category for the purpose of this study.

MPI. Radionuclide perfusion imaging was performed with two different protocols: thallium-201 (Tl-201) stress-redistribution scanning or a dual-isotope protocol. In the thallium protocol, patients received approximately 3.0 to 3.3 mCi of Tl-201 intravenously at peak stress. Exercise was continued for 60 to 90 s after radioisotope injection, and gated stress SPECT imaging commenced within 10 min from the time of injection. All patients then had redistribution scans obtained at 3 to 4 h. Thallium imaging was performed on a triple-headed Picker camera (PRISM 3000XP, Picker International Inc., Highland Heights, Ohio) with a 360° acquisition.

In the dual-isotope protocol, patients received approximately 3.0 to 3.3 mCi of Tl-201 at rest and had rest SPECT MPI performed 15 to 30 min after injection. They then received 25 to 30 mCi of technetium-99m sestamibi at peak stress, exercised for 60 to 120 s more, and underwent stress imaging approximately 30 to 60 min later. Dual-isotope imaging was performed on a dual-headed ADAC Cardio-Epic camera (ADAC Laboratories, Milpitas, California) with a 180° acquisition (from 45° right anterior oblique to 225° left posterior oblique). All scans were collected in the gated mode, which allows interpretation of wall motion and ejection fraction from gated myocardial perfusion images. All scans were interpreted both qualitatively and quantitatively with standard, commercially available software.

Scans were interpreted by physicians with extensive experience blinded to patient's HRT status. Scans were considered normal if uptake of tracer during stress was homogeneous and if results of wall motion and ejection fraction from gated imaging were normal. Scans were considered to reflect ischemia if there was a stress-induced defect that was not observed or had decreased significantly on the redistribution or resting scans. Infarction was defined as a focal decrease in radionuclide concentration with stress that was unchanged at rest or redistribution and that had a

Table 1. Patients' Baseline Characteristics

	No HRT (n = 31)	ERT (n = 75)	EPRT (n = 34)
Age (yrs)	64 ± 8	61 ± 8	63 ± 7
Family history of CAD	5 (18%)	16 (21%)	7 (20%)
Hypertension	14 (47%)	39 (52%)	17 (49%)
Diabetes mellitus	3 (11%)	7 (9%)	2 (6%)
Hypercholesterolemia	7 (28%)	25 (33%)	10 (29%)
Smoking	6 (21%)	14 (19%)	8 (23%)
Exercise duration (min) ± SD	6 ± 1	6 ± 1	7 ± 2
Peak HR (beats/min) ± SD	140 ± 19	140 ± 18	139 ± 16
Peak SBP (mm Hg) ± SD	159 ± 21	158 ± 23	159 ± 22

No significant differences were seen in the three groups. Family history of CAD = first-degree male relatives with coronary artery disease before 55 years of age, female relatives before 65 years of age. Hypertension = SBP >140 mm Hg or DBP >90 mm Hg. Diabetes mellitus = fasting blood glucose >126 mg/dl. Hypercholesterolemia = cholesterol >200 mg/dl, low-density lipoprotein >160 mg/dl.

CAD = coronary artery disease; DBP = diastolic blood pressure; EPRT = estrogen plus progesterone replacement therapy; ERT = estrogen replacement therapy; HR = heart rate; HRT = hormone replacement therapy; SBP = systolic blood pressure.
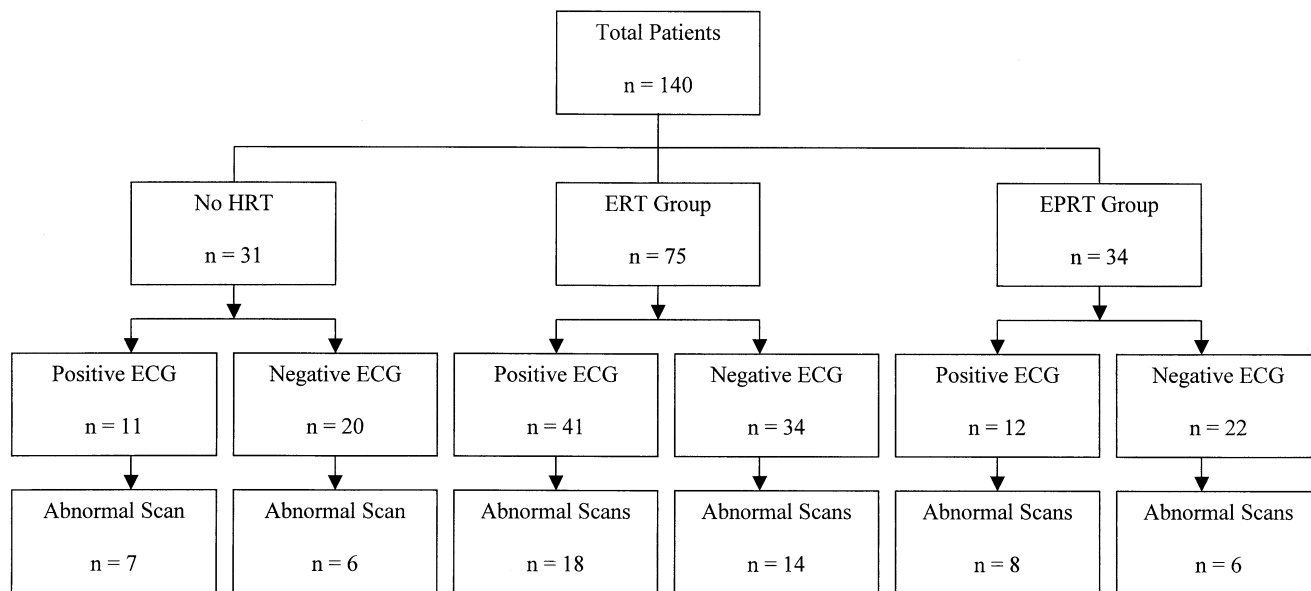
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                        │ Total Patients  │
                        │                 │
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Figure 1. Flow diagram of the postmenopausal women studied. Abnormal scans predominantly reflect ischemia (see text). ECG = electrocardiogram; EPRT = estrogen plus progesterone replacement therapy; ERT = estrogen replacement therapy; HRT = hormone replacement therapy.

regional wall motion abnormality in the same segment. Single-vessel disease (SVD) was defined as a scintigraphic pattern characterized by the presence of perfusion defects in only one coronary artery territory, and multivessel disease (MVD) was defined by the presence of perfusion defects in two or more coronary artery territories.

Statistics. Results of the stress ECG were compared with MPI results. The overall sensitivity of stress-gated MPI in our laboratory compared with cardiac angiography (50% coronary luminal narrowing defined as angiographic obstruction) is 93%.

Data are presented as mean ± SD. Differences between groups were compared with the Fisher exact test, with $p < 0.05$ considered statistically meaningful. Continuous variables were compared using analysis of variance, while the differences of categorical variables were assessed by the chi-square test.

RESULTS

Of the 140 women, 31 were in the no-HRT group, 75 were in the ERT group, and 34 were in the EPRT group. No statistically significant difference was seen in exercise duration, peak heart rate, or peak systolic blood pressure between groups (Table 1).

For the purposes of this study, an abnormal scan was that in which ischemia or infarction was present. Of the total of 59 patients with abnormal scans, all had ischemia and 3 had a combination of both ischemia and infarction. Thus, the majority of patients with "abnormal" scans had ischemia.

Of the 31 postmenopausal women taking no HRT, 11 (35%) had a positive stress ECG and 20 (65%) had a negative stress ECG. Of 11 women with positive stress ECG, 7 (64%) had an abnormal MPI (4 SVD; 3 MVD). Of

20 women with negative stress ECG, 6 (30%) had an abnormal MPI (5 SVD; 1 MVD) (Fig. 1). Overall, the sensitivity of the stress ECG compared with MPI in the group was 54%, and specificity was 78% (Fig. 2). The sensitivity of the stress ECG for detecting SVD in this group of women was 44%, and it was 75% for detecting MVD (Fig. 3).

Of the 75 women in the ERT group, 41 (55%) had a positive ECG on stress testing and 34 (45%) had a negative stress ECG. Of 41 women with positive ECGs, 18 (45%) had an abnormal myocardial perfusion scan (8 SVD; 10 MVD). Of 34 women with negative ECGs, 14 (41%) had abnormal MPI (11 had SVD; 3 had MVD) (Fig. 1).
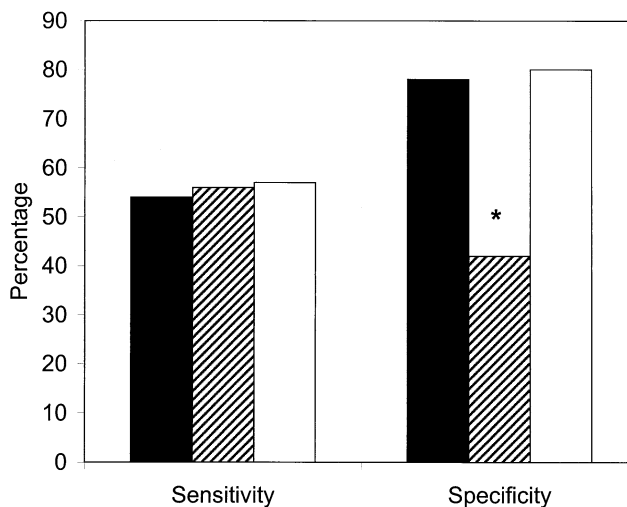
Figure 2. Overall sensitivity and specificity for the stress ECG compared to gated myocardial perfusion imaging in the groups. *$p < 0.01$. **Solid bar** = No HRT; **lined bar** = ERT; **open bar** = EPRT. For abbreviations, see Figure 1.
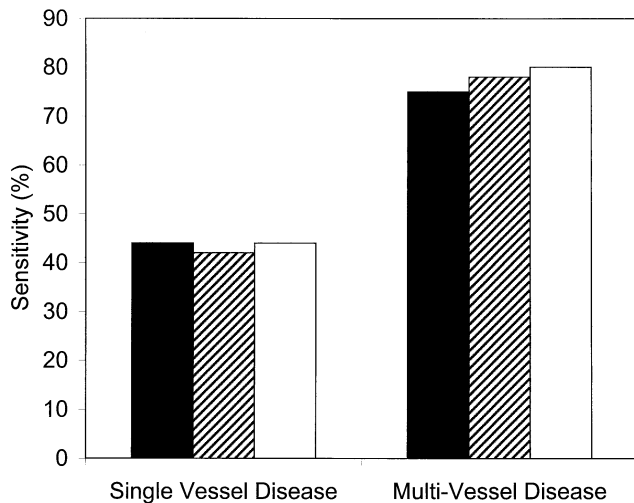
Figure 3. Specificity of the stress ECG compared to gated myocardial perfusion imaging in the postmenopausal women studied for detecting coronary artery disease in those with single-vessel as compared to multivessel disease. **Solid bar** = No HRT; **lined bar** = ERT; **open bar** = EPRT. For abbreviations, see Figure 1.

Compared with MPI, in women taking ERT the overall sensitivity of the stress ECG was 56%, and the specificity was 46% (Fig. 2). The sensitivity for detecting SVD was 42%, and it was 78% for detecting MVD (Fig. 3).

Of the 34 women taking EPRT, 12 (35%) had positive ECGs on stress testing and 22 (65%) had negative stress ECGs. Of the 12 with positive stress ECGs, 8 (67%) had positive MPI (4 SVD; 4 MVD). Of 22 women with negative ECGs, 6 (27%) had positive MPI (5 SVD; 1 MVD) (Fig. 1). Sensitivity was therefore 57%, and specificity was 80% (Fig. 2). The sensitivity for detecting SVD in women on EPRT was 44%, and it was 80% for detecting MVD (Fig. 3).

Thus, comparing the stress ECG to gated MPI, no significant difference was seen between the sensitivity of detecting CAD in women between those on ERT, EPRT, or those not taking HRT (Figs. 2 and 3). In contrast, the specificity of the women taking EPRT or those not taking HRT was significantly higher than those women taking estrogen alone (p < 0.01) (Fig. 2).

DISCUSSION

Our results show that postmenopausal women referred for chest pain or dyspnea with an intermediate likelihood of CAD and taking estrogen alone have a higher rate of false positive ST-segment changes on the exercise stress ECG compared with patients taking a combination of estrogen plus progesterone or those not taking HRT.

Exercise ECG. Exercise ECG testing began with the observation of abnormal downsloping ST-depression and T-wave inversion in the ECG of three male patients experiencing anginal attacks after climbing the stairs to a physician's office in 1928 (11). Profant was the first to report that exercise-induced ST-depression was more common in

normal women than in men (12). Concerning the effects of hormones, the earliest study was by Jaffe (13), who observed ST-segment changes in 51 patients (33 men, 18 women) after two weeks of estogen therapy and reversal of the effect six weeks after discontinuation. A study by Morise et al. (9) found positive ECG treadmill stress tests in 22% (24/109) of postmenopausal women with normal coronary angiograms. Fourteen of 24 (58%) patients were receiving estrogen HRT. Rovang et al. (14) performed treadmill exercise echocardiography in 47 postmenopausal women free of CAD prior to and following six weeks of ERT therapy. Additionally, 10 women (21%) with negative ECGs at baseline had positive ECG response after ERT replacement therapy without new wall motion abnormalities on echocardiography (15).

Several studies have documented the lack of diagnostic value of the stress ECG in women on ERT (sensitivity ranging from 0.32 to 0.80; specificity from 0.41 to 0.68) (16,17). Compared with the exercise ECG, stress MPI offers improved sensitivity (83% to 90%) and specificity (80% to 93%), especially when combined with gating (18,19). Also, MPI is a more accurate predictor of prognosis than either the exercise ECG or even coronary angiography (20).

The mechanism of the false positive exercise ECG response to estrogen is unknown. Several explanations have been proposed. Estrogen has a similar chemical structure to digitalis, a known cause of false positive ST-depression (21). There is also some evidence that estrogen may be a vasoconstrictor to coronary arterioles (22). The true cause of the increased false positive rate of exercise tests is nevertheless still being debated. Conversely, androgens have been shown to decrease ST-depression (23), and though the exact mechanism by which progesterone acts on ST-segments is unknown, it is possible that this androgen effect balances the effects of estrogen.

Study limitations. Our study was limited in that none of the patients in our study underwent coronary angiography, presently considered the gold standard for the diagnosis of CAD. Although angiography is more accurate for the diagnosis of CAD, studies based on invasive techniques are more likely to be influenced by referral bias (24). In our study, gated MPI was the noninvasive strategy used for delineation of myocardial perfusion abnormalities. Exercise MPI has a good diagnostic accuracy, with an overall sensitivity of 83% to 90% and an overall specificity of 80% to 93% (17,18). In addition, the use of gating greatly improves the specificity of interpretation of MPI, especially in women (18).

Significant differences in sensitivity were not detected in this study. This is not surprising as the power to detect sensitivity differences of 10% was only 0.09, whereas the power to detect the actual observed differences in sensitivity was <0.04 (alpha = 0.05).

Conclusions. In summary, the stress ECG is more specific in postmenopausal women not taking HRT or those taking

a combination of estrogen and progesterone than in patients taking estrogen alone. However, the overall sensitivity for detection of CAD in women based on the stress ECG in comparison with MPI is only about 50% and not related to estrogen. Thus, even though the stress ECG is more specific in postmenopausal women either not taking HRT or on EPRT, women referred for stress testing should undergo imaging for optimal detection of CAD.

Acknowledgments

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