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CLINICAL INVESTIGATIONS

False-positive stress testing: Does endothelial vascular dysfunction contribute to ST-segment depression in women? A pilot study

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Background: The utility of exercise-induced ST-segment depression for diagnosing ischemic heart disease (IHD) in women is unclear.

Hypothesis.: Based on evidence that IHD pathophysiology in women involves coronary vascular dysfunction, we hypothesized that coronary vascular dysfunction contributes to exercise electrocardiography (Ex-ECG) ST-depression in the absence of obstructive coronary artery disease, so-called false positive results. We tested our hypothesis in a pilot study evaluating the relationship between peripheral vascular endothelial function and Ex-ECG.

Methods: Twenty-nine asymptomatic women without cardiac risk factors underwent maximal Bruce protocol exercise treadmill testing and peripheral endothelial function assessment using peripheral arterial tonometry (Itamar EndoPAT 2000) to measure reactive hyperemia index (RHI). The relationship between RHI and Ex-ECG ST-segment depression was evaluated using logistic regression and differences in subgroups using 2-tailed *t* tests.

Results: Mean age was 54 ± 7 years, body mass index 25 ± 4 kg/m^2, and RHI 2.51 ± 0.66. Three women (10%) had RHI <1.68, consistent with abnormal peripheral endothelial function, whereas 18 women (62%) met criteria for positive Ex-ECG based on ST-segment depression in contiguous leads. Women with and without ST-segment depression had similar baseline and exercise vital signs, metabolic equivalents achieved, and RHI (all $P > 0.05$). RHI did not predict ST-segment depression.

Conclusions: Our pilot study demonstrates high prevalence of exercise-induced ST-segment depression in asymptomatic, middle-aged, overweight women. Peripheral vascular endothelial dysfunction did not predict Ex-ECG ST-segment depression. Further work is needed to investigate the utility of vascular endothelial testing and Ex-ECG for IHD diagnostic and management purposes in women.

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KEYWORDS

Exercise Electrocardiography, Reactive Hyperemia Index, ST Depression, Women

1 | INTRODUCTION

The American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend exercise electrocardiography (Ex-ECG) as the initial diagnostic test for women and men with an intermediate pretest probability of ischemic heart disease (IHD).[1] However, for the diagnosis of obstructive coronary artery disease (CAD), Ex-ECG frequently has false-positive results,[2] which are more common in women than in men.[3–5] Due to the relatively higher prevalence of false-positive Ex-ECGs, women with ST-segment depression but no obstructive CAD are often given noncardiac diagnoses, and further cardiologic testing or treatment is not pursued.[6] Thus, the utility of ST-segment depression for the diagnosis of IHD in women, which can be caused by processes other than obstructive CAD, remains unclear.[7]

Despite the poor specificity of Ex-ECG for the diagnosis of obstructive CAD, Ex-ECG paradoxically has strong prognostic value, even in individuals with low pretest probability of CAD.[8–10] The association between exercise capacity and mortality has been well established.[11] Additionally, ST-segment deviation during exercise is an independent predictor of mortality, as shown by several large cohort studies of asymptomatic patients without a history of cardiovascular (CV) disease.[10,12] In the Lipids Research Clinics subset study, a positive Ex-ECG was a stronger predictor of CV death than high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, smoking, hyperglycemia, or hypertension.[10] A variety of factors have been proposed to explain the false-positive rate of ST-segment depression in women, including digoxin-like effect of estrogen, more prevalent resting ST-T wave changes, and Bayesian principles related to lower obstructive CAD prevalence.[13] However, these factors do not explain the diagnostic-prognostic paradox of Ex-ECGs in women.

Endothelial dysfunction is also a potent predictor of adverse CV prognosis. A synthesis of 15 published reports on coronary and peripheral testing for endothelial dysfunction demonstrates an overall relative risk ratio for abnormal findings of nearly 10-fold, comparable with that of advancing imaging.[7,14] Based on the growing evidence that IHD pathophysiology in women involves coronary vascular dysfunction, we hypothesized that coronary vascular dysfunction contributes to false-positive Ex-ECG results in women. We tested our hypothesis in a pilot study by evaluating the relationship between peripheral vascular endothelial function and Ex-ECG in asymptomatic reference control women.

2 | METHODS

2.1 | Patient selection

Asymptomatic women in the greater Los Angeles area were recruited through print and online media to join a study determining female-specific reference control limits for an advanced cardiac imaging study (cardiac magnetic resonance imaging). Inclusion criteria included female subjects age ≥ 18 years, without signs and symptoms of myocardial ischemia, without cardiac risk factors according to Framingham/National Cholesterol Education Program criteria, age- and body mass index-matched to cases in the Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction (WISE-CVD) study.[15] Exclusion criteria included inability to walk at a moderate pace on a treadmill, women who were pregnant or lactating, or women with an abnormal resting ECG. Based on these criteria, the recruited women had a low (<1%) Bayesian likelihood of obstructive CAD.

2.2 | Ex-ECG testing

Study participants underwent maximal Bruce protocol exercise treadmill testing (Cardiac Assessment System for Exercise Testing; GE Healthcare, Wauwatosa, WI). Computer-generated ST-segment values were recorded. A cardiologist blinded to the study design and the peripheral vascular endothelial function results interpreted the Ex-ECG as to the presence of ST-segment depression. In cases of discordance between computer-generated ST value and cardiologist interpretation of the ECG, the cardiologist's interpretation was used. A positive Ex-ECG was defined as 1 mm horizontal or downsloping ST-segment depression in 2 contiguous leads at any time during exercise that persisted for ≥3 beats. The ST segment was defined from the J-point to 0.08 ms after the J-point, and the ST segment was compared with the PR segment to determine amplitude of deviation. The ST/heart rate (HR) index was calculated by dividing the maximal change in ST-segment depression during exercise by the change in HR from rest to peak exercise.[16] Target HR was defined as achievement of ≥85% of maximal predicted HR for age calculated as 220 - age (in years).

2.3 | Peripheral endothelial function

Peripheral endothelial function was assessed subsequently using peripheral arterial tonometry (PAT; EndoPAT 2000, Itamar Medical Ltd., Caesarea, Israel) to measure reactive hyperemia index (RHI). A fingertip plethysmograph measured beat-to-beat arterial pulse wave signal of both hands. One arm remained the control arm with no occlusion, and the other arm was occluded for 5 minutes using a blood pressure cuff after baseline measurement was taken. An RHI was defined as the ratio of the post- and pre-occlusion baseline period corrected for signal of the nonoccluded control arm.[17] A RHI of <1.68 is defined as endothelial dysfunction.[18] All RHI measurements were conducted in the morning, with women fasting for ≥4 hours and withholding caffeine for 24 hours. A blinded physician independently reviewed and validated each PAT.

2.4 | Statistical analysis

The data were analyzed using both categorical and continuous variables. For categorical analysis, women were divided into subgroups based on negative vs positive Ex-ECG and normal vs abnormal RHI. Statistical comparisons were made using the Welch *t* test and Mann-Whitney test where appropriate. To evaluate relationships between RHI as a continuous variable and exercise variables, we used logistic regression for positive Ex-ECG and linear regression for Duke Treadmill Score and ST/HR index. Diagnostics were performed using residual plots. All hypotheses were 2-sided and tested considering a significance level of 5%. Calculations were performed using R, version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Baseline characteristics

From March 2008 to September 2014, 29 women who met inclusion criteria for the advanced cardiac female-specific reference control study underwent peripheral vascular endothelial function testing a mean of 2.3 years after Ex-ECG testing. Demographic characteristics of the women are provided in Table 1 and depict a study population of predominantly midlife, postmenopausal, overweight subjects. Most subjects (93%) were able to achieve target HR during the Ex-ECG.

3.2 | Peripheral vascular endothelial function, Ex-ECG, and Duke Treadmill Score results

The mean RHI was 2.51 ± 0.66. Three women (10%) had a RHI of <1.68, consistent with endothelial dysfunction. Demographics did not differ between women with normal vs abnormal RHI (data not shown). Eighteen (62%) of the 29 women met criteria for a positive Ex-ECG. There was no significant difference in demographics between women with and without ST-segment depression (data not shown). Women with ST-segment depression had similar baseline and exercise vital signs, as well as metabolic equivalents (METs) achieved, compared with women without ST-segment depression (Table 2).

3.3 | Peripheral vascular endothelial function and Ex-ECG

In analyzing categorical variables, there was no significant difference in RHI between women with vs without a positive Ex-ECG (Table 2). Vice versa, the prevalence of positive Ex-ECG was 33% (1/3) in women with abnormal RHI and 65% (17/26) in women with normal RHI (*P* = 0.54). Additionally, using regression modeling, there was no significant relationship between RHI as a continuous variable and Ex-ECG variables including presence of positive Ex-ECG, Duke Treadmill Score, or ST/HR index (Table 3) adjusted for age, exercise time, METs achieved, and HR recovery.

TABLE 1 Baseline characteristics

Characteristic	N = 29	
Ethnicity		
Caucasian/white	20 (68.9)	
African American/black	4 (13.8)	
Asian/Pacific Islander	2 (6.9)	
Hispanic/Latino	3 (10.3)	
Postmenopausal	22 (75.9)	
	Exercise Treadmill Testing	PAT
Mean age, y	53.8 ± 7.1	56.6 ± 7.8
BMI, kg/m^2	25.0 ± 4.4	25.1 ± 4.7
Resting HR, bpm	69.7 ±9.7	64.9 ±10.3
Resting SBP, mm Hg	124.0 ±14.7	114.3 ±12.7
Resting DBP, mm Hg	76.2 ±9.1	70.6 ±8.7
Exercise capacity, METs	10.7 ±1.9	N/A
Total exercise time, min	9.1 ±1.7	N/A
Exercise max HR, bpm	162.4 ±15.3	N/A
Exercise max SBP, mm Hg	158.8 ±18.7	N/A
Women who attained target HR	27 (93)	N/A

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; max, maximum; MET, metabolic equivalent; N/A, not applicable; PAT, peripheral arterial tonometry; SBP, systolic blood pressure; SD, SD. Data are presented as n (%) or mean ±SD.

4 | DISCUSSION

In our pilot study of asymptomatic, middle-aged, overweight women recruited to establish female-specific advanced cardiac imaging reference limits, we observed a relatively high percentage of Ex-ECG ST-segment depression. RHI did not predict Ex-ECG ST-segment depression in these women, indicating that endothelial dysfunction and ST-segment depression may not be related and, instead, may independently predict poor CV outcomes.

Compared with the current study results, previous studies reported lower incidences of Ex-ECG ST-segment depression in

TABLE 2 Exercise variables and RHI between patients with and without ST-segment depression (n = 29)

Variable	No ST-Segment Depression, n = 11	ST-Segment Depression, n = 18	*P* Value
Resting HR, bpm	70.4 ±10.1	69.3 ±9.7	0.79
Resting SBP, mm Hg	127.1 ±11.5	122.2 ±16.5	0.11
Exercise max HR, bpm	162.0 ±12.2	162.7 ±17.2	0.90
Exercise max SBP, mm Hg	161.6 ±12.3	157.1 ±21.9	0.64
METs achieved	10.7 ±1.9	10.7 ±2.0	0.56
HR recovery, bpm	49.6 ±23.4	43.2 ±11.0	0.86
RHI	2.4 ± 0.7	2.6 ±0.6	0.36

Abbreviations: HR, heart rate; RHI, reactive hyperemia index; SBP, systolic blood pressure; SD, SD. Data are presented as mean ±SD.

TABLE 3 Regression modeling of exercise variables as outcome considering continuous RHI (n = 29)

Variable	OR/Estimate (95% CI)	*P* Value
Positive Ex-ECG[a]	2.1 (0.6 to 8.5)	0.27
DTS	−0.9 (−2.5 to 0.8)	0.30
ST/HR index	−0.2 (−0.5 to 0.2)	0.44

Abbreviations: CI, confidence interval; DTS, Duke Treadmill Score; Ex-ECG, exercise electrocardiography; HR, heart rate; OR, odds ratio; RHI, reactive hyperemia index; ST, ST-segment depression.
[a] Outcome is OR; all others are estimates.

asymptomatic women, but there are important differences between this study and previous studies that may explain our observations. In our study, mean age was 54 years, average METs achieved was 11, and 93% of women achieved target HR. In the Lipid Research Clinics Prevalence Study, Mora et al.. reported an Ex-ECG ST-segment depression incidence of 4.7% among approximately 3000 asymptomatic women. However, the women in the study were on average 10 years younger than the women in our population, achieved a mean of 7.2 METs, and only approximately 65% of women achieved target HR.[19] Similarly, in the St. James Women Take Heart Project cohort, Gulati et al.. reported a ST-segment depression incidence of 6.2% among 5721 asymptomatic women. Although the women in this study were similar in age to the women in our study, they also only achieved an average of 8 METs.[20] Finally, Balady et al reported a ST-segment depression incidence of 3.8% among 1612 asymptomatic female offspring of the original Framingham Heart Study participants. Again, the average age was 10 years lower and exercise treadmill testing was stopped when 85% of maximal HR was reached, regardless of the participant's ability to continue exercising, which the authors identified as a potential reason for decreased frequency of ST-segment depression.[21] In contrast, in our population, the mean maximum HR achieved was 97%. To further support the idea that older age contributed to our current findings, Profant et al. demonstrated a 67% incidence of Ex-ST-segment depression in asymptomatic women age ≥ 60 years, compared with only 5% in women age 30 to 39 years.[22]

A further explanation for the increased incidence of positive Ex-ECG results may be a result of the methods used in this study. We used 12-lead ECG analysis, whereas some other studies have based their analyses on the orthogonal lead system. In the studies mentioned above, the Lipid Research Clinics Prevalence Study used the orthogonal lead system rather than the 12-lead system, and the St. James Women Take Heart Project did not specify the leads they analyzed for ST-segment depression.[19,20] Another study by Cournot et al. found that 10% of asymptomatic women had ST-segment depression on Ex-ECG; but again, they looked at the orthogonal leads and leads V_1 through V_6.[23] For this study, we looked at all 12 leads and found that 83% of ST-segment depression occurred in leads II, III, and aVF. With studies looking only at precordial leads and orthogonal leads, ST-segment depression may be missed.

The peripheral vascular endothelial function test results seen in our study are consistent with those of prior studies. As aforementioned, the mean RHI in our population was 2.51 (range, 1.41-4.34). Mulvagh et al... published a study on endothelial function of healthy, recently menopausal women (age 42-59 years) without a history of CV disease or symptoms and reported a mean RHI of 2.4 (range, 1.26-5.44).[24] Lind's study of middle-aged individuals (average age 50 years) reported a mean RHI of 2.3.[25] Both Mulvagh et al and Lind also showed that RHI was not associated with standard risk-assessment algorithms.[24,25] Similarly, in this study we did not see any significant differences between the normal and abnormal RHI groups in age, body mass index, HR, blood pressure, or exercise variables including METs achieved, exercise duration, and Duke Treadmill Score. As has been suggested by several studies, RHI is not associated with traditional Framingham risk factors but is associated with adverse CV outcomes, and therefore it may be useful as an additional, independent component to stratify CV risk.[24,26]

4.1 | Study limitations

Our Ex-ECG ST-segment testing and peripheral endothelial testing were conducted at times of convenience on average 2.3 years apart, although under similar fasting and testing conditions. Additionally, in choosing to study asymptomatic, middle-aged, overweight women, we had relatively few women with abnormal endothelial function, and therefore were likely underpowered to detect relationships. Although we assumed that the subjects in our population were free of obstructive CAD, given that they all were asymptomatic and without any traditional CV risk factors, the presence of obstructive CAD cannot be entirely excluded. Finally, our self-referred cohort may have a referral bias that could have contributed to the relatively high rate of abnormal Ex-ECG response.

5 | CONCLUSION

Our pilot study demonstrates a relatively high prevalence of ST-segment depression and peripheral vascular endothelial dysfunction in asymptomatic, middle-aged, overweight reference control women. Peripheral vascular endothelial dysfunction did not predict Ex-ECG ST-segment depression. Either endothelial function testing and Ex-ECG testing provide CV prognostic risk stratification independently, or our pilot study may have been underpowered to detect relations to Ex-ECG ST-segment depression, as the sample size of women with abnormal peripheral endothelial function was small. Our work highlights the need for a larger, more definitive study investigating the utility of both vascular endothelial testing and Ex-ECG for IHD diagnostic and management purposes in women.

Conflict of interest

The authors declare no potential conflicts of interest.

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