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Clinical Investigations

Electrocardiogram Abnormalities Predict Angiographic Coronary Artery Disease in Women with Chest Pain: Results from the NHLBI WISE Study

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Summary

Background and hypothesis: Noninvasive risk stratification for coronary artery disease (CAD) is less accurate in women than in men. Based on recent reports that gender-specific exercise electrocardiogram (ECG) parameters predict CAD, we evaluated the independent predictive value of the resting ECG for angiographic CAD in women with chest pain.

Methods: Women (n = 850, mean age 58 years) with chest pain in the NHLBI Women's Ischemia Syndrome Evaluation (WISE) underwent 12-lead ECG testing and quantitative coronary angiography.

Results: Significant angiographic CAD (≥ 50% stenosis in ≥ 1 coronary) was present in 39% of women. Q waves in ≥ 2 contiguous ECG leads were present in 107 women (13%), including 49 of 657 (7%) without history of infarction. Among 585 women without prior infarction or revascularization, 48% of those with Q waves in contiguous leads versus 26% of others, had significant CAD (p = 0.003; odds ratio [OR] = 2.5, 95% confidence interval [CI] = 1.3–4.8). Women with Q waves in ≥ 2 inferior ECG leads were particularly likely to have CAD (63 vs. 26% of others, p < 0.001; OR = 4.6, 95% CI = 2.0–10.8). Other ECG findings predictive of CAD were any ST-T abnormality (OR = 1.9, 95% CI = 1.3–2.8) and T-wave inversion (OR = 2.4, 95% CI = 1.3–4.2). In risk-adjusted analysis, inferior Q waves and T-wave inversion independently predicted significant CAD. When considered together with radionuclide perfusion test results, T-wave inversion on resting ECG added significant independent predictive value (OR = 2.8, 95% CI = 1.1–7.2, p = 0.03).

Conclusions: Selected resting ECG parameters independently predict angiographic CAD in women with chest pain, including women who have also undergone radionuclide stress testing. Prospective studies should consider resting ECG parameters in diagnostic algorithms for CAD in women.

Key words: coronary artery disease, chest pain, women, electrocardiogram

Introduction

Among American women, atherosclerotic coronary artery disease (CAD) is the leading cause of death.[1] While chest pain is the most common initial presentation of CAD in women, it has been well established that women presenting with chest pain are substantially less likely to have angiographic CAD than men presenting with comparable symptoms.[2] Given the expense and patient burden of coronary angiography, it would be advantageous to obtain an approximate assessment of a

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woman's risk of having CAD, using less costly and less invasive diagnostic methods.

The resting electrocardiogram (ECG) has been used for many years for the diagnosis of heart disease. Recent reports have indicated that when applied in a gender-specific fashion, novel exercise ECG parameters may be predictive of CAD in women.[3] To determine the independent and additive predictive value of the resting ECG for angiographic CAD in women, the Women's Ischemia Syndrome Evaluation (WISE) examined the prevalence of ECG abnormalities and the independent diagnostic value of ECG parameters for angiographic CAD in women with chest pain.

Materials and Methods

Study Design

The National Heart, Lung and Blood Institute-sponsored WISE study is a four-center study whose primary aim is to develop optimal methods for the diagnosis of CAD in women with chest pain.[4] Briefly, women undergoing clinically indicated angiography for chest pain symptoms or suspected myocardial ischemia, outside of the setting of recent infarction or coronary intervention, were approached for enrollment in the study if other inclusion criteria were met.[4] Each participating center obtained appropriate institutional review board approval and written participant consent before the initiation of testing. This report examines 850 women consecutively enrolled in WISE who had an interpretable resting ECG and underwent coronary angiography. Age and self-reported risk factors (hypertension, dyslipidemia, diabetes requiring therapy, history of cigarette smoking, and any family history of CAD) were recorded at study entry.

Electrocardiogram Interpretation

A resting 12-lead ECG was performed at study enrollment. The ECGs were masked to subject identifiers and were interpreted at a core reading laboratory by a single investigator (SER). Parameters evaluated included heart rhythm and rate, presence of left ventricular hypertrophy using a validated gender-specific definition,[5] standard intervals (PR, QRS, QT_c), presence and type of intraventricular conduction delay, ST-T wave abnormalities (ischemic-appearing ST depression or elevation, ST-segment strain, symmetrical T-wave inversions [≥ 1 mm] in at least two contiguous leads, nonspecific ST-T changes [e.g., T-wave flattening]), and Q waves (≥ 0.04 s or ≥ 25% of R-wave amplitude; QS complexes ≥ 0.04 s were tabulated as "Q waves").

Angiographic Data Assessment

All women enrolled in WISE underwent clinically indicated coronary angiography. Quantitative analysis was performed off-line at the WISE angiographic core laboratory by staff blinded to all other subject data (Rhode Island Hospital, Providence, R.I.). Luminal diameter was measured at all stenoses and at nearby reference segments using an electronic ciné projector-based "cross hair" technique (Vanguard Instrument Corporation, Melville, N.Y., USA). This technique is analogous to electronic calipers built into the hood of the ciné projector, removes viewer parallax, and compares favorably with methods using automated edge detection (standard deviation of the mean difference in measured percent stenosis between the two methods was < 8%).[6] The ciné view chosen for quantitative analysis minimized vessel foreshortening and overlap. Women with one or more ≥ 50% diameter stenoses were classified as having significant CAD.

Noninvasive Stress Testing

Because the WISE study did not include a standard protocol for stress testing, subjects underwent a variety of clinically indicated stress tests prior to coronary angiography. Exercise ECG tests were defined as positive if there were no baseline abnormalities (ST changes or left bundle-branch block), and exercise was associated with ST-segment depression of ≥ 1 mm in at least two contiguous leads.

Radionuclide perfusion studies were performed according to site-specific protocols and interpreted on site. These studies, either exercise or pharmacologic stress tests assessed with various scan methodologies, were classified as positive if at least one redistributing perfusion abnormality was noted. Dobutamine stress echocardiograms were evaluated using previously described standard techniques;[7] results were classified as positive if the peak dobutamine score for systolic thickening and excursion was greater than the baseline score in ≥ 1 segment.

Statistical Methods

Association of dichotomous outcomes with dichotomous and unordered variables including proportions was performed using the chi-square test or Fisher's exact test when any expected cell size was < 5. Association of outcomes with ordered categorical variables was assessed using the Mantel-Haenszel chi-square statistic. Logistic regression was used to examine and quantify associations of ECG parameters with presence of significant CAD. Multivariate models were constructed using forward stepwise selection, with a p value of ≤ 0.05 for entry. Reported CIs for ORs use Wald confidence limits, and p values given are based on the Wald test for significance of the corresponding coefficient in the logistic model. In this exploratory analysis, a level of 0.05 is reported as statistically significant.

Results

Subject Characteristics

The study cohort of 850 women, 81% of whom were Caucasian, ranged in age from 20 to 86 years (mean 58.0 ±

11.6). Of these, 84% were postmenopausal, defined as having had either a prior hysterectomy and bilateral oophorectomy or no menstrual period within the past year. Atherosclerosis risk factors were frequently reported: diabetes in 26%, hypertension in 59%, dyslipidemia in 55%, any family history of CAD in 67%, and history of cigarette smoking in 54% of the women. Prior myocardial infarction (MI) was self reported in 21% of women; 7% had prior coronary artery bypass graft surgery (CABG) and 15% had prior percutaneous catheter-based intervention (PCI). Overall, a history of CAD (MI, PCI, or CABG) was reported in 29%. Quantitative coronary angiography, which was technically adequate in 837 of these women, demonstrated that 330 women (39%) had significant CAD.

Prevalence of Electrocardiogram Abnormalities in the WISE Population

Q waves: Q-wave MI, defined as Q waves in at least two contiguous ECG leads, was present in 107 (12.6%) of the 849 women who had interpretable ECGs in all leads. Specifically, 57 women (6.7%) had Q waves in at least two of the inferior leads (II, III, aVF), 6 (0.7%) had Q waves in either both of the high lateral leads (I, aVL) or two adjacent anterolateral leads (V_4, V_5, V_6), and 56 (6.6%) had Q waves in at least two anteroseptal leads (V_1, V_2, V_3). Q waves were more prevalent among women with a prior documented MI ($p < 0.001$ vs. women without prior MI, Fig. 1). However, among the 171 women with a history of MI, fewer than one-third (54, or 31.6%) had Q waves, suggesting that non-Q-wave MI occurred more commonly than Q-wave MI in this population. It was of interest that of the 657 women without a history of prior MI, Q waves in at least two contiguous leads were noted in 49 (7.5%), suggesting that these women may have had "silent" MIs.

Other ECG parameters: Mean PR interval was 161 ± 28 ms (range 100–330), QRS duration was 88 ± 17 ms (range 60–200), and QTc interval was 430 ± 30 ms (range 300–566). While 670 women (78.8%) had no intraventricular conduction delay (IVCD), left bundle-branch block (LBBB) was reported in 5.4% of women (2.6% complete, 2.8% incomplete), right bundle-branch block in 2.5% (1.6% complete, 0.9% incomplete), nonspecific conduction delay in 12.6%, and other conduction delays including bifascicular block in 0.6%. Normal ST-T waves were noted in 538 women (63.3%), while 20.1% had nonspecific ST-T-wave changes, 11.3% had symmetrical T-wave inversions in at least two contiguous leads, 2.4% had ST elevation, and 2.7% showed a strain pattern. Left ventricular hypertrophy was detected in 12.4% of women.

Association between Q Waves and Angiographic Coronary Artery Disease

To improve the noninvasive diagnosis of angiographic CAD in women with chest pain in the absence of a prior history of CAD, we studied the predictive value of ECG findings for CAD in 585 women with chest pain and no prior history of MI, CABG, or PCI (i.e., no known CAD). Of these, 163 (27.9%) were found to have significant angiographic CAD. Analysis of ECG findings demonstrated that angiographic CAD was present in 20 of 42 (47.6%) women with Q waves in at least two contiguous leads, versus 143 of 542 (26.4%) women without Q-waves ($p = 0.003$ for association of Q waves with CAD). Women with at least two Q waves in any set of contiguous leads had more than 2.5 times higher odds of significant angiographic CAD than those without Q waves (OR = 2.54, 95% CI = 1.34–4.79, $p = 0.004$ for Wald test that OR is different from 1).

Analysis of specific leads demonstrated that inferior Q waves had the greatest predictive value for CAD in these women with chest pain (Fig. 2). Specifically, the 24 women with Q waves in at least two inferior leads (II, III, aVF) had 4.6-fold higher odds of having significant CAD than the 560

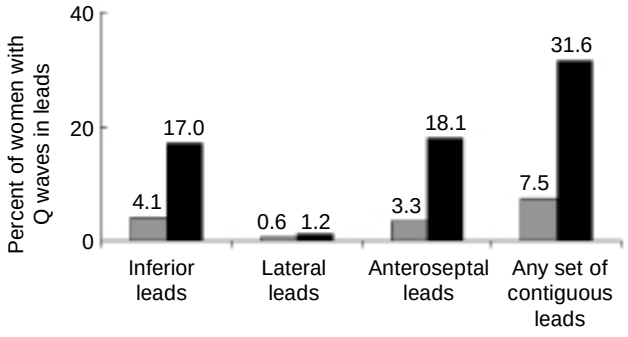

FIG. 1 Evidence of Q-wave myocardial infarction (MI) in leads, according to history of previous MI. ($p < 0.001$ for test of association between history of previous MI and each of: Q waves in inferior leads, Q waves in lateral leads, Q waves in anteroseptal leads, and Q waves in any set of contiguous leads.) ▭ = No history of MI, ■ = history of MI.

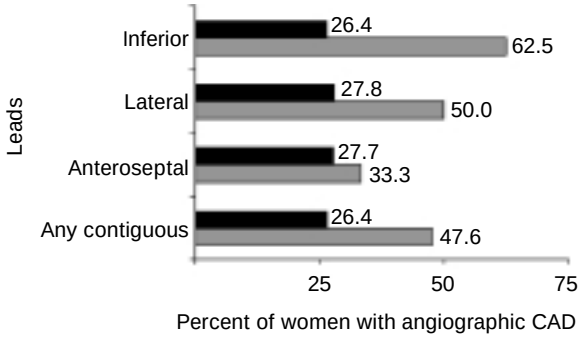

FIG. 2 Prevalence of angiographic coronary artery disease (CAD), according to presence or absence of Q waves in leads, among women without previous myocardial infarction, percutaneous intervention, or coronary artery bypass graft. ($p < 0.001$ for test of association between significant CAD and Q waves in inferior leads; $p = 0.003$ for test of association between significant CAD and Q waves in any set of contiguous leads). ▭ = Q waves present in leads, ■ = no Q waves present in leads.

women without inferior Q waves (OR = 4.64, 95% CI = 1.99–10.83, p < 0.001). In contrast, Q waves in the anteroseptal leads V_1–V_3, observed in 18 women, were not significantly associated with increased odds of CAD (OR = 1.30, 95% CI = 0.48–3.53). Of note, CAD was present in two of nine women with Q waves in leads V_1 and V_2 only, and in four of nine women with Q waves in all three anteroseptal leads. Q waves in the lateral leads (I, aVL or $V_{4–6}$), noted in only four women, were also not significantly predictive of CAD.

Inferior Q waves were infrequent among women without CAD. Thus, this ECG pattern has a high specificity (97.9%) but a relatively poor sensitivity (9.2%) for angiographic CAD among women without previous history of CAD. The rarely observed Q waves in the anteroseptal and lateral leads also had extremely high sensitivity (97.1 and 99.5%, respectively) and negligible sensitivity (3.7% and 1.2%) for detecting CAD. Among all women studied, including those with CAD history, specificity and sensitivity of inferior Q waves for CAD were 97.2 and 13.0%, respectively. Use of the diagnostic criterion of Q waves in any set of contiguous leads increased sensitivity for significant CAD to 12.3% with slightly decreased specificity (94.8%) among women without CAD history; corresponding values for the entire cohort of women studied were 20.9% sensitivity and 92.7% specificity.

Other Electrocardiogram Parameters Associated with Angiographic Coronary Artery Disease

Table I shows the prevalence of significant angiographic CAD according to other ECG parameters among the 585 women without a prior history of CAD. The absence of normal sinus rhythm was not associated with CAD (sensitivity of any abnormal rhythm for detecting CAD = 22.1%, specificity = 76.8%), nor was left ventricular hypertrophy (sensitivity = 12.1%, specificity = 90.3%). There was a statistically significant association between CAD and longer PR and QT_c intervals (interval measures are presented classified into quartiles as much as is possible given data clustering; sensitivity of PR interval ≥ 180 ms = 30.0% and specificity = 78.4%; sensitivity of QT_c interval ≥ 450 ms = 29.6% and specificity = 79.8%). The IVCD pattern was not significantly associated with CAD, although there was a trend toward more CAD among the 28 women with complete or incomplete left bundle-branch block, 42.9% of whom had CAD versus 27.1% of others (p = 0.07; sensitivity of complete/incomplete LBBB for predicting CAD = 7.4%, specificity = 96.2%). Presence of any ST-T abnormalities was significantly associated with angiographic CAD. Of women with any such abnormality (vs. normal ECG or presence of strain pattern), 37.4% had significant CAD, compared with 23.8% of women without ST-T abnormalities (OR = 1.90, 95% CI = 1.30–2.79, p < 0.001; sensitivity = 39.9% and specificity = 74.2%). This association is in large part due to a particularly strong relationship of T-wave inversions to presence of angiographic CAD. Of the 55 women with T-wave inversions, 45.5% had CAD compared with 26.0% of all other women (OR = 2.37, 95% CI = 1.35–4.17, p = 0.003; sensitivity = 15.3% and specificity = 92.9%).

TABLE I Proportion of women without previous myocardial infarction, coronary artery bypass graft, or percutaneous coronary intervention (i.e., no preexisting coronary artery disease [CAD]) who were found to have significant angiographic CAD according to various electrocardiogram parameters

	No. of women with characteristic	Proportion with significant CAD (%)
Underlying rhythm		
Normal sinus	451	28.2
Sinus bradycardia	110	27.3
Sinus tachycardia	15	26.7
Atrial fibrillation	6	33.3
Other	3	0
Left ventricular hypertrophy		
Present	59	32.2
Absent	510	27.1
Intervals (ms)		
PR [b]		
< 140 ms	77	16.9
140–150 ms	183	26.8
160–170 ms	178	28.1
≥ 180 ms	138	34.8
QRS		
< 80 ms	66	34.8
80 ms	247	29.6
90 ms	156	19.9
≥ 100 ms	113	31.0
QT_c [a]		
< 408 ms	132	22.7
408–424 ms	154	26.6
425–449 ms	164	26.2
≥ 450 ms	133	36.1
Intraventricular conduction delay (IVCD)		
None	476	27.5
LBBB	16	37.5
Incomplete LBBB	12	50.0
RBBB	10	30.0
Incomplete RBBB	6	33.3
Nonspecific IVCD	63	23.8
Other	2	0
ST-T waves [b]		
Normal	399	23.8
ST-T-wave changes	111	31.5
T-wave changes	55	45.5
ST elevation	6	66.7
Strain pattern	12	25.0
Other	2	50.0

[a] p < 0.05.

[b] p < 0.01 for significance of test of association between characteristic and presence of significant angiographic CAD.

Abbreviations: LBBB = left bundle-branch block, RBBB = right bundle-branch block.

Incremental Predictive Value of Electrocardiographic Findings for Coronary Artery Disease

Electrocardiogram findings such as significant Q waves, ST-T abnormalities, conduction delays, and abnormal intervals were considered along with traditional atherosclerosis risk factors (age, menopausal status, smoking, diabetes, and hypertension) as predictors of CAD in the 585 women without prior CAD. While age and diabetes were the strongest predictors of CAD in the final multivariate logistic model, the presence of Q waves in at least two inferior leads (II, III, aVF) and the presence of T-wave inversions were also independent predictors of significant angiographic CAD (OR = 3.37, 95% CI = 1.35–8.41, p = 0.009 and OR = 2.53, 95% CI = 1.35–4.72, p = 0.004, respectively). No other ECG findings were found to be significant multivariate predictors.

Exploratory analysis was performed to evaluate the predictive value of noninvasive stress tests for angiographic CAD in women without prior CAD after adjustment for age and diabetes. A positive exercise test was not significantly predictive of significant CAD in 218 women studied (OR = 1.44, 95% CI = 0.73–2.84, p = 0.29). A positive dobutamine stress echocardiogram was not significantly predictive of CAD in 124 women studied (OR = 1.25, 95% CI = 0.35–4.47, p = 0.74). A positive radionuclide perfusion test (≥ 1 redistribution abnormality) was significantly predictive of CAD after adjustment for other factors in 288 women studied (OR = 2.39, 95% CI = 1.36–4.19, p = 0.002). When baseline ECG parameters were considered, the presence of T-wave inversions added significant predictive value to that of an abnormal radionuclide perfusion test in the multivariate model (OR = 2.82, 95% CI = 1.11–7.16, p = 0.03). None of the Q-wave abnormalities considered, including perfusion test results, were statistically significant in multivariate models, although presence of inferior Q waves showed a strong trend (adjusted OR = 3.15, 95% CI = 0.90–10.97, p = 0.07).

Discussion

Coronary artery disease is the leading cause of death among American women. There is a need for developing improved algorithms to diagnose CAD in women because the sensitivities and specificities of traditional noninvasive tests used to evaluate chest pain are lower in women than in men,[8–12] and women are less likely to be referred for invasive coronary angiography to evaluate chest pain.[13, 14] Our results indicate that the resting ECG provides independent prognostic information for the diagnosis of significant angiographic CAD in women with chest pain that is severe enough to warrant referral for coronary angiography. Furthermore, when used in conjunction with a radionuclide perfusion stress test, the resting ECG provides incremental predictive value for angiographic CAD in these women.

The clinical evaluation of chest pain in women frequently poses a diagnostic dilemma. Resting ECGs are commonly abnormal in women, possibly related to the digitalis-like chemical structure of circulating estrogen.[15, 16] As a result, clinicians may underestimate the utility of the resting ECG in the risk stratification of women with chest pain. Previously, the predictive value of the resting ECG was suggested by the observed association between inferior Q waves and angiographic CAD in a predominantly male cohort with depressed left ventricular systolic function.[17] Our study of women with chest pain and normal ventricular function confirms that Q waves in the inferior leads, and symmetrical T-wave inversions, are independent highly specific predictors of angiographic CAD. In view of the fact that women are less likely than men to undergo invasive diagnostic evaluation of CAD,[13, 14] our results suggest that the presence of inferior Q waves or symmetrical T-wave inversions should increase the clinical suspicion of CAD in women with chest pain.

Women with chest pain who are suspected to have CAD are commonly risk stratified by noninvasive stress tests. In general, the limitations of these various tests are more pronounced in women than in men, due in part to the lower prevalence of CAD in women and the infrequent use of gender-specific criteria.[7–12] Because these various stress tests have limited positive predictive value for CAD, it is important to develop clinical models that will improve the accuracy of screening women with chest pain. Our findings suggest that the simple and inexpensive ECG may provide incremental diagnostic utility for CAD when considered in the context of findings from a stress radionuclide perfusion study. Specifically, we found that the presence of symmetrical T-wave inversions on the resting ECG in women with chest pain is associated with nearly three-fold increased odds of angiographic CAD after controlling for radionuclide stress test results. Therefore, in women with chest pain, resting ECG parameters should be analyzed in conjunction with radionuclide stress tests performed to determine the clinical probability of CAD. Future studies implementing uniform testing protocols are needed to elucidate myocardial territory-specific relationships between ECG abnormalities, perfusion test results, and angiographic CAD.

Our study also provides epidemiologic insight into the clinical manifestations of CAD in women. First, we found that fewer than one-third of all women with a known history of MI had significant Q waves on their resting ECG. This suggests that most women with an MI diagnosed prior to enrollment in WISE had a non-Q-wave infarction, although it is possible that the prevalence of old Q-wave infarcts may have been underestimated due to Q-wave regression. Second, a small but appreciable proportion (7.5%) of women without a previous history of MI had significant Q waves on the resting ECG. These data likely represent the prevalence of "silent" MI in this cohort of women with severe chest pain. Given the strong association between Q waves and angiographic CAD demonstrated in our study, these data suggest that women with chest pain and Q waves on their resting ECG should be considered for further evaluation of CAD regardless of their prior cardiac history.

Of the women without history of CAD, 30.5% reported unstable symptoms during the 6 weeks prior to enrollment. Our key findings, including association of inferior Q waves with

CAD and the incremental predictive value of T waves combined with radionuclide testing, remained highly significant when these women were excluded from the analysis.

Limitations

The WISE study evaluated the utility of ECG testing in a large, multicenter population of women with chest pain who underwent diagnostic coronary angiography. This study design limits the generalization of our findings to other clinically important groups of women, including those without chest pain and those with mild chest pain that has not prompted further clinical evaluation. In addition, despite the strong association of several ECG findings with the presence of angiographic CAD, the utility of these measures for CAD diagnosis may be limited by poor sensitivity, which was at most in the 20% range. Finally, our criteria for defining ECG abnormalities, while consistent with those used in clinical practice, vary slightly from those used in other reports including the recent Joint European Society of Cardiology/American College of Cardiology (ESC/ACC) definitions.[18] Nevertheless, the specificity and positive predictive values of these parameters are relatively high, suggesting that the resting ECG may have clinical utility in determining the probability of angiographic CAD in women with chest pain, even in those who have also undergone radionuclide stress testing.

Conclusions

Our results suggest that significant Q waves or T-wave inversions on the resting ECG are independent predictors of angiographic CAD in women with chest pain. The presence of resting T-wave inversions also provides incremental predictive value for angiographic CAD when considered in conjunction with results from radionuclide stress tests. Future prospective studies should evaluate the use of resting ECG parameters as a component of multivariate clinical models to predict the presence of angiographic CAD in women with chest pain.

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