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Electrocardiographic Predictors of Cardiovascular Outcome in Women

The National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study

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OBJECTIVES We sought to analyze the value of infrequently measured parameters of the 12-lead electrocardiogram (ECG) in predicting cardiovascular events in women with suspected myocardial ischemia who were referred for cardiac catheterization.

BACKGROUND Routinely analyzed ECG parameters have low predictive value for cardiovascular events in women with preserved left ventricular function and suspected myocardial ischemia. The predictive value of ECG parameters for cardiovascular disease has not been fully determined.

METHODS Women enrolled in the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) study who had complete digital 12-lead ECG and quantitative angiography data were studied. Clinical and ECG predictors of cardiovascular disease events, defined as death, congestive heart failure, and non-fatal myocardial infarction, were determined.

RESULTS Of 143 women with ECG and angiographic data (mean age 59 ± 13 years, left ventricular ejection fraction 64.1 ± 8.6%), 13% had events during a mean follow-up period of 3.3 ± 1.6 years. Independent predictors of event occurrences included a wider QRS-T angle (i.e., the spatial electrical angle between the QRS complex and the T-wave; $p = 0.0005$), wider QRS complex ($p = 0.004$), longer QTrr (i.e., age- and gender-adjusted QT interval; $p = 0.0004$), a more depressed ST-segment in precordial lead V_5 ($p = 0.0002$), and a higher coronary artery disease severity score ($p = 0.02$).

CONCLUSIONS Several 12-lead ECG parameters, such as the QRS-T angle and the QRS and QTrr duration, are predictive of future cardiovascular events in women with suspected myocardial ischemia. (J Am Coll Cardiol 2005;46:51–6) © 2005 by the American College of Cardiology Foundation

Routinely measured and novel parameters of the surface electrocardiogram (ECG) have been shown to be predictive of cardiovascular outcomes in select populations. Prolongation of the QRS interval, for example, has been shown to be a predictor of mortality in patients with congestive heart failure (CHF) (1). The rate-adjusted QT interval (QTrr) and the spatial electrical angle between the QRS complex and the T-wave (QRS-T), two parameters that characterize ventricular repolarization, also have been found to confer prognostic value (2,3). However, ECG abnormalities suggestive of ischemic heart disease are less likely to be diagnostic in women than in men (4). In the present study, we analyzed the 12-lead ECGs of women enrolled in the Women's Ischemia Syndrome Evaluation (WISE) study, which aims at improving diagnostic testing in women with ischemic cardiovascular disease (5). All women were referred for clinically indicated cardiac catheterization to evaluate for suspected myocardial ischemia. In this report, the independent predictive values of both routinely measured and sophisticated ECG parameters, such as QRS-T angle, QRS interval, and the gender-adjusted QTrr interval, for cardiovascular events were evaluated.

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METHODS

Study design. The WISE study, a National Heart, Lung, and Blood Institute-sponsored four-center study, aims to improve diagnostic testing in the evaluation of ischemic heart disease in women. Between 1996 and 2000, 954 women with suspected myocardial ischemia that prompted clinical referral for diagnostic coronary angiography were

Abbreviations and Acronyms

CAD = coronary artery disease
CHF = congestive heart failure
CI = confidence interval
ECG = electrocardiogram/electrocardiographic
HR = hazard ratio
MI = myocardial infarction
QRS-T = spatial electrical angle between the QRS complex and the T-wave
QTrr = age- and gender-adjusted QT interval
WISE = Women's Ischemia Syndrome Evaluation

enrolled. Each site obtained institutional review board approval and participant consent before testing. Major exclusion criteria for the WISE study were comorbidity that would compromise one-year follow up, pregnancy, contraindications to provocative diagnostic testing, cardiomyopathy, New York Heart Association functional class III to IV CHF, recent myocardial infarction (MI), significant valvular or congenital heart disease, and a language barrier to questionnaire testing. Details of the design of the WISE study have been published elsewhere (5).

Baseline evaluation included a physical examination and collection of clinical and laboratory data, including use of medication. Age and self-reported risk factors (history of hypertension, diabetes, cigarette smoking, any family history of coronary artery disease [CAD], and history of CHF) were recorded at study entry. For analyses, dyslipidemia was defined as use of lipid-lowering medication (statins and others), a low-density lipoprotein cholesterol value of ≥130 mg/dl for women without any angiographic evidence of CAD, or a low-density lipoprotein cholesterol level of ≥100 mg/dl for those with angiographic evidence of CAD. Cholesterol levels were analyzed at the WISE lipid core laboratory at the Cedars Sinai Medical Center, which is enrolled in the Centers for Disease Control and Prevention lipid standardization program.

This report examined 143 women from the University of Pittsburgh WISE site who had complete angiographic and baseline data and who had ECGs that were stored digitally. Women with left or right bundle branch block patterns or with non-specific ventricular conduction abnormalities on their surface ECG were excluded from analyses.

ECGs. A resting 12-lead ECG was performed at study enrollment. The ECGs were masked to subject identification, digitized at acquisition, and sent to a core laboratory for interpretation using previously reported methods for ECG analyses (6,7). Measured variables included the heart rate and the PR, QRS, and QT intervals (both before and after adjustment for gender and race). We also measured ECG parameters that are infrequently analyzed, such as the root mean square of heart rate variations; the J point, ST-segment, and T-wave amplitudes in various leads; the QRS-T angle; the non-dipolar components of the QRS and T waves; the third component as well as the ratio of the third to second component of the Chebyshev waveform vector magnitude; the elevation and azimuth of mean T vector; the mean T vector spatial magnitude; and the interval from the first to second inflection point of the T-wave. A full description of the derivation methods for these parameters is described in detail elsewhere (6–8). Variables were selected for use in these analyses because of their association with repolarization, risk assessment, or myocardial ischemia. The spatial angle between the mean QRS and T vectors (QRS-T angle) was derived from waveform vector analysis, similar to principal component analysis or singular value decomposition (6). The amplitude of the ST-segment in precordial lead V_5 60 ms after the end of the QRS complex, measured in microvolts ($ST60V_5$), has been previously associated with myocardial ischemia (8).

Angiographic data. All women in the WISE study underwent clinically indicated coronary angiography. Quantitative analysis was performed off-line at the WISE angiographic core laboratory at Rhode Island Hospital according to methods that have been previously published (9). Significant CAD was defined as the presence of at least one angiographic stenosis ≥50% of the luminal diameter. The CAD severity score was defined as an aggregate of percent luminal stenosis, extent and location of stenosis, and degree of collateral vessels (9).

Follow-up. An experienced nurse and/or physician collected in person or by telephone interview follow-up data at six weeks and then yearly thereafter. Each woman was queried for the occurrence of adverse outcomes such as hospitalization for angina, CHF, stroke, vascular conditions, MI, and death. When an adverse outcome was identified, the referring physician was contacted for confirmation, dates, and documentation.

Statistical analyses. Clinical and demographic data are summarized as means and standard deviations for clinical variables and as frequencies for categorical variables. Electrocardiographic variables are presented as medians with the interquartile range shown. Data also are presented as event rates for the median split for each of the ECG parameters. Comparisons of ECG variables in women with and without adverse events were done using two sample signed rank Wilcoxon tests. Coronary artery disease was defined as a dichotomous variable (CAD/no CAD) and as a continuous variable (severity score). Univariate and multivariable Cox proportional hazards regression models were used to identify predictors of adverse events. Cross correlations between ECG variables were examined before running any multivariate analyses. These events were defined as composite end points in two ways: 1) CHF, non-fatal MI, or death or 2) hospitalization for angina, CHF, non-fatal MI, or death. Variables were chosen for entry into the multivariable Cox models based on univariate associations using a stepwise procedure. For the Cox proportional hazards model, the hazard ratio (HR) and 95% confidence intervals (CIs) were calculated. Hazard ratios are shown per 10 units for ease of understanding. All tests were two-sided, and p values <0.05

Table 1. Demographic Characteristics and Coronary Artery Disease Risk Factors of the Study Population (n = 143)

Variables	Mean ± SD or %
Age (yrs)	59 ± 13
Non-white (%)	16.1
Postmenopausal (%)	73.2
Current hormone replacement therapy (%)	30.1
Total cholesterol (mg/dl)	189 ± 47
HDL-C (mg/dl)	53 ± 12
LDL-C (mg/dl)	108 ± 42
Triglycerides (mg/dl)	140 ± 92
Systolic blood pressure (mm Hg)	138 ± 23
Diastolic blood pressure (mm Hg)	77 ± 12
Pulse rate (beats/min)	73 ± 12
Body mass index (kg/m^2)	29.7 ± 6.8
Angiographic severity score of CAD	20 ± 17
Left ventricular ejection fraction (%)	64.1 ± 8.6
History of diabetes (%)	31.7
History of dyslipidemia (%)	57.4
History of hypertension (%)	59.4
Current smoking (%)	20.3
History of congestive heart failure (%)	7.7
Angiographic CAD (≥50% stenosis in one or more epicardial artery) (%)	57.3
Antiarrhythmic agents (%)	0.7
ACE inhibitors (%)	27.3
Beta-blockers (%)	51.0
Calcium channel blockers (%)	29.4
Other antihypertensive medication (%)	30.1
Lipid-lowering medication (%)	34.3
Aspirin (%)	74.1
Antidepressants (%)	17.5

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

were considered statistically significant. All statistics were analyzed using SAS version 8.2 (SAS Institute, Cary, North Carolina).

RESULTS

Study population. Table 1 shows the baseline demographic data and CAD risk factor profiles of the 143 women included in our analysis. Primary events, defined as death, CHF, or non-fatal MI, were documented in 18 (13%) during a mean follow-up of 3.3 ± 1.6 years.

Parameters and events. Because we examined the event rates using the median split of the ECG variables, median, interquartile range, and cardiovascular event rates for women below and above the median are presented in Table 2. Only those variables with p values >0.1 are shown. In both groups, ECG parameters of heart rate and PR, QRS, and QTrr intervals were within previously reported normal limits for women. However, women with documented death, CHF, or non-fatal MI during follow-up had significantly higher (mean ± SD) heart rates (80 ± 13 beats/min vs. 71 ± 14 beats/min, p = 0.01) and wider QRS-T angles (78 ± 31° vs. 50 ± 26°, p = 0.0008) on their baseline ECG compared with women with no events. They also had a significantly more depressed ST-segment in the lateral precordial ECG leads V_5 (−14 ± 61 μV vs. 11 ± 52 μV, p = 0.03) and V_6 (−0.78 ± 90 μV vs. −19.8 ± 51 μV, p = 0.03). There was a trend toward wider QRS complexes (93 ± 12 ms vs. 87 ± 12 ms, p = 0.08) and QTrr intervals (437 ± 36 ms vs. 420 ± 21 ms, p = 0.05) in women with events.

Using an alternative composite end point of death, CHF, non-fatal MI, or angina requiring hospitalization (62 [43%] women), the ECG findings were similar and the QRS duration was significantly longer (mean ± SD) in the women with compared with those without events (91 ± 11 ms vs. 85 ± 13 ms, p = 0.005).

Univariate analysis. Univariate analysis of all ECG parameters are shown in Table 3. The correlation between significant univariate ECG predictors is shown in Table 4. Clinical and ECG predictors of outcome in the study population are presented in Table 5. Clinical characteristics that predicted the occurrence of death, CHF, or non-fatal MI included a history of diabetes mellitus (HR 3.71; 95% CI 1.44 to 9.59; p = 0.007), dyslipidemia (HR 9.21; 95% CI 1.21 to 70.20; p = 0.03), hypertension (HR 3.83; 95% CI 1.11 to 13.25; p = 0.03), and CAD measured by

Table 2. Medians, Interquartile Range, and Cardiovascular Event Rates for Women Below and Above the Median for Each Variable

Variable	Median	Interquartile Range	Event Rates (%)		
			≤ Median	> Median	p Value
Heart rate (beats/min)	71	62–81	8.0%	17.7%	0.01
QRS interval (ms)	88	80–94	9.5%	17.0%	0.08
Gender- and race-adjusted QT interval (ms)	419	405–433	7.9%	17.9%	0.05
J-point amplitude in lead V_6 (μV)	−5	−15–24	16.2%	8.7%	0.05
ST-segment 60 ms amplitude in V_5 (μV)	10	−10–29	17.6%	7.3%	0.03
ST-segment 60 ms amplitude in V_6 (μV)	5	−14–19	14.8%	9.1%	0.03
QRS-T angle (degrees)	49	32–72	5.6%	19.7%	0.0008
Ratio of the third and second Chebyshev waveform vector magnitude (%) (roundness of T vector loop)	26.6	16–36	16.7%	8.5%	0.07
T amplitude in V_1 (μV)	0	−92–102	5.2%	21.2%	0.003
T amplitude in V_5 (μV)	205	39–336	18.1%	7.0%	0.008
T amplitude in V_6 (μV)	170	43–292	20.3%	4.4%	0.003
Azimuth of mean T vector (degrees)	22.1	0.9–40.1	5.6%	19.7%	0.005

Table 3. Univariate Predictors of Outcomes

Variable	p Value
Heart rate	0.01
PR interval	0.65
QRS interval	0.03
QT interval	0.90
Gender- and race-adjusted QT interval	0.003
Heart rate variation, root mean square	0.82
J-point amplitude in lead V_5	0.12
J-point amplitude in lead V_6	0.24
ST-segment 60 ms amplitude in V_5	0.08
ST-segment 60 ms amplitude in V_6	0.58
QRS-T angle	0.0002
Non-dipolar components of QRS	0.34
Third Chebyshev waveform	0.81
Ratio of the second/third waveform	0.07
T amplitude in V_1	0.04
T amplitude in V_5	0.02
T amplitude in V_6	0.04
Mean T vector spatial magnitude	0.36
Non-dipolar components of T-wave	0.78
Azimuth of mean T-vector	0.13
Elevation of mean T-vector	0.35
Interval from the first to second inflection point of the T-wave	0.14

the angiographic severity score (HR 1.27 per 10-U increase in score, 95% CI 1.00 to 1.62; p = 0.05).

Univariate analyses also demonstrated that ECG predictors of events included wider QRS (HR = 1.60 per 10-ms widening, p = 0.03) and QTrr (HR = 1.25 per 10-ms widening, p = 0.003) intervals, higher heart rate (HR = 1.49 per 10 beats/min increase in heart rate, p = 0.01), and a wider QRS-T angle (HR = 1.36 per 10° increase in angle, p = 0.0002) (Table 5). Similar results were obtained when the composite event was defined as death, CHF, non-fatal MI, or angina leading to hospitalization (data not shown).

Multivariate analysis. A Cox regression model was used for multivariate analyses of clinical and ECG predictors of cardiovascular events (Table 5). Variables entered into this stepwise regression model included a diagnosis of diabetes mellitus, dyslipidemia, hypertension, and ECG variables of QRS-T angle, QRS duration, QTrr, and $ST60V_5$. These analyses demonstrated that independent predictors of death, CHF, and non-fatal MI included a wider QRS-T angle (HR = 1.50 per 10° increase in the angle, p = 0.0005), a wider QRS complex (HR = 1.75 per 10-ms widening, p = 0.004) intervals, a longer QTrr (HR = 1.46 per 10-ms increase in duration, p = 0.0004), a more depressed ST segment in precordial lead V_5 (HR = 0.80 per 10 μV of depression in the ST-segment, p = 0.0002), and a higher angiographic severity score (HR = 1.40 per 10-U increase in score, p = 0.02).

DISCUSSION

Our data indicate that wider spatial QRS-T angle, QRS duration, and QTrr intervals are predictors of adverse cardiovascular events independent of CAD severity in women with suspected myocardial ischemia. These results are clinically plausible; for instance, the spatial QRS-T angle is a parameter that has been proposed to be an ECG measure of ventricular repolarization. It is defined as the angle between the main electrical axes of ventricular depolarization and repolarization; the greater the angle, the more heterogeneous and abnormal ventricular repolarization is thought to be. Abnormalities in ventricular repolarization can stem from damaged or inhomogeneous areas of myocardium, which can potentially be responsible for ventricular arrhythmias and fatal cardiovascular disease events. Clinical conditions that lead to ECG abnormalities include, among other entities, myocardial ischemia, which can be secondary to epicardial atherosclerosis or microvascular disease and systemic hypertension, which can result in myocardial hypertrophy. These diseases and others have been clearly associated with ECG abnormalities of conduction and repolarization.

Our findings are consistent with those of previous studies, which showed that increases in the spatial QRS-T angle were predictive of cardiac mortality (3). Furthermore, our study demonstrated the predictive nature of the spatial QRS-T angle in a relatively young female population, with a range of angiographic CAD, as compared with the elderly population that was previously studied (3). In addition, previous studies analyzed the predictive value of borderline and abnormal QRS-T angles, defined as QRS-T angles in the range of 105° to 135° and in the range of 135° to 180°, respectively. Our findings further expand the predictive

Table 4. Cross Correlations of ECG Variables With Each Other

Variable	HR	QRS	QTrr	QRS-T Angle	$ST60V_5$	Ratio of 2/3	T Amp in V_1	T Amp in V_5	T Amp in V_6
HR	—	−0.11	−0.14	0.07	−0.07	−0.60†	0.13	−0.13	−0.16
QRS	—	—	0.11	0.14	−0.008	−0.15	0.15	−0.18*	−0.22†
QTrr	—	—	—	−0.01	0.06	0.47‡	−0.06	−0.003	−0.02
QRS-T angle	—	—	—	—	−0.09	−0.27†	0.41†	−0.13	−0.25†
$ST60V_5$	—	—	—	—	—	−0.05	−0.07	0.62†	0.56†
Ratio 2/3	—	—	—	—	—	—	−0.26†	0.13	0.15
T amp V_1	—	—	—	—	—	—	—	−0.20*	−0.32‡
T amp V_5	—	—	—	—	—	—	—	—	0.93‡
T amp V_6	—	—	—	—	—	—	—	—	—

*p < 0.05; †p < 0.01; ‡p < 0.001.
Amp = amplitude; ECG = electrocardiographic; HR = heart rate; QTrr = age- and gender-adjusted QT interval; $ST60V_5$ = ST-segment 60 ms amplitude in lead V_5.

Table 5. Hazard Ratios and 95% Confidence Intervals for Significant Univariate and Multivariate Predictors of Cardiovascular Events

Variable	Single ECG Variable Model		Multivariable Models*	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
QRS interval per 10-ms increase	1.60 (1.06–2.43)	0.03	1.75 (1.20–2.55)	0.004
QTrr per 10-ms increase	1.25 (1.08–1.44)	0.003	1.46 (1.18–1.79)	0.0004
QRS-T angle per 10-degree increase	1.36 (1.16–1.60)	0.0002	1.50 (1.19–1.89)	0.0005
$ST60V_5$ per 10-mV increase	0.94 (0.88–1.01)	0.08	0.80 (0.71–0.89)	0.0002
Heart rate per 10-beat increase	1.49 (1.09–2.04)	0.01	—	—
Severity score per 10-U increase	1.27 (1.00–1.62)	0.05	1.40 (1.06–1.85)	0.02
History of diabetes	3.71 (1.44–9.59)	0.007	—	—
Dyslipidemia	9.21 (1.21–70.20	0.03	—	—
History of hypertension	3.83 (1.11–13.25)	0.03	—	—

*Cox proportional hazard regression model. Variables available for entry into the model included the significant univariate predictors as shown above.
CI = confidence interval; ECG = electrocardiographic; other abbreviations as in Table 4.

value of this variable into the normal range (<105°); we showed an increased risk for cardiovascular events that is independent of established cardiovascular risk factors in women with suspected myocardial ischemia. This finding has potentially significant clinical applicability.

The QRS duration on a 12-lead surface ECG variable also was found to be a strong predictor of cardiovascular outcome in women with suspected myocardial ischemia and normal left ventricular ejection fraction. Interestingly, we found that increases in the QRS duration within the "normal range" (i.e., <100 ms in duration) were associated with a higher risk of death, CHF, non-fatal MI, and angina requiring hospitalization. These findings are consistent with the known association between conduction abnormalities and left ventricular mechanical dysfunction (10), where a QRS prolongation of >100 ms is associated with reduced left ventricular ejection fraction. QRS prolongation also has been well studied in patients with symptomatic CHF (1,10–14) or with hypertension (15). Our data are consistent with data from these studies that suggest that QRS prolongation is an independent predictor of increased mortality in patients with CHF. However, most of these heart failure studies defined QRS prolongation as QRS duration of >120 ms to 130 ms. These previous findings support the practice of using cardiac resynchronization therapy in patients with advanced heart failure and a prolonged QRS complex on (16,17). Our results have broader implications because they demonstrate that a wider QRS complex is associated with a worse outcome in women with chest pain with preserved left ventricular function and no history of clinical CHF. They further suggest that even slight prolongation in the QRS duration well within the normal range, in a relatively healthy female population, may be associated with an increased risk for cardiovascular events.

The diagnostic value of ST60 in the precordial leads of the surface ECG in patients with coronary ischemia has been shown in a variety of contexts, including studies performed in the cardiac catheterization laboratory during angioplasty balloon inflation (18,19). Changes in the ST-segment of the surface ECG typically are documented during an acute coronary syndrome. However, our findings show that an elevation in the ST60 on a resting baseline ECG can have prognostic implications for women presenting with chest pain, even if they were asymptomatic at the time of the ECG acquisition. As to the QTrr interval, its prolongation has been clearly associated with cardiac events, primarily arrhythmic in nature, whether due to genetic (20) or acquired (21) causes. In keeping with these findings, our results also demonstrate an increased even rate with longer QTrr intervals, but most of those events were none arrhythmic. In our population, the longer QTrr could merely represent abnormal repolarization, possibly secondary to CAD.

Study limitations. It should be recognized that there are several potential limitations to our study. First, our study is a prospective analysis of the clinical and ECG predictors of cardiovascular events in women with suspected myocardial ischemia. It therefore focuses on a selected symptomatic group of patients, and the results presented here may not apply to other groups of women. Second, our patient population consisted solely of women and, therefore, our results do not necessarily apply to men. Finally, each patient in this study had one 12-lead surface ECG obtained at baseline. We recognize that some of the ECG parameters measured may not be constant or stable over time, which is a possibility that can potentially affect the predictive utility of these parameters. Nevertheless, our study demonstrates that several uncommonly used ECG parameters that are derived from a single random 12-lead ECG are predictive of subsequent cardiovascular events in women with suspected myocardial ischemia, independent of the presence and angiographic severity of preexisting angiographic CAD.

Conclusions. The present study supports the hypothesis that several ECG parameters are predictive of subsequent cardiovascular events in a relatively healthy population of women with suspected myocardial ischemia. A wider QRS-T angle, a wider QRS duration, and a longer QTrr were all found to be statistically significant independent predictors of death, CHF, and non-fatal MI. The novelty of this study lies in the fact that abnormalities of these ECG parameters were predictive of events in a relatively healthy population of women even when their values were within

the accepted normal range. The results of this study raise the issue of incorporation of these sophisticated ECG parameters as part of a global risk factor score. Future prospective studies that evaluate a general asymptomatic population are needed to extend the findings of our study. If verified, these measurements could provide a noninvasive and relatively inexpensive means of assessing cardiovascular risk.

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