Electrocardiography in Women
Taking the Initiative

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In the just over 100 years since the first ECG was performed,¹ the ECG has become the most extensively used noninvasive diagnostic and prognostic tool in cardiology. Used both at rest and during provocative exercise, the 12-lead ECG has impressive, if imperfect, utility for rhythm analysis, detection of ischemic and hypertrophic heart disease, and outcome prediction in a variety of clinical settings, with a large body of literature that illustrates and supports these applications. The first observation of gender differences in the ECG was published 85 years ago by Bazett,² demonstrating that women have significantly longer QT intervals than men despite having higher heart rates. However, despite a growing body of literature demonstrating significant gender differences in QRS amplitudes and duration,³–⁶ QT intervals,⁵,⁷,⁸ ST-segment deviation,⁹,¹⁰ and novel, significant gender differences in the ECG was published 85 years ago by Bazett,² demonstrating that women have significantly longer QT intervals than men despite having higher heart rates. However, despite a growing body of literature demonstrating significant gender differences in QRS amplitudes and duration,³–⁶ QT intervals,⁵,⁷,⁸ ST-segment deviation,⁹,¹⁰ and novel, computer-based measurements of T-wave complexity,⁸,¹¹ few ECG criteria routinely use gender-specific diagnostic criteria, and there has been a relative paucity of data on the prognostic performance of ECG variables in women.

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Two studies in the current issue of Circulation by Rautaharju and colleagues¹²,¹³ provide a wealth of new findings and impetus for further study of the ECG in women. Using well-validated computerized ECG methodology, the authors examined the value of a number of ECG variables for predicting incident coronary heart disease and its mortality, incident congestive heart failure, and total mortality in more than 38 000 women participating in the dietary modification trial of the Women’s Health Initiative. Although both studies reconfirm the predictive value of ECG evidence of prior Q-wave myocardial infarction (MI), the principle new findings are the strong predictive value of various ECG measures of repolarization, and in particular of the QRS/T angle,¹²,¹³ a measure of the spatial angle between mean QRS and T vectors. In the single-ECG multivariable models that adjusted for standard demographic and clinical risk factors, nearly all T-wave and ST-segment variables and the QRS/T angle, as well as novel measures of repolarization derived from singular value decomposition of the derived vectorcardiogram, were significant predictors of outcome. When all ECG variables were examined together in these models, the QRS/T angle retained its predictive value along with a number of other ECG measures, including rate-corrected QT interval, heart rate variability, and ECG evidence of prior Q-wave MI.

These 2 reports build on a number of previous studies that examined the prognostic value of the ECG in women alone¹⁴ or compared predictive value in men and women.¹⁵–¹⁷ Earlier reports that included large numbers of women and men¹⁵–¹⁷ predominantly demonstrated significant predictive value of standard ECG measures of old MI and major and minor repolarization abnormalities by Minnesota coding for cardiovascular and all-cause mortality. In all of these studies, however, identical criteria were used in men and women despite known gender differences in many of these variables, which potentially underestimated the value of these findings in women. In contrast, the present findings are strongly supported by a recent report in a small subset of the Women’s Ischemia Syndrome Evaluation (WISE) study.¹⁴ In 143 women undergoing diagnostic catheterization, QRS/T angle, QRS duration, rate-corrected QT interval, and ST depression in V₅ all remained predictive of a combined outcome of cardiovascular disease end points that included cardiovascular death, congestive heart failure, and nonfatal MI; however, the small number of events among this subset of women (n=18) precluded the inclusion of all of the ECG variables in the final multivariable models, as was reported,¹⁴ which limits the conclusions that can be derived with respect to the independent value of these ECG variables in this population.

There are numerous strengths of the studies by Rautaharju et al.¹²,¹³ First, the size of the population and large number of events allowed adequate statistical power to assess specific outcomes in relation to multiple different ECG variables. Second, the authors used well-documented and readily reproducible computerized ECG measurements and criteria, as opposed to more qualitative and descriptive analyses that have been all too often employed in ECG-based studies.¹⁸ In addition, for the most part, the investigators took advantage of quantitative measurements of continuous variables to derive threshold partitions based on findings in the most abnormal decile or quartile of values, which allowed for the use of test partitions specific to women. It is somewhat unfortunate that the authors did not follow a similar approach to analysis of prior Q-wave MI but instead utilized well-validated Novacode criteria that were previously derived in both men and women.¹²,¹³

Several potential weaknesses of these studies should also be noted. First, although the strong predictive value of the QRS/T angle for events is one of the most important results, this measurement is not familiar to most clinicians and is not routinely available from computerized ECG analysis software.
Discussion of the possible mechanisms for the gender differences in ECG measures is beyond the scope of this editorial. However, a recent review of sex differences in cardiac repolarization provides an extensive discussion of the experimental data and potential gender differences in cellular-level ionic currents and the possible roles played by sex hormones in some of the better-characterized gender differences in cardiac repolarization.

The findings by Rautaharju and colleagues have important implications and provide direction for future investigation. Despite the widespread misconception that the ECG is of limited utility in women, these studies clearly demonstrate the value of the ECG for risk stratification in women, in particular the strong prognostic value of ECG measures of abnormal repolarization when using threshold criteria derived in men. Taken together with the wealth of information documenting the predictive value of the ECG in men, these findings strongly support the routine clinical application of computer-based ECG measurements for risk stratification in women. The known gender differences in QRS duration and amplitudes raise the question of whether sex-specific criteria for MI or bundle-branch blocks may be indicated to further enhance the predictive value of these ECG variables in women. Additional comparisons of ECG measurements in men and women will be necessary to more clearly delineate true mechanistic differences in ECG variables between men and women from differences that may be attributable to gender differences in left ventricular mass, body size, and composition, with application of these findings to improve accuracy of the ECG in both women and men.

In light of the low cost and widespread availability of the ECG and the increasing economic pressures on the practice of medicine, it is imperative that we continue to improve the diagnostic and prognostic performance of the ECG in women. Now that we have seized the initiative with respect to ECG research in women, we should not let it go to waste.

References


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