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Normal Standards for Computer-ECG Programs for Prognostically and Diagnostically important ECG variables Derived from a Large Ethnically Diverse Female Cohort: The Women's Health Initiative (WHI)†

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Abstract

Background—Substantial new information has emerged recently about the prognostic value for a variety of new ECG variables. The objective of the present study was to establish reference standards for these novel risk predictors in a large, ethnically diverse cohort of healthy women from the Women's Health Initiative (WHI) study.

Methods and results—The study population consisted of 36,299 healthy racially diverse women. Racial differences in rate-adjusted QT end (QT_{ea}) and QT peak (QT_{pa}) intervals as linear functions of RR were small, leading to the conclusion that 450 ms and 390 ms are applicable as thresholds for prolonged and shortened QT_{ea} and similarly, 365 ms and 295 for prolonged and shortened QT_{pa}, respectively. As a threshold for increased dispersion of global repolarization ($T_{peak}T_{end}$ interval), 110 ms was established for white and Hispanic women and 120 ms for African-American and Asian women. Normal standards were derived using lead transformation matrix computed from 116 lead body surface potential maps to derive normal standards for ST

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monitoring with limb electrodes in Mason-Likar positions and chest leads V3-V6 at the level of V1-V2 and for bipolar vessel-specific left anterior descending (LAD), left circumflex (LCX) and right coronary artery (RCA) leads. The results support the choice 150 μV as a tentative threshold for abnormal ST onset elevation for all monitoring leads. Body mass index (BMI) had a profound effect on Cornell voltage and Sokolow-Lyon voltage in all racial groups and their utility for left ventricular hypertrophy classification remains open.

Conclusions—Common thresholds for all racial groups are applicable for QT_{ea}, and QT_{pa} intervals and ST elevation. Race-specific normal standards are required for many other ECG parameters.

Keywords

electrocardiogram; normal standards; QT; TpTe; ST; monitoring

Introduction

Substantial new information has emerged recently about the prognostic value of a variety of ECG variables including QRS non-dipolar voltage (RNDPV) (1,2), QRS duration in the absence of bundle branch blocks (3-5), widened QRS/T angle (6-10), T wave axis deviation (11,12) , prolonged Tpeak-Tend interval (T_pT_e) (13-17), and T wave complexity (18). Normal standards for these potentially important ECG predictors of future risk of adverse cardiovascular events have not been established. There are abundant electrocardiographic (ECG) data on QT rate adjustment formulas, including a previous report from the Women's Health Initiative (WHI) study containing normal standards for rate-adjusted QT (19). Prognostic value for rate-adjusted QT has been well established for a variety of clinical and general populations (20). However, QT prolongation as a risk marker is known to have many limitations (21-25). Some drugs may prolong QT without inducing malignant arrhythmic events while some other cardioactive agents associated with adverse outcomes may not prolong QT.

The objective of the present study was to establish normative reference standards for an extensive set of ECG variables in a large, ethnically diverse cohort of healthy women from the Women's Health Initiative (WHI) study.

Methods

Study population The WHI is a 40-center, national United States study of risk factors and the prevention of common causes of mortality, morbidity, and impaired quality of life in women. Women aged 50 to 79 years representing an ethnically diverse population of postmenopausal women were recruited from 1994 to 1998. Details of the study design, protocol sampling procedures, and selection and exclusion criteria have been published elsewhere (26). A total of 68,132 women were enrolled in the clinical trial component of the study. Excluded from the present study were women with one or more of the following conditions at the baseline: (1) prior coronary heart disease (CHD) (history or clinical diagnosis of myocardial infarction (MI), angina pectoris, coronary artery bypass surgery or coronary angioplasty); (2) prior (silent) MI by Minnesota Code (MC) criteria (MC 1.1 or MC 1.2 or MC1.3 with MC 4.1-.2 and/or MC 5.1-5.2); (3) history of stroke; (4) diabetes (self report of medication use); (5) congestive heart failure; and (6) use of antihypertensives, calcium channel blockers, antipsychotics or antidepressants; and (7) significant arrhythmias at baseline ECG (MC 8.1.2 through 8.6.4), heart rate <40/min or ≥ 100/min or QRS duration >115 ms, poor ECG quality or lead reversals.

Additional exclusions on the basis of the follow-up through September 2010 were the following conditions: (1) incident MI (WHI definition); (2) incident coronary artery bypass graft or coronary angioplasty; and (3) incident congestive heart failure. A majority of the women excluded had more than one condition meeting the exclusion criteria above. Finally, 133 women with American-Indian ethnicity were excluded because of small sample size and 463 with ethnicity coded as "other", leaving a total of 36,299 women for the present study for the establishment of normal reference values for ECG parameters.

Electrocardiographic method Standard 12-lead ECGs were recorded in all women in the supine position using MAC PC electrocardiographs (GE Marquette, Inc., Milwaukee, Wisconsin). ECG technicians in all participating centers were trained to use carefully standardized procedures for ECG acquisition including locating the chest electrodes in precise positions using a special device (27) whereby V4 electrode was placed on the breast at 45° angle between midsternal line and the left midaxillary line, V5 halfway between V4 and V6 and V3 halfway between V2 and V4 (27). All electrocardiograms received at the Central ECG Laboratory (EPICARE Center, Dalhousie University, Halifax, Canada and later at Wake Forest University, Winston-Salem, North Carolina) were inspected visually to detect technical errors, missing leads, and inadequate quality, and such records were rejected from ECG data files. The ECGs were processed by the Marquette 12SL program (GE Marquette, Inc., Milwaukee, Wisconsin).

Because of the special importance of QT peak (QT_p) and QT end (QT_e) for the parameters used in the repolarization model, special algorithms were developed to detect QT_p and QT_e outlier measurements. Gender-specific predicted values were first computed for QT_e, QT_p and QT onset interval (QT_o). Measured interval values above the 99th percentile of the absolute difference (QT-predicted QT) were replaced by the predicted value. The replacement occurred for QT_e >488 ms, QT_p >396 ms and QT_o >282 ms These outlier measurements were observed mostly with signal quality problems and for QT_e often with the uncertainty of locating T wave end when low-amplitude U wave was overlapping the end portion of the T wave. Subsequently, linear rate-adjustment formulas listed in the middle section of Table 1 were applied to obtain rate adjusted QT_p and QT_e (QT_{pa} and QT_{ea}, respectively).

Because the application of separate rate adjustment formulas for QT_e and QT_p rate adjustment is an added complexity in clinical applications, an alternative expression for QT_{pa} was derived as shown in Table 1 using QT_{ea} and the T_pT_e interval. Although in some other population samples T_pT_e interval has been found to be rate-invariant (15,28), in the present study group of healthy women $T_pT_e$interval was not independent of heart rate (R-square 0.18). Therefore, a simple rate correction factor was derived (Table 1) which adds 5 ms to measured T_pT_e for each HR increment of 10/min above 60/min and subtracts 5 ms for HR 10/min below 60/min.

Repolarization parameters from the repolarization model The orthogonal Frank XYZ leads were obtained from the 8 independent components (leads I, II, V1-V6) using a transformation matrix from the 116 lead body surface map library of Horáĉek containing recordings for 892 adults aged 16 to 85 years (29) (Supplementary Table 1). Transformation coefficients were also computed specifically for the present study for a set of ST monitoring leads from 8 independent components of the standard 12-lead ECG. These coefficients were used to derive normal standards for ST onset (ST_o) corresponding to the ST J-point elevation and depression in these monitoring leads with body surface electrode locations at Mason-Likar positions for limb leads (RA and LA electrodes at the right and left subclavicular fossa and LL electrode above left iliac crest), and V3-V6 electrode locations at the level of V1-V2. In addition, three vessel-specific bipolar leads were computed using the

coefficients listed in Supplementary Table 1. The vessel specific leads were derived by Horáĉek as the most sensitive bipolar leads for detecting acute ischemic response to coronary obstruction of left anterior descending (LAD), left circumflex (LCX) and right coronary artery (RCA) (30). Bipolar LAD lead is recorded from 1/2 intercostal space below V8 to V3 position, LCX from 1/2 intercostal space above V2 to 1/2 intercostal space above V8, and RCA 1 intercostal space above V2 (at third intercostal space) to left iliac crest.

Repolarization measurements were made utilizing temporal reference points derived from the "global" T wave, the spatial T vector magnitude curve derived from the XYZ leads. RNDPV and a set of 18 repolarization-related ECG variables from our repolarization were chosen for evaluation because of their functional role in generation of normal and abnormal repolarization waveforms or because of their previously shown value as risk predictors (1-18). QRS duration was included as the second depolarization-related parameter in addition to RNDPV because even moderate QRS prolongation has been shown to induce secondary repolarization abnormalities associated with adverse cardiac events (3-5).

The conceptual model used to derive repolarization time (RT) subintervals and other model parameters for the present study has been described in detail in previous publications (6,7,25). RT peak (RT_p), the key repolarization model parameter, is considered to represent RT of left ventricular (LV) myocytes at the time of global T wave peak (T_p) when the majority of LV lateral wall myocytes are at some point of phase 3 of their action potential. RT_p is computed as a function of QT_{pa}. In normal subjects with normal spatial direction of the repolarization sequence, QT_p represents RT of the subepicardial myocyte layers (RT_{epi}). Briefly, $RT_p = QT_{pa} - (1-Cos\theta(T_p|T_{ref}) * (TpTxd)/2$, where $\theta(T_p|T_{ref})$ is the spatial angle between the T_p vector and T_{ref} is the reference normal T_p vector with unit xyz components (0.75,0.57,-0.33). T_pT_{xd} in turn, is the interval from T_p to T_{xd}, where T_{xd} is the inflexion point (the steepest negative slope) at global T wave downstroke. Thus, RT_p is obtained from QT_{pa} by modifying it by the degree of deviation of direction of the initial repolarization from the direction of normal repolarization. LV RT at time point T_{xd} (RT_{xd}) is obtained with an algorithm similar to that for RT_{epi}, whereby $RT_{xd} = QTpa - (1+Cos\theta(T_p|T_{ref})* (T_pT_{xd})/2$. In normal subjects with normal spatial direction of repolarization RT_{xd} is considered as a representative value for subendocardial myocyte layers (RT_{endo}). In addition to $\theta(T_p|T_{ref})$ noted above, a number of other spatial angles between various QRS and T vectors and other interval and amplitude variables were used in various phases of the study. Their definitions are listed in the footnotes of the corresponding tables.

Statistical methods Frequency distributions of all variables used in various analyses were first inspected to rule out anomalies and outliers. QT_e distributions were skewed, but otherwise, no anomalies influencing analyses were observed. QT_e and QT_p prediction accuracy was evaluated by comparing R-square values of the fit on QT distribution by various QT prediction functions. QT_e, QT_p and QT_o intervals varied substantially with heart rate and race-specific rate adjustment formulas as well as common formulas combining all four racial subgroups were established (Table 1). The stability of the adjusted QT intervals for different QT adjustment functions was compared over various ventricular rates, covering the range of heart rates from 45 to 99/min. Mean values with standard deviations and 96 % normal ranges were established for different racial subgroups for ECG variables considered diagnostically or prognostically important and selected for evaluation. The second and 98^{th} percentile limits rather than the fifth and 95th limits were chosen to define the normal range because this study group was chosen with relatively strict selection criteria to exclude women with CVD at baseline and related outcome events during the subsequent 14 year follow-up. Student's t-test (2 sided) was used to determine the significance of the differences in the mean values between white women and the other racial groups. Data analyses

including descriptive statistics and graphics were done using Microsoft Excel 2007version 5.0 (Microsoft Corporation, Redmond, Washington).

Results

Characteristics of the study group Characteristics of the study population are listed in Supplementary Table 2. Of special interest in relation to ECG amplitude is the body mass index (BMI). BMI was 2.9 kg/m^2 higher in African-American women than in white women. The impact on BMI on ECG amplitudes will be considered under the subheading “R and S wave amplitudes, Cornell voltage and Sokolow-Lyon voltage”.

Racial differences in rate-adjusted QT and QT subintervals The slope coefficients for rate adjustment as linear function of RR differed relatively little from those of white women in the other 3 ethnic groups (Table 1, top section), and the common linear rate adjustment function was used for rate adjustment when deriving other repolarization-related variables for our repolarization model. Rate adjustment functions for QT_p and QT_e intervals show that rate adjustment by linear functions of the RR interval gave R-square values as high as the power functions with optimal exponents from log-log regression (middle section in Table 1). Thus, the simpler linear functions were chosen for rate adjustment of QT and QT subintervals.

Formulas 15-18 at the bottom section of Table 1 show the residual dependence on heart rate (HR) of the rate-adjusted QT_e by Bazett's (QT_{bz}) (31), Fridricia's (QT_{fr}) (32), Framingham (QT_{frm}) (33) and Hodge's (QT_{hg}) (34) formulas. It is noted that these commonly used formulas left a notable bias with increasing HR in women of our study population, ranging at HR 90 bpm from -22 ms for QT_{hg} to +16 ms for QT_{bz}. It appears that the QT_e rate sensitivity in this postmenopausal group of healthy women is higher than in the populations where these other formulas were derived. This is noted for instance by comparing the slope coefficient for RR in Formula 12 ($QT_{ea}=QT_e+182*(1-RR)$) with the corresponding coefficient in the Framingham formula ($QT_{frn}=QT_e+154*(1-RR)$) and similarly, the slope coefficients for HR in Formula 13 ($QT_{ea}=QT_e+2.48*(HR-60)$ and the corresponding coefficient in Hodge's formula ($QT_{hg}= QT_e+1.75*(HR-60)$.

Normal standards for ECG Intervals Normal values for PR, QRS and rate-adjusted QT and QT subintervals are listed in Table 2. Most of the mean differences in African-American and Hispanic women from white women are statistically significant although in general these differences can be considered quite small from the clinical point of view. For rate-adjusted QT and QT subintervals, the following values were established as thresholds for interval prolongation: 450 ms for QT_{ea}, 365 for QT_{pa} and 270 for QT_{oa}. The corresponding thresholds for shortening of these intervals were 390 ms for QT_{ea}, 295 for QT_{pa} and 210 ms for QT_{oa}. The PR interval was 6 to 9 ms longer in African-American women than in the other racial groups. The value of 220 ms can be recommended as the upper normal limit for African-American women and 210 ms for white, Hispanic and Asian/Pacific women. Also, the upper normal limit for QT_{pa}- QT_{ea} was 5 to 8 ms longer in African-American women than in the other 3 racial groups. QT_{pa}- QT_{ea} is the rate-adjusted T_pT_e interval ($(T_pT_e)_a$), the temporal global RT_{grad} considered to represent global RT dispersion. The upper normal limit of $(T_pT_e)_a$ interval was 10 ms longer in African-American women than in white women. The value of 110 ms can be recommended for the upper normal limit for $(T_pT_e)_a$ interval for white, Hispanic and Asian/Pacific women and 120 ms for African-American women.

T_pT_{xd} interval is considered to represent regional dispersion of the initial repolarization period dominated by crossmural repolarization of the LV lateral wall. The upper normal

limit for T_pT_{xd} interval was 54 ms in white women, 10 ms longer (64 ms) in African-American women, 58 ms in Hispanic and 60 ms in Asian/Pacific women.

Normal limits for key repolarization-related ECG parameters Normal values for repolarization-related ECG variables from our repolarization listed in Table 3 show several notable racial differences particularly in African-American women compared to white women and to Hispanic and Asian/Pacific women. The differences in upper normal limits were relatively large for instance for RNDPV, $\theta(T_{init}|T_{term})$ and for vector magnitudes ST_oV, T_oV, T_pV and the ratio T_oV/T_pV.

For many of the ECG variable, the upper limits in Hispanic and Asian/Pacific women were similar to those in white women and differed more widely in African-American women for instance for angular ECG variables. It thus appears that race-specific normal limits are necessary for these novel ECG parameters from our repolarization.

Normal limits for Q wave durations The prevalence and the upper normal limits for significant Q waves (≥100 μV followed by R wave ≥100 μV) are shown in Supplementary Figure 1. The prevalence was 15% for lead III and the upper limit was 49 ms. The prevalence of the Q waves considered significant was 11% or less for the other leads shown and 0.6% or less for chest leads V1-V3 (not shown). Importantly, the limits for Q wave duration were <35 ms for aVL and aVF and <30 ms for leads I, II, V4-V6.

R and S wave amplitudes, Cornell voltage and Sokolow-Lyon voltage Normal limits for R and S wave amplitudes (Supplementary Figure 2) show the expected trends for R and S wave amplitudes, with R wave amplitudes increasing from V1 to V5 and S wave amplitudes decreasing grom V2 to V6. The amplitudes in limb leads were substantially lower than in the chest leads because of lower lead vector strength and QRS vector loop projection differences. Clinically more relevant than the R and S wave amplitudes in different leads are the upper limits for Cornell voltage (CV) and Sokolow-Lyon voltage (SLV) used in clinical criteria for left ventricular hypertrophy (LVH) (Figure 1). The values in Black, Hispanic and Asian women differ significantly from white women, suggesting that rate-specific limits are warranted.

Figure 2 shows the mean values and upper second percentile limits for CV in African-American, Hispanic and Asian/Pacific women for lean and obese women with obesity status matched for body mass index (BMI) in white women (BMI < 23 kg/m^2 for lean women and BMI >32 kg/m^2 for obese BMI group). The horizontal dashed line represents the commonly used CV (35) threshold for LVH derived in predominantly white women. The limits are above the 2000 μV threshold for LVH in lean white, African-American and Asian/Pacific women but considerably below the threshold in lean Hispanic women and in obese women in all ethnic groups. CV reduction was particularly pronounced in extreme obesity.

Normal standards for T wave amplitudes The statistics in Supplementary Table 3 show that T wave amplitudes in most ECG leads were lower in African-American and Hispanic women than in white and Asian-Pacific women. Race specific limits may be necessary for T wave amplitudes although combined limits for white and Asian-Pacific women and African-American and Hispanic women could also be considered. TV1 and TV2 can be biphasic, most commonly positive/negative. In V1, the amplitude of the positive initial component is low. Figure 3 summarizes for the combined group of women the normal 96 % range (2^{nd} to 98^{th} percentile) for T wave amplitudes in chest leads including initial T V1 amplitude for biphasic positive/negative (+/-) T wave.

Normal limits for ST onset elevation and depression in standard and monitoring leads Normal ranges (from 2^{nd} to 98^{th} percentile) for ST J-point amplitude (labeled as $ST_o$for ST

onset) for standard leads I, II, aVL, aVF and V1-V6 for the combined group of women (Supplementary Figure 4) show that the upper normal limits for ST_o were all well below 100 μV with the exception of lead V2 (112 μV) . The upper limits for ST_o in monitoring leads were also below 100 μV except 106 μV for V2 (Figure 3). Although not shown, the upper normal limits for monitoring leads M-I and M-II were higher than in standard leads I and II but still below 100 μV. Lower normal limits were approximately 50 μV for monitoring chest leads V1-V6 and approximately 100 μV for vessel specific bipolar leads.

Discussion

The primary goal of the present investigation was to establish normal reference values for an extensive set of ECG variables in post-menopausal women. Previously available normal standards for women have been largely in younger age groups of white women, with limited sample size in older age groups and in other racial groups. Normal values were established for several novel repolarization-related ECG variables such as rate-adjusted QT_p and QT_e and the T_pT_e interval which is considered to represent global RT dispersion. Normal standards for these rate-adjusted intervals have not been available before except for QT_{ea}. Similarly, normal standards have not been available previously for $\theta(R_m|T_m)$ and $\theta(T_p|T_{ref})$, prognostically important spatial angles reflecting deviations of repolarization from normal direction of repolarization sequence.

Rate-adjustment for QT_e and QT_p In this group of healthy postmenopausal women, formulas for QT_{ea} and QT_{pa} as linear functions of the RR interval gave as high R-square values as the power functions with optimal exponents from log-log regression. Racial differences in rate sensitivity (slope coefficients of regression on RR interval) were small in these healthy women and a common linear rate adjustment formula gave an adequate rate adjustment in all racial groups. QT measurements in the present study were made by the Marquette 12SL program. QT measurements made by different algorithms differ slightly due to differing procedures for identification of T wave end (36). Outlier QT and QT subinterval values were replaced in the present study by predicted interval values which can be expected to enhance the stability of the upper normal limits established for rate-adjusted intervals.

Common upper normal limits for all racial groups combined were established as 450 ms for QT_{ea}, and 365 ms for QT_{pa}. T_pT_e interval which reflects global RT dispersion also retained a slight rate dependence and for this reason rate adjusted T_pT_e was calculated as $T_{pa}T_{ea}$ interval, the difference between rate adjusted QT_e and QT_p. Alternatively, rate adjusted T_pT_e interval $(T_pT_e)_a$ can be computed by the formula: $(T_pT_e)_a = T_pT_e + 0.5*(HR-60)$, so that 5 ms is added to T_pT_e for each heart rate increment by 10 bpm above 60/min. This simpler approach was also used to derive rate adjusted QT_p from QT_{ea} and T_pT_e (Formula 14 in Table 1). Considering the upper normal limit for rate-adjusted T_pT_e interval (last row in Table 2), 110 ms can be recommended as practical limits for white and Hispanic women and 120 ms for African-American women and Asian/Pacific women.

The normal standards established for QT and QT subintervals are primarily intended for use in evaluation of QT prolongation prevalence in epidemiological studies and for prognostic evaluation of their utility in risk prediction. The upper normal limit of 450 ms for QT_{ea} established for the healthy women in our study can be compared with the 98^{th} percentile limits rate-adjusted QT of 457 ms by Bazett's formula and 445 ms by Fridericia's formulas documented in a combined group of 79,743 men and women by Mason et al. in an ECG measurement file from pharmaceutical company–sponsored clinical trials (37). That document contained extensive evaluation data with 16 tables on QT and three other ECG variables (PR and QRS interval and frontal plane QRS/T angles). However, potential

residual rate-dependent bias for QT adjustment formulas was not evaluated in their study population which may limit the utility of these standards at higher heart rates. Also, the study of Mason et al. did not consider the known gender differences in QT rate sensitivity (38) which leaves open the question of the applicability to women of the formulas from combined gender groups.

Monitoring for ST elevation and depression Limb electrodes placed by clinical ECG monitoring personnel in Mason-Likar positions can be considered already as a de facto standard clinical procedure in ST monitoring. The results from the present study suggest that normal standards for ST elevation and depression in women for standard leads with electrodes placed on the breast are also applicable for monitoring chest leads with chest electrodes placed on the breast at V1-V2 level.

The lower limits for ST change (mean - 2SD) in special vessel-specific monitoring leads as a response to induced acute ischemia in the report of Horáĉek et al. (30) were 114 μV for LAD, 53 μV for LCX and 24 μV for RCA, indicating that approximately 98% of the ischemic changes exceeded these limits. The upper normal limits for ST_o in Figure 3 for monitoring leads and Supplementary Figure 4 for standard leads support the choice of 150 μV for all monitoring leads as a tentative value for abnormal ST elevation evaluated during stable artifact- free recording periods as ensured by ST monitoring quality control software. The threshold can be modified upwards for instance to 200 μV if less stable periods cause too many alarms. For monitoring of the change in ST elevation or depression, 50 μV increase or decrease from baseline ST_o value can be suggested as a tentative triggering threshold for alarm.

Only 0.6% of the ECGs were associated with horizontal or downsloping ST segments (MC 4.2 or 4.1) and thus the ST elevations in these normal women were associated with upwards-sloping ST segments. ST elevation associated with J-point “notches” has recently been the focus of investigations on ST segment patterns considered by some investigators to represent early repolarization (39). This topic was not considered in the present investigation.

Effective display formats are available for ST monitoring applications such as introduced by Pelter et al. using a 3-D plot of ST onset elevation values over the monitoring period in all 12 ECG leads (40). The 150 μV threshold introduced here can be applied for acute ischemia. A simple ST Index (STI) can also be considered for monitoring of ST elevation status in patients suspected for acute coronary syndrome using the formula: $STI = 100*ST_o / BLST_o$ where $BLST_o$ is the baseline ST_ovalue at admission. A threshold value can then be selected for ST elevation change alarm as 10% or 15% change in STI.

Normal standards for QRS/T angle and other repolarization-related ECG parameters Normal standards for $\theta(R_m|T_m)$, $\theta(T_p|T_{ref})$ and other angular variables reflecting deviations of repolarization from normal direction of repolarization sequence revealed that race-specific normal limits are necessary to identify prognostically important repolarization abnormalities. These race-specific upper normal limits are listed in Table 3, including normal values for RT_p, RT_{xd} and spatial vector magnitudes for ST_o, T_o and T_p.

Electrode placement, obesity, breast protuberance and ECG amplitudes Ancillary analyses (Figure 2) indicated that CV and SLV values differed substantially with BMI in all ethnic groups. In particular, both CV and SLV were lower in obese than in lean women, suggesting possible effect of increased distance from cardiac source to the body surface in obese women with large breast. However, a previous investigation in 6814 women in the Atherosclerosis in Communities (ARIC) study concluded that breast protuberance alone had

only a relatively small effect on CV and SLV (R-square < 0.01) and n contrast, chest size (ellipsoidal approximation of bony thorax circumference) was a dominant factor influencing CV and SLV than breast protuberance (27). There is a scarcity of data with direct comparison of chest lead amplitudes with electrode placement under the breast and on the breast. Macfarlane et al. compared R wave amplitudes in V3-V6 in 84 women and noted that R amplitude in V4 was 28 μV higher (95% CI -9 to +65μV) and in V6 134 μV lower (95% CI-160 to -108 μV) with electrode placed under the breast vs. in standard positions on the breast (41). Repeatability of measured amplitudes was higher with electrodes placed on the breast than under the breast. The role of constitutional factors as determinants of CV and SLV appears complex and the question of the utility of current ECG criteria for LVH remains open.

The electrode placement issue has also baring on normal standards for ST_o in monitoring leads, derived in the present investigation with chest electrodes placed on the breast rather than under the breast. Since the chest size rather than breast protuberance is the dominant factor influencing chest lead amplitudes, it appears reasonable to conclude that the normal standards for monitoring leads would not differ substantially whether derived from source data with electrodes on the breast or under the breast. Limited data available for ST J-point amplitude in older women with chest electrodes placed under the breast reveal that the upper normal limit for ST J-point amplitude in women 40 years old and over is 140 μV or less in V2, 80 μV or less in V4 and 60 μV or less in V6 (42). The corresponding upper normal limits in Supplementary Figure 4 for chest leads V2, V4 and V6 with electrodes placed on the breast are 102 μV, 78 μV and 63 μV respectively, and in Figure 3 for monitoring leads V2, V4 and V6 106 μV, 78 μV and 54 μV, respectively. These differences can be considered relatively unimportant considering other sources of variability in the monitoring setup.

Clinical perspectives As noted in the Introduction, substantial new information has emerged recently about prognostic value for a variety of novel depolarization- and repolarization-related ECG variables. Of particular clinical interest among these novel ECG parameters are T_pT_e interval and spatial angles $\theta(R_m|T_m)$ and $\theta(T_p|T_{ref})$. T_pT_e interval is considered to represent global dispersion of repolarization thought to be a marker of the risk of arrhythmic events and sudden cardiac death (13-17). $\theta(R_m|T_m)$ and $\theta(T_p|T_{ref})$ are of clinical interest as measures of abnormal deviation of spatial direction of repolarization sequence associated with acute coronary syndrome and CHD mortality risk (7-10). The present report also introduces guidelines for practical clinical monitoring of ST elevation in women. A recent report from the Practical Use of the Latest Standards for Electrocardiography (PULSE) Trial concluded that there is overutilization particularly of arrhythmia monitoring in the hospital settings but at the same time there is underutilization of ischemia monitoring and QT monitoring when the need of monitoring is clinically indicated (43). Another comprehensive consensus report covering all aspects of hospital cardiac care monitoring commented on the lack of adequate guidelines for QT monitoring and noted that quality control problems cause frequent false alarms in QT and ST monitoring hindering their wider acceptance (44). There is scarcity of normal ECG standards particularly for older women. For instance, the most comprehensive reference document in Electrocardiology (51) contains normal standards derived from a sample of white women but it contains only 79 women in age group 50 years old and older. The extensive set of normal standards introduced in the present communication from racially diverse cohort of postmenopausal women should provide a valuable supplement to available ECG reference data.

Limitations of the study Our study group consisted of healthy postmenopausal women. A separate investigation is required to evaluate gender differences in normal reference values in younger women and to establish normal reference standards for men not yet available for a variety of newer ECG predictor variables. ST elevation associated with J-point “notches”

considered by some investigators to represent early repolarization was not considered here and the topic will require a separate investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix and Short list of WHI investigators

Short List of whi Investigators

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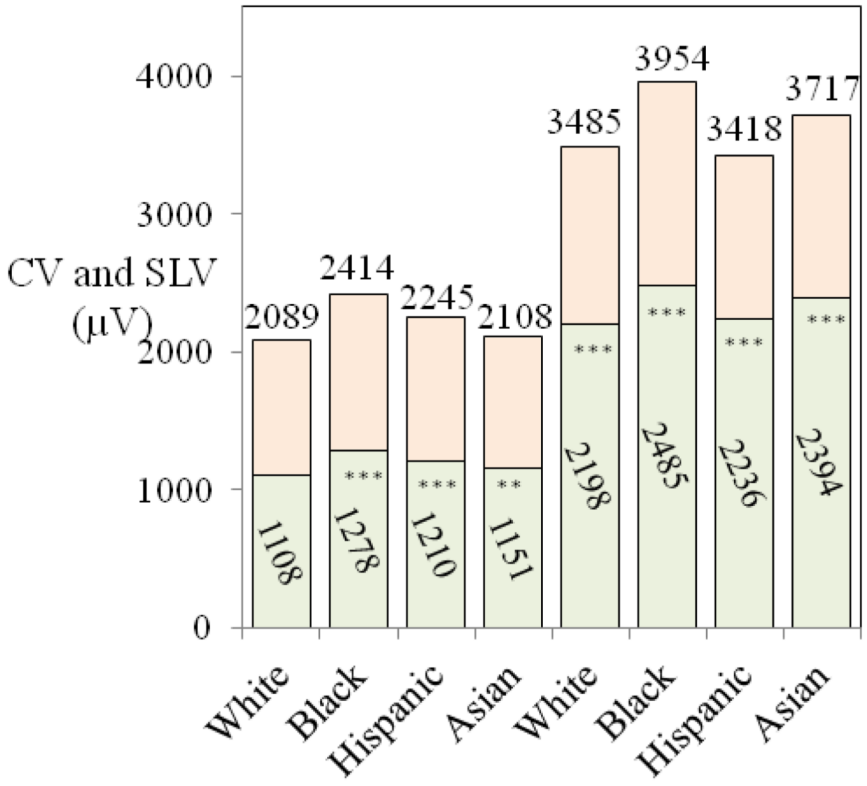

Figure 1.

Mean values (in lower columns) and upper normal limits (98th percentiles, listed on top for Cornell Voltage (CV) (four columns on the left) and Sokolow-Lyon Voltage (SLV) (four columns on the right) by ethnicity. The mean values and the upper limits in black, Hispanic and Asian women differ significantly from white women and race-specific upper normal limits are necessary.

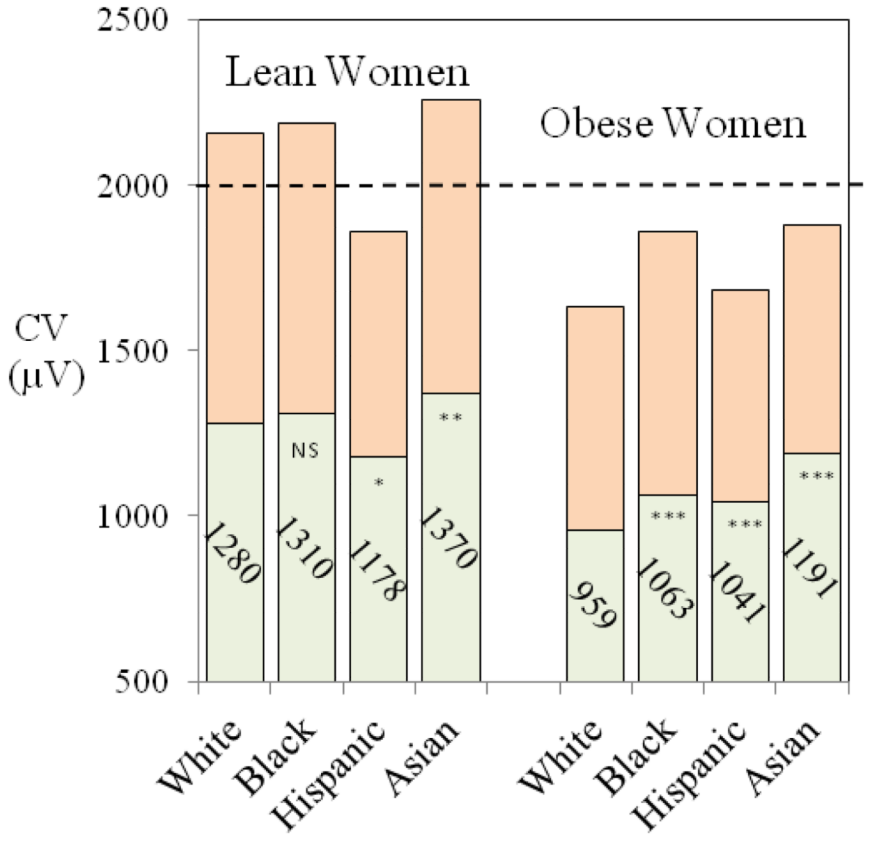

Figure 2.

Mean values (lower columns) and upper normal limits (98th percentiles, top columns) for Cornell Voltage in women by ethnic group with obesity status matched for body mass index (BMI) in white women (BMI < 23 kg/m^2 for lean women and BMI >32 kg/m^2 for obese BMI group). The limits are above the 2000 μV threshold for LVH in lean white, African-American and Asian/Pacific women but considerably below the threshold in lean Hispanic women and in obese women in all ethnic groups.

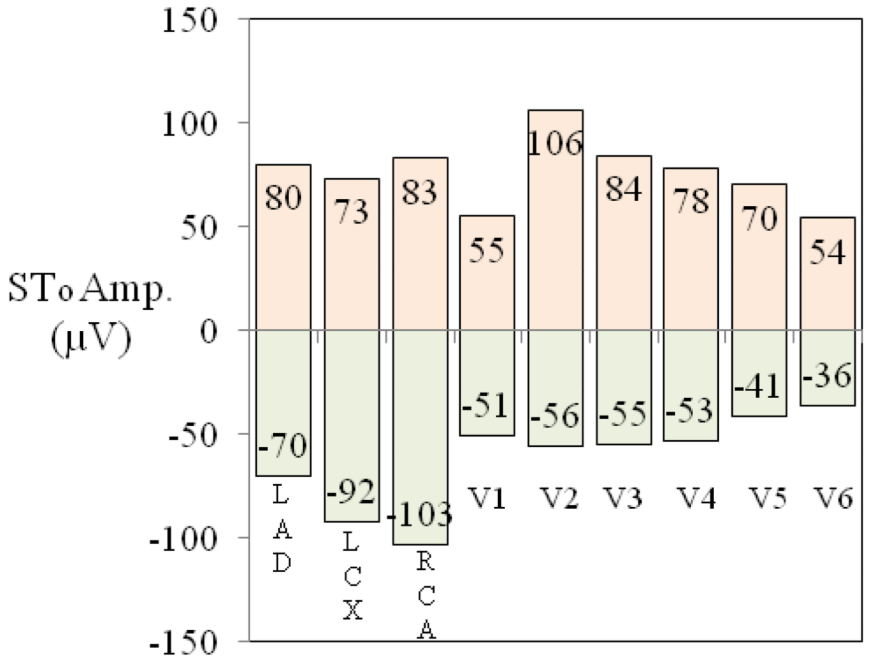

Figure 3.

Normal limits (96% range) for STonset (ST_o, the J-point amplitude) in vessel-specific bipolar left anterior descending (LAD), left circumflex (LCX) and right coronary artery (RCA) leads and in chest leads V1-V6 for the combined group of women. Bipolar LAD lead is recorded from 1/2 interspace below V8 to V3, LCX from 1/2 interspace above V2 to 1/2 interspace above V8, and RCA 1 interspace above V2 (at third interspace) to left iliac crest. Electrode placements for limb leads are the same as for Mason-Likar leads and V3-V6 positions for monitoring leads are at the level of V1 and V2.

Table 1
Rate-adjustment Formulas for QTpeak and QTend by Ethnicity

	Ethnic Group	Linear Functions of RR†	R-Square
‡ QT_p	White	1. $QT_{pa} = QT_p + 132*(1-RR)$	0.508
	African-American	2. $QT_{pa} = QT_p + 131*(1-RR)$	0.461
	Hispanic	3. $QT_{pa} = QT_p + 138*(1-RR)$	0.480
	Asian/Pacific	4. $QT_{pa} = QT_p + 142*(1-RR)$	0.496
§ QT_e	White	5. $QT_{ea} = QT_e + 182*(1-RR)$	0.735
	African-American	6. $QT_{ea} = QT_e + 184*(1-RR)$	0.701
	Hispanic	7. $QT_{ea} = QT_e + 187*(1-RR)$	0.701
	Asian/Pacific	8. $QT_{ea} = QT_e + 179*(1-RR)$	0.650
	All Women	Power and Linear Functions	R-Square
QT_p	Power Function of RR	9. QT_{pa}=QTp+319*(1-RR^0.40-1)	0.505
QT_e	Power Function of RR	10. $QT_{ea} = QT_e$+319*(1-RR^0.40)	0.728
QT_p	Linear Function of RR	11. $QT_{pa} = QT_p + 132*(1-RR)$	0.502
QT_e	Linear Function of RR	12. $QT_{ea}=QT_e$+182*(1-RR)	0.731
QT_e	Linear Function of HR	13. QTea = QT_e + 2.48*(HR-60)	0.705
/ QT_{pa} from QT_{ea} and T_pT_e intervals		14. $QT_{pa} = QT_{ea} - (T_pT_e) + 0.5*$ (HR-60)	
	## Other Formulas for QTe	Residual HR-dependence	r
QT_{bz}	15. $QTbz = QT/RR^{1/2}$	QTbz = 382 + 0.53*HR	0.31
QT_{fr}	16. $QTfr = QTe/RR^{1/3}$	QTfr = 446-0.53*HR	0.31
QT_{frm}	17. QTfrm = QTe+154*(1-RR)	QTfrm = 436 - 0.38*HR	0.24
QThg	18. QThg = QTe + 1.75*(HR-60)	QThg = 459 - 0.73*HR	0.42

† RR interval (=60/heart rate (HR) is in seconds, all other intervals in milliseconds in this and in the other tables.

‡ QT_p and QT_{pa} refer to QTpeak and rate-adjusted QTpeak, respectively.

§ QT_e and QT_{ea} refer to QTend and to rate-adjusted QTend, respectively.

/ A practical formula for QT_{pa} as (QT_{ea} - TpT_e) with T_pT_e adjusted for HR.

Formulas 17-20 show the residual dependence on HR of the rate-adjusted QTe by Bazett's (QTbz), Fridricia's (QTfr), Framingham (QTfrm) and Hodge's (QThg) formulas.

Table 2

Mean values of ECG Intervals with Standard Deviations and the Range of Normal Limits from the 2nd to 98th Percentile by Race

	All Women	White	African-American	Hispanic	Asian/ Pacific
Heart Rate (bpm)	66; 9.2 49 → 88	66; 9.2 49 → 87	67; 9.8*** 50 → 89	66; 8.8^{NS} 50 → 87	67; 9.1^{NS} 51→ 88
PR (ms)	158; 33.9 118 → 212	157; 34.6 118 → 212	164; 34.9*** 124 → 220	155; 22.0** 118 → 204	158; 20.9^{NS} 124→ 209
QRS (ms)	85; 8.1 70 → 104	85; 8.0 70 → 104	84; 8.5*** 68 → 104	85; 8.2^{NS} 70 → 104	85; 8.1^{NS} 70 → 104
$^{\dagger}QT_{ea}$ (ms)	413; 14.2 388 → 449	413; 14.0 388 → 448	414; 14.9^{NS} 388 → 452	414; 15.0* 389 → 451	418; 16.1*** 393 → 460
$^{\dagger}QT_{pa}$ (ms)	328; 17.0 294 → 366	328; 16.7 295; 365	326; 18.9*** 288 → 368	328; 17.6^{NS} 294 → 366	331; 17.4*** 299 → 372
$^{\ddagger}QT_{oa}$ (ms)	236; 15.3 207 → 271	237; 15.2 208 → 271	233; 16.2*** 202 → 271	234; 15.1*** 207 → 269	232; 14.4*** 206 → 266
$^{\S}T_pT_{xd}$ (ms)	33; 8.5 20 → 56	33; 8.2 20 → 54	35; 10.3*** 20 → 64	34; 9.1*** 20 → 58	35; 9. 3*** 22 → 60
$^{\#}(T_pT_e)_a$ (ms)	85; 11.2 63 → 112	85; 10.9 64 → 111	87; 13.5*** 61 → 119	86; 11.8*** 60 → 113	87; 14.1^{NS} 54 → 121

*** signifies $P<0.0001$,

** $P<0.001$,

* $=P<0.05$ and NS nonsignificant for mean difference from white women.

$^{\dagger}QT_{ea}$ and QT_{pa} are rate-adjusted QTend (QT_e) and QTpeak (QR_p) intervals by formulas listed in Table 1.

$^{\ddagger}QT_{oa}$ is the rate adjusted QTonset (QT_o) interval by formula $QT_{oa} = QT_o + 107*(1-RR)$.

$^{\S}T_pT_{xd}$ signifies crossmural left ventricular repolarization time gradient, equal to the interval from T_p to T_{xd} where T_{xd} is the time point of maximum slope at the global T wave downstroke (see methods).

$^{\#}T_pT_e$ computed as the difference (QT_{ea}-QT_{pa}) or as $T_pT_e + 0.5*(HR-60)$.

Table 3

Mean Values, Standard Deviations and Normal 2nd to 98th Percentile Range for Key ECG Parameters from the Repolarization Model by Race

	All Women	White	African-American	Hispanic	Asian/Pacific
† RT_{epi}	327 ; 17.1 293→364	327 ; 16.8 294→364	324 ; 19.2 ** 284→366	326; 17.7 NS 292→365	330 ; 17.4 *** 298→369
† RT_{xd}	296; 20.2 254→339	297 ; 19.7 256→339	292 ; 23.7 *** 240→343	294 ; 21.1 *** 249→338	297; 21.7 NS 252→345
‡ APD_{epi}	288; 17.1 253→325	288; 16.8 254→324	286; 19.1 NS 246→326	288; 17.8 ** 253→327	293; 17.7 *** 258→332
‡ APD_{xd}	286 ; 20.2 244→329	287 ; 19.7 246→329	282 ; 23.7 *** 230→333	284 ; 21.1 *** 239→328	287 ; 21.7 NS 242→335
§ QR_p	39 ; 4.8 30→50	39 ; 4.8 30→50	38 ; 4.8 *** 30→50	38 ; 4.8 *** 30→50	39 ; 4.9 * 30→50
/ RNDPV	41 ; 15.7 19→82	41 ; 15.3 22→70	46 ; 17.6 *** 21→93	43 ; 15.7 *** 20→85	47 ; 18.0 *** 20→96
# $\theta(R_m\|T_m)$	43 ; 21.6 9→97	43 ; 21.4 13→82	43 ; 24.0 NS 8→108	40 ; 21.7 *** 8→96	39; 22.0 *** 9→99
†† $\theta(R_p\|T_p)$	33 ; 22.1 5→103	33 ; 21.7 8→72	36 ; 25.3 *** 6→116	30 ; 22.4 *** 5→105	30 ; 24.0 *** 5→118
## $\theta(T_p\|T_{ref})$	17 ; 13.3 2→53	17 ; 12.8 4→38	21 ; 17.4 *** 3→74	18 ; 13.2 NS 3→53	17 ; 13.4 NS 2→51
§§ $\theta(T_{init}\|T_{erm})$	31.2 ; 11.5 10→58	31.4 ; 11.3 15→50	30.9 ; 13.1 * 8→61	30.6 ; 11.8 ** 10→59	27.8 ; 10.4 NS 8→52
// $\theta(T_{init}\|Tr_{ef})$	18 ; 13.4 3→53	18 ; 13.0 4→40	**22** ; 16.8 *** 3→72	18 ; 12.7 NS 3→52	17 ; 13.1 NS 2→49
## $\theta(T_{term}\|T_{ref})$	28 ; 9.0 11→39	27 ; 8.5 16→36	30 ; 13.7 *** 11→51	29 ; 8.5 *** 14→39	28 ; 8.9 ** 13→40
††† ST_oV	32 ; 17.1 6→74	31 ; 16.3 9→62	42 ; 20.2 *** 10→93	35 ; 17.4 *** 6→76	40 ; 19.5 *** 9→85
††† T_oV	103 ; 39.6 38→198	102 ; 38.6 46→171	114 ; 44.1 *** 42→221	110 ; 41.6 *** 39→205	122; 45.7 *** 48→235
††† T_pV	346 ; 123.8 122→629	349 ; 122.0 163→565	314 ; 131.8 *** 95→648	340; 128.4 ** 111→624	366 ; 136.7 *** 118→628
### T_oV/T_pV	0.31 ; 0.079 0.18→0.52	0.30 ; 0.073 0.20→0.42	0.38 * ; 0.097 0.22→0.64	0.33 ; 0.083 *** 0.20→0.55	0.35 ; 0.084 *** 0.21→0.55

*** Signifies $P<0.0001$,

** $P<0.001$,

* $=P<0.05$ and NS nonsignificant for mean differences from white women.

† RT_{epi} is epicardial repolarization time and RT_{xd} a representative value of subendocardial repolarization time.

‡ $APD_{epi} = RT_{epi} - ET_{epi}$, and $APD_{endo} = RT_{xd} - ET_{endo}$, where ET_{epi} and ET_{endo} are epicardial excitation time (=QRp) and endocardial excitation time (taken as 10 ms).

§ QRp = interval from QRSonset to the peak of QRS vector magnitude curve.

/ RNDPV = QRS nondipolar voltages (square roots of the total variance of components 4 to 8 from singular value decomposition).

$\theta(R_m|T_m)$ = spatial angle between the mean QRS and T vectors.

†† $\theta(Rp|T_p)$ = spatial angle between the peak QRS and T vectors.

‡‡ $\theta(T_p|T_{ref})$ = spatial angle between the Tp vector and the reference T vector (Tref), signifying spatial deviation angle of repolarization direction from the direction of the normal repolarization sequence.

§§ $\theta(T_{init}|T_{erm})$ = spatial angle between the mean initial and terminal T vectors from quintiles 1-3 and quintiles 4-5 of global T wave, respectively.

// $\theta(T_{init}|T_{ref})$ = spatial angles between the mean initial T vector and Tref vector.

$\theta(T_{term}|T_{ref})$ = spatial angle between the mean terminal T vector and Tref vector.

††† Symbol 'V' with ST_oV, T_oV and T_pV signifies vector magnitude of ST_o, T_o and T_p, respectively.

T_oV/T_pV is the magnitude ratio of T_oV and T_pV vectors.