Sexual Dimorphism in the Electrocardiographic Dynamics of Human Ventricular Repolarization
Characterization in True Time Domain

Michael H. Lehmann, MD; Hua Yang, PhD

Background—Previous characterizations of sex differences in ST-T waveform voltages have largely focused on amplitudes at selected time points during repolarization, subject to potential distortions from variations in heart rate (HR) or reliance on a JT-normalized time scale.

Methods and Results—Using digitized 12-lead ECGs from 553 normal adults (426 males) with HRs confined to 60±1, 70±1, or 80±1 bpm, we derived X, Y, and Z lead voltages and then generated, for each HR category by sex, summary (population mean) resultant spatial vector amplitudes (ST-TXYZ) and instantaneous slopes (dV/dtXYZ) at successive 4-ms intervals following the J point. Within each HR category, there was an early intersex divergence of ST-TXYZ trajectories (95% CIs nonoverlapping), with men exhibiting 2- to 3-fold greater dV/dtXYZ values during the ST segment and achieving greater maximum TXYZ and dV/dtXYZ values than women; descending TXYZ limbs were relatively more concordant between sexes but still steeper in men. The early sex differences in repolarization dynamics persisted in multiple regression analyses that took into account age and a morphometric index of left ventricular mass. In men, absolute values of extrema of TXYZ and dV/dtXYZ varied inversely with HR.

Conclusions—At physiological resting HRs, the spatial ST-T vector voltage time trajectory is steeper in men than in women, beginning virtually from the J point. In addition to its mechanistic implications, the demonstration of marked sensitivity of ST-TXYZ and especially dV/dtXYZ to sex raises the possibility that these time-based, ECG-derived parameters might be informative in pathophysiological studies of ventricular repolarization.

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Key Words: electrocardiography ■ sex ■ heart rate

Recent awareness of an increased susceptibility of women to development of torsade de pointes ventricular tachycardia1 has highlighted the need to understand better the nature and extent of sex modulation of normal human ventricular repolarization. The existence of quantitative sex differences in the ECG manifestations of myocardial repolarization has been appreciated since the early 20th century, when Bazett2 reported that women have a longer average rate-corrected QT interval (QTc) than men. Such a sex disparity has since been confirmed repeatedly and found to apply to various ECG indices of repolarization duration.3–8 Over the years, investigators have also described differences between the sexes with respect to selected ST- and T-wave amplitudes, ie, typically higher mean values in men.3,4,9–11 These studies, however, did not correct for variations in heart rate (HR), a deficiency that other researchers attempted to remedy by reliance on a JT-normalized time scale.12–14 Thus, to date, a systematic comparison of the ST-T voltage trajectory and its dynamics, as a true function of time, in men and women has not been accomplished.

In the present study, we circumvented rate-related or temporal distortions inherent in previous methodologies by utilizing ECG data obtained at uniform HRs. This enabled us, for the first time, to compare by sex successive (4 ms) ST-T spatial vector voltages and first derivatives of those voltages in true time domain.

Methods
We used a database of ECGs recorded on a MAC-12 System (Marquette Electronics Inc) in normal adults, as described previously.5,8 In brief, subjects contributing to the database had normal histories and physical examinations and were not taking any cardioactive medication. None had ECG evidence of ventricular hypertrophy, intraventricular conduction disturbance, or myocardial infarction. The study subset was limited to individuals in the database whose resting HR by ECG fell into 1 of 3 narrow ranges: 60±1, 70±1, and 80±1 bpm, hereafter designated as HR 60, HR 70, and HR 80, respectively.

The 12-lead ECG signals were digitized and recorded at 250 Hz (4-ms sampling intervals). HRs, as well as markings of P onset, QRS onset and offset (ie, J point), and T offset, based on the median beat, were calculated by the MAC-12 software (12SL program) as...
Instantaneous Slopes (dV/dt) of ST-T Waveform

For any given sequence of ST-T(t) voltages, the raw instantaneous slope (change in voltage, or dV/dt) of the ST-T(t) curve at t = ti, is approximated by [ST-T(t + Δt) − ST-T(t)]/Δt, provided t − t−1 is sufficiently small (4 ms in our study). Owing to the jagged nature of the resulting dV/dt of ST-T waveform, we used a 7-point moving average of this raw dV/dt (centered at each t) to generate a smoothed dV/dt of ST-T waveform, beginning at 16 ms after the J point. Throughout the remainder of this article, dV/dt is assumed to refer to smoothed dV/dt.

Using the dV/dt values for each ST-Txyz curve, designated dV/dtxyz, it was then possible to calculate for the n-sized population of interest, at any sample time t (beginning 16 ms after the J point), a summary (population mean) instantaneous slope of the spatial ST-T voltage vector magnitude waveform, as follows:

\[
\frac{1}{n} \sum_{k=1}^{n} \frac{dV}{dt}_{xyz}(t_k)
\]

A more mathematically precise notation for this parameter is dV/dt_{xyz}dt, but we have opted for dV/dt_{xyz} as a simpler linear notation, with the understanding that the spatial subscript (XYZ) actually applies to the ST-T voltage (V) rather than time (t).

Feature Extraction

Specific parameters were extracted from the summary (not individual) ST-T_{xyz} and dV/dt_{xyz} curves. Three extrema were derived: Max T_{xyz}, the peak value of T_{xyz}; and Max (or Min) dV/dt_{xyz} the peak positive (or peak negative) value of dV/dt_{xyz}. Two duration parameters were extracted: J-to-Max T_{xyz}, the time from the J point to the peak of T_{xyz}; and J-to-Jend T_{xyz}, the time from the J point to the nadir between T_{xyz} and U_{xyz}.

Statistical Analysis

Summary values of a given parameter with corresponding 95% CIs were plotted on a graph to depict quantitative differences in summary waveforms between the sexes. Inasmuch as age is known to affect various ECG parameters of depolarization and repolarization, we repeated our sex comparisons within HR categories dichotomized by a 40-year age cut point. ST-T_{xyz} and dV/dt_{xyz} were also recalculated as parameters normalized for each subject’s height (in meters) to the 2.7 power and, alternatively, body surface area estimated from height and weight to the 1.5 power. These morphometric indices (especially the former) have been shown to largely adjust for sex differences in echocardiographically measured left ventricular mass.

Intersex and intrasex comparisons of mean age, height, and QRS duration for the 3 HR categories were performed initially with ANOVA, followed where appropriate by Student’s unpaired t test.

Lehmann and Yang Sexual Dimorphism of the ST-T Waveform
Within each HR category, multiple regression analysis was used to assess the potential influence of sex, age (as a continuous variable), and height^{2.7} on both ST-TXYZ and dV/dtXYZ at 40, 80, and 120 ms after the J point and on the extrema Max T_{XYZ}, Max dV/dt_{XYZ}, and Min dV/dt_{XYZ}. Analogous multiple regression analyses were performed to analyze the potential influence of HR on these extrema of T_{XYZ} and dV/dt_{XYZ} for each sex. Statistical significance in these analyses was defined as P<0.05.

**Results**

Table 1 provides age, morphometric, and QRS duration data for study subjects by HR category. Within each HR category, men were younger, with greater mean height^{2.7} and QRS duration. For each sex, there were no significant differences across HR categories with respect to any of the 3 parameters except for age in men, at HR 60 versus HR 80 (P<0.03).

**ST-T_{XYZ} and dV/dt_{XYZ} in Men vs Women**

Figure 1 shows, for each HR category, a comparison by sex of summary ST-T_{XYZ} voltages (top panels) and summary dV/dt_{XYZ} voltages (bottom panels) as a function of time (referred to the J point). At each HR, the ST-T_{XYZ} mean voltages, from the J point through the entire ascending limb of T_{XYZ}, achieved greater values and peaked 28 to 32 ms sooner in men. The 95% CIs for these mean voltages, at each 4-ms sample time, were nonoverlapping between the sexes from the J point (or just beyond) through their respective T_{XYZ} peak amplitudes. Although the J-to-End T_{XYZ} interval was also shorter in men (by 20 to 36 ms), mean spatial vector voltages were relatively more concordant between sexes over the course of the descending limb of T_{XYZ} after transient overlap of 95% CIs, with mean voltages declining more rapidly in men. The U_{XYZ} peak also occurred earlier (by 32 to 52 ms) in men than in women.

As evident from the dV/dt_{XYZ} curves in Figure 1, for each HR category, early values of dV/dt_{XYZ} as well as absolute maximum and minimum values, were consistently greater in men. At each HR, the 95% CIs for mean instantaneous slopes of dV/dt_{XYZ}, as a function of time, in men (♂) and women (♀) at 3 common HRs. Upper panels show ST-T_{XYZ} waveforms and lower panels dV/dt_{XYZ} waveforms, with left, middle, and right vertical panel pairs corresponding to HR 60, HR 70, and HR 80 bpm, respectively. Time scale is absolute (nonnormalized), referenced to J point (0 ms). Vertical bars extending above and below data points demarcate 95% CIs for depicted summary values; when these bars are not shown for particular data points, size of corresponding 95% CI is actually smaller than diameter of plotted symbol.

**ST-T Voltages in ECG-Derived Orthogonal Leads**

Figure 2 shows summary ST-T voltages at successive 4-ms intervals in each of the 3 mathematically synthesized orthogonal component leads that were used to reconstruct successive ST-T_{XYZ} vectors, at HR 70. Although mean ST-T voltages until the T-wave peak were of greater absolute magnitude in men for each of the 3 orthogonal leads (but most apparent in leads X and Z), the algebraic signs of these components from the J point onward were similar in both sexes (ie, positive in X, positive in Y, and negative in Z), yielding a spatial orientation of each instantaneous resultant vector that was grossly comparable (directed leftward, inferiorly, and anteriorly) in men and women. Similar results were obtained at HR 60 and HR 80 (data not shown).

**Adjustment for Age and Body Size**

The sexual dimorphism in ST-T_{XYZ} voltages and dV/dt_{XYZ} observed at HR 70 (Figure 1) was maintained when ECGs were dichotomized with a 40-year age cut point (Figure 3; more evident in the younger age group) or when the analysis was performed with ST-T voltages normalized by height^{2.7}. After the initial crossing of the male and female dV/dt_{XYZ} curves (near Max dV/dt_{XYZ} in women), the 95% CIs were again nonoverlapping through the timing of Min dV/dt_{XYZ} in men. Subsequently, in their terminal portions, these dV/dt_{XYZ} curve pairs exhibited somewhat greater concordance. Max dV/dt_{XYZ} was attained 28 to 40 ms and Min dV/dt_{XYZ} 24 to 36 ms sooner in men than in women.

Even at the 40- and 80-ms points of the ST segment, the male to female ratios for summary parameters ST-T_{XYZ} and dV/dt_{XYZ} ranged approximately from 1.2 to 2.5 and from 2.3 to 3.6, respectively, at each HR, with nonoverlap of even 99% CIs between the sexes for ST-T_{XYZ} and dV/dt_{XYZ} values (Table 2). In all 3 HR categories, the sex ratios for these ST-related parameters (especially dV/dt_{XYZ}) typically exceeded the female to male ratios (range 1.1 to 1.2) for either of the repolarization duration indices, J-to-Max T_{XYZ} or J-to-End T_{XYZ}.

Figure 1. Summary (population mean) spatial vector voltage amplitudes during repolarization (ST-T_{XYZ}) and concomitant summary instantaneous slopes (dV/dt_{XYZ}) as a function of time, in men (♂) and women (♀) at 3 common HRs. Upper panels show ST-T_{XYZ} waveforms and lower panels dV/dt_{XYZ} waveforms, with left, middle, and right vertical panel pairs corresponding to HR 60, HR 70, and HR 80 bpm, respectively. Time scale is absolute (nonnormalized), referenced to J point (0 ms). Vertical bars extending above and below data points demarcate 95% CIs for depicted summary values; when these bars are not shown for particular data points, size of corresponding 95% CI is actually smaller than diameter of plotted symbol. ST-T_{XYZ} waveform plots consist of contiguous ST_{XYZ} and T_{XYZ} portions, followed by low-amplitude U_{XYZ}. Plots of dV/dt_{XYZ} begin at 16 ms after J point (see Methods); mV/s units are equivalent to μV/ms. Format similar in subsequent figures, except as indicated.
Qualitatively similar results were obtained at HR 60 and HR 80 (data not shown). For all 3 HR categories, the described sex differences also persisted when morphometric normalization was performed with body surface area$^{1.5}$ rather than height$^{2.7}$ (data not shown).

Within HR groups, multiple regression analysis was performed to assess the possible predictive effects of sex, age, and height$^{2.7}$, specifically on early spatial vector amplitudes and slopes, at 40, 80, and 120 ms after the J point. Sex was found to be a highly significant independent predictor of the 3 early ST-TXYZ parameters ($P<0.001$ at HR 60 and HR 70, $P<0.004$ at HR 80) and the 3 early dV/dt XYZ parameters ($P<0.0001$ at HR 60 and HR 70, $P<0.001$ at HR 80). Age was also a significant independent (inversely related) predictor of these various parameters at HR 60 and HR 70 ($P<0.001$) but not at HR 80. Height$^{2.7}$, however, was virtually never an independent predictor of any of the 6 parameters (exception mainly at 40 ms).

When extrema of TXYZ and dV/dtXYZ were similarly analyzed by multiple regression analysis, within HR categories, sex was independently predictive of Max TXYZ at all 3 HRs ($P<0.001$), Max dV/dtXYZ at HR 60 and HR 80 ($P<0.02$), and Min dV/dtXYZ at HR 60 and HR 70 ($P<0.05$). For all 3 HRs, age, but not height$^{2.7}$, was a significant (inverse) predictor of Max TXYZ ($P<0.02$) and absolute values of Max (P<0.03) and Min (P<0.01) dV/dtXYZ.

### Effect of HR on ST-TXYZ and dV/dtXYZ
Superimposed HR plots of ST-TXYZ and dV/dtXYZ for men and women are shown in Figure 5. When extrema of TXYZ and dV/dtXYZ were compared by HR, within each sex, multiple regression analysis (incorporating age and height$^{2.7}$) revealed a statistically significant HR effect in men such that the absolute values for Max TXYZ, Max dV/dtXYZ, and Min dV/dtXYZ varied

### TABLE 2. Spatial ST Vector Voltages and Instantaneous Slopes Within 80 ms of the J Point

<table>
<thead>
<tr>
<th>Time After J Point, ms</th>
<th>ST$_{XYZ}$ Magnitude,* Mean (99% CI), $\mu$V</th>
<th>dV/dt$_{XYZ}$,* Mean (99% CI), mV/s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>HR 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>37.76</td>
<td>57.44</td>
</tr>
<tr>
<td></td>
<td>(30.67–44.85)</td>
<td>(52.00–62.88)</td>
</tr>
<tr>
<td>40</td>
<td>39.94</td>
<td>89.75</td>
</tr>
<tr>
<td></td>
<td>(32.03–47.85)</td>
<td>(83.60–95.89)</td>
</tr>
<tr>
<td>80</td>
<td>53.22</td>
<td>130.52</td>
</tr>
<tr>
<td></td>
<td>(42.70–63.74)</td>
<td>(121.84–139.20)</td>
</tr>
<tr>
<td>HR 70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>45.24</td>
<td>53.62</td>
</tr>
<tr>
<td></td>
<td>(37.17–53.31)</td>
<td>(48.02–59.22)</td>
</tr>
<tr>
<td>40</td>
<td>49.38</td>
<td>86.07</td>
</tr>
<tr>
<td></td>
<td>(41.08–57.68)</td>
<td>(78.41–93.74)</td>
</tr>
<tr>
<td>80</td>
<td>65.87</td>
<td>130.07</td>
</tr>
<tr>
<td></td>
<td>(55.28–76.46)</td>
<td>(118.72–141.42)</td>
</tr>
<tr>
<td>HR 80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>43.83</td>
<td>53.15</td>
</tr>
<tr>
<td></td>
<td>(31.45–56.22)</td>
<td>(44.96–61.34)</td>
</tr>
<tr>
<td>40</td>
<td>51.48</td>
<td>88.38</td>
</tr>
<tr>
<td></td>
<td>(38.11–64.85)</td>
<td>(76.10–100.66)</td>
</tr>
<tr>
<td>80</td>
<td>68.65</td>
<td>139.70</td>
</tr>
<tr>
<td></td>
<td>(50.65–86.66)</td>
<td>(121.52–157.88)</td>
</tr>
</tbody>
</table>

M indicates male; F, female.

**"Mean" data shown here are actual values of the summary (population mean) parameters ST$_{XYZ}$ and dV/dt$_{XYZ}$.

†Based on ST$_{XYZ}$ or dV/dt$_{XYZ}$ values before 2-decimal-point rounding.

Figure 2. Summary spatial vector voltage amplitudes during repolarization in 3 derived orthogonal leads, X, Y, and Z, as a function of time, in men and women at HR 70. Lead Z is directed positively toward posterior thorax. Left, middle, and right panels depict ST-T$_1$, ST-T$_2$, and ST-T$_3$ waveforms, respectively.
inversely with HR (\(P<0.0001\), HR 70 and HR 80 versus HR 60 for Max \(T_{XZ}\), \(P<0.02\), HR 80 versus HR 60 for Max \(dV/dt_{XZ}\) and \(P<0.0001\), HR 80 versus HR 60, and \(P<0.01\), HR 70 versus HR 60, for Min \(dV/dt_{XZ}\)). There were no statistically significant differences among values of these parameters in women, however, when compared by HR. In both sexes, the multiple regression analysis also showed age, but not height\(^{2.7}\), to be a significant (inversely related) predictor of the absolute values of Max \(T_{XZ}\), Max \(dV/dt_{XZ}\), and Min \(dV/dt_{XZ}\) (\(P<0.0001\) for men, \(P<0.02\) for women).

**Discussion**

The present study is the first to compare at common HRs in men and women successive mean ECG-derived spatial vectorcardiographic voltages (ST-\(T_{XZ}\)) and concomitant mean instantaneous slopes (\(dV/dt_{XZ}\)) at high temporal resolution during ventricular repolarization. At each of the 3 physiological resting rates studied (HR 60, HR 70, and HR 80), our findings attest to clear quantitative sex differences in the ECG dynamics of repolarization, with more brisk dynamics of ST-T-wave generation seen in men. This sex difference largely persisted after adjustment for age and body size.

Conventional\(^{3,4,9,10}\) and orthogonal\(^{11}\) lead scalar ECG studies have demonstrated in men greater peak T-wave amplitudes (especially anteriorly), select ST-segment voltages, and precordial mean ST angles.\(^{19}\) Limiting these prior investigations, however, was the fact that measured ST-T parameters were averaged within study groups regardless of intersubject variations in HR. In contrast, Green et al\(^{14}\) used a time-normalization procedure on digitized body-surface potential maps in normal subjects and reported “slightly” larger average ST potentials and greater average early and mid T-wave potentials in men than in women. Analogous observations were made in previous scalar orthogonal lead ECG studies in which intersex time-normalized repolarization voltages were compared at successive 1/8 time divisions of the JT interval.\(^{12,13}\) More recently, Macfarlane\(^{20}\) found men to have greater average ST angles, as measured between the J point and 3/8 of the JT interval (P.W. Macfarlane, PhD, personal communication, 1999), in selected conventional ECG leads. The time-normalization approach, however, is ac-
The present study design was intended to overcome limitations of the earlier methodologies by focusing on ECGs at common HRs, thereby permitting direct and comprehensive comparisons of derived 3D vectorcardiographic voltages as a true function of time (at 4-ms intervals) during ventricular repolarization. We demonstrated greater and more rapidly attained absolute values of maximal instantaneous slopes of the ascending and descending limbs of the spatial T vector waveform in men, extending our findings in lead V5.8 Importantly, the present study enabled us to trace systematically the temporal origin of these more brisk male dynamics of T-wave generation back to the ST segment (Figure 1), where dV/dtXYZ values were already some 2- to 3-fold greater in men (Table 2). Thus, at each study HR, a steeper ST-T XYZ voltage time trajectory was found in men relative to women, essentially from the ECG inception of ventricular repolarization. Moreover, sex differences in early ST-T amplitudes and slopes persisted in multiple regression analyses that included age and height.27

Mechanistic Considerations

The ST-T waveform is primarily a manifestation of successive, instantaneous net transmural ventricular voltage gradients during repolarization, with superimposed effects of regional, ie, “geographic,” differences in electrical recovery properties (especially within the more rapidly repolarizing epicardial layer).21 The general concordance in orthogonal lead distribution of early ST-T voltages in men and women (Figure 2), however, argues against a gross sex disparity in geographic sequence of repolarization as the basis for the observed sexual dimorphism in ST-TXYZ dynamics.

More tenable is the hypothesis that during repolarization, there are sex-related quantitative differences in the action potential voltage time course of 1 or more ventricular transmural cell types that may have an effect on the morphology of the ST-T waveform. This conjecture is motivated by experimental data implying that the aggregate ventricular repolarization gradient reflected in the ST-T waveform until the peak of the T wave is driven largely by the voltage time dynamics of phases 2 and 3 of action potentials in the epicardium relative to those of deeper myocardial cell layers.22

Sex steroids (especially androgens) appear likely mediators of the peripubertal shortening of QTc6 and the lower propensity to JTc prolongation24 and torsade de pointes1 exhibited by men versus women. By extension, these hormones, which are capable of affecting repolarizing currents,25,26 also could have a modulating influence on the transmural voltage gradients that contribute to the genesis and dynamics of the ST-T waveform. This hypothesis is supported by a recent report describing differences in precordial lead T-wave amplitudes and average ST angles under altered androgenic states.27

Influence of HR and Age

Our findings, at least in men, of a decrease in Max TXYZ as resting HR increases (Figure 5) confirm definitively earlier scalar ECG impressions.3 Such behavior, implying the need for “rate correction” of maximum T-wave amplitude measurements, is consistent with observations in the perfused left ventricular wedge preparation.28 We further documented a similar inverse relationship in men between absolute value of Max (and Min) dV/dtXYZ and HR.

In both men and women, age was found to be an independent (inverse) predictor of the absolute values of the extrema of TXYZ.
and $dV/dt \text{ XYZ}$ (at all 3 HRs), as well as the values of these parameters during the ST segment (at HR 60 and HR 70). Although of unclear mechanistic origin, these observations at controlled HRs extend traditional ECG analyses showing age-related declines in ST-T parameters, especially in men, during adulthood.49,10

Study Limitations
Conceivably, differences in resting HR among the study population may have reflected, in part, variations in other physiological parameters, eg, sympathetic and parasympathetic tone. Such an HR selection artifact could have had a confounding influence on the quantitative comparison of repolarization dynamics among the HR categories we studied but would not be expected to negate the highly consistent sex difference we documented within each HR group. We recognize that the onset of detectable ventricular repolarization actually precedes the J point (our operational “time zero”) by an average of $\sim 5$ to 12 ms.29 However, slight interindividual differences in true $t_0$ would not explain the consistent early upward displacement of the $dV/dt\text{ XYZ}$ curves and steeper ST$_{XYZ}$ trajectory in men relative to women. The relative paucity of women in our study population (<1.3 female:male ratio) may have limited our ability to precisely define the relationship between HR and Max $T_{1/2}$, Max $dV/dt\text{ XYZ}$, and Min $dV/dt\text{ XYZ}$ in women (Figure 5). Expanded studies are needed to address this issue and to explore ST-T dynamics in nonwhite populations, older subjects, and groups with defined levels of physical activity.

Implications
The present findings add to accumulating evidence for the existence of fundamental differences between the sexes in the physiology of ventricular repolarization. Our observations of the marked sex sensitivity of instantaneous ST-T spatial vector amplitudes, and particularly slopes, raise the possibility that these time-based parameters may convey information regarding a variety of processes capable of modulating repolarization.30

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