Menstrual Cycle and ST Height

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Background: Sex hormones and menstrual cycle effects on ST height have not yet been clearly identified.

Methods: Twenty-two young, healthy women (aged 22–32 years) were included in this study. Twelve-lead ECGs were registered during menses, follicular and luteal phase of the menstrual cycle at baseline, and after double autonomic blockade (DAB). Chest leads V2–V4 and limb leads I and II were chosen for analysis. ST height was measured manually at J-Point and 40 ms after the J-Point, and values were corrected for QRS amplitude (J-Point/QRS, 40 ms/QRS). Repeated measure ANOVA was used to analyze differences in ST height among the three phases of the menstrual cycle. A P-value < 0.05 was considered as significant.

Results: At baseline, ST height, QTc, and T wave amplitude were not significantly different among the three phases of the menstrual cycle. After double autonomic blockade, ST height at 40 ms, J-Point/QRS, and 40 ms/QRS was significantly higher during follicular versus luteal phase (0.152 ± 0.413 mm versus -0.007 ± 0.427 mm, $P = 0.0059$ at 40 ms; -0.001 ± 0.030 versus -0.015 ± 0.032 , $P = 0.0039$ at J-Point/QRS; 0.013 ± 0.031 versus -0.004 ± 0.032 , $P = 0.0005$ at 40 ms/QRS) as was the QTc. ST height differences at J-Point were not significantly different (-0.046 ± 0.395 mm follicular, -0.167 ± 0.448 mm luteal, and -0.083 ± 0.492 mm menses, $P = 0.1014$).

Conclusion: ST height and QTc varied among the three phases of the menstrual cycle, predominantly after double autonomic blockade. Female sex hormones that vary throughout the menstrual cycle may modulate measures of repolarization.

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Early repolarization (ER) is a term that has been used to characterize ECGs that show ST elevation in an upward curving pattern that is thought to be a normal variant. It occurs in approximately 1–2% of the population, mostly young and athletic men,¹ throughout all races.^{1,2} There are specific features that characterize this syndrome, most notably the elevated, concave ST segment, commonly located in the precordial leads.^{2,3}

It has long been recognized that there are gender differences in ER, and it is well established that men generally have higher values of ST height and T-wave slopes describing ER than women.^{1–7} However, prior studies have not yet been able to clearly identify the origin of this syndrome, nor the mechanism for its gender differences.

It has been suggested that ER may be due to an enhanced activity of the right sympathetic nerves,⁸ increased vagal activity,^{9–11} with slower heart rates in men,^{1,10,11} or simply the slower heart rate itself as responsible mechanisms.¹²

The identification of testosterone and estrogen receptors in the heart provided a rationale for investigating hormonal modulation of repolarization. Theoretically, both female and/or male sex hormones were proposed to be possibly responsible for the gender differences in cardiac repolarization and ST height^{13–16} although some prior data suggest that testosterone may be more important than female sex hormones.^{17,18}

The purpose of this study was to examine the hypothesis that variations in female hormone

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levels during the normal menstrual cycle influence ST height and early repolarization.

METHODS

The study group consisted of 22 young, healthy women, ranging from 22 to 32 years old (mean age 26.1 ± 3.6), all of whom gave informed consent to participate in a protocol approved by the Northwestern University Institutional Review Board. Twelve-lead ECGs were taken at baseline and after double autonomic blockade (DAB) with atropine and propranolol during three different phases of the menstrual cycle. The subjects were healthy volunteers with a normal physical examination and electrocardiogram and no history of cardiovascular or medical disease. None was a trained athlete. Exclusion criteria included the presence of significant arrhythmias, current use of medications known to affect the ST segment or QT interval, or the presence of significant medical problems, including bronchospastic disease or glaucoma. For women, irregular menstrual periods, pregnancy, or the current use of hormonal replacement therapy or oral contraceptive pills were exclusion criteria. A urinary ovulation predictor was used to time ovulation (OVU-Kit, Monoclonal Antibody Inc., San Diego, CA). The menstrual phase study, when both estrogen and progesterone are low, was performed within 4 days of the onset of menses, which was determined by history. The follicular phase study, when estrogen is high and progesterone is still low, was performed on days 12 to 14 of the cycle, before a urinary ovulation predictor turned positive. The luteal phase study, when progesterone is high and estrogen is slightly lower, was performed 6 to 8 days after ovulation, which was usually day 20 to 24 of the cycle. The luteal phase was confirmed by a serum progesterone level of greater than 5 mg/ml. All studies were performed in the morning after an overnight fast. After a supine rest period of 30 minutes, baseline 12-lead electrocardiograms were performed for a duration of 20 seconds, using a Marquette Model MAC I recorder. None of the baseline electrocardiograms showed any diagnostic abnormalities, and patients were in sinus rhythm. Double autonomic blockade (DAB) was then administered intravenously, consisting of propranolol 0.2 mg/kg infused at a rate of 1 mg per minute followed by atropine 0.04 mg/kg infused at a rate of 1 mg/min. An electrocardiogram was repeated 10 minutes after the administration of atropine. These doses of

atropine and propranolol have been shown to result in complete blockade of the beta-adrenergic and parasympathetic nervous system.^{19,20} Twelve-lead ECGs, recorded at 25 or 50 mm/s with a gain of 10 mm/mV, were taken at baseline and after double autonomic blockade during the menstrual, follicular, and luteal phases of the menstrual cycle.

ECGs were computer scanned and magnified approximately 7 to 8 times the original size, and ST height was measured with an on-screen-measuring tool to the nearest 1/5th mm (0.2 mm). Leads I, II, V2, V3, and V4 were chosen for analysis. The QT interval, corrected QT interval using Bazett's correction (QTc), and T-wave amplitude were measured. The isoelectric baseline was defined as the height of the midpoint of a line drawn from the end of the previous T wave to the beginning of the QRS complex, and ST height in relation to the baseline was measured at cut points of J-Point and 40 ms after J-Point (J-Point 40 ms). QRS amplitude was also measured to the nearest 0.2 mm. J-Point height and ST height 40 msec after J-point were each divided by the QRS amplitude to give QRS-corrected J-Point/QRS and J-Point 40 ms/QRS. Heart rates achieved during each stage were also measured. A subset of measurements was made by a second observer to validate this method of measurements ($n = 525$ ST height measurements) with an intra-class correlation coefficient of 0.83.

Data Analysis

Data are expressed as mean $\pm$ standard deviation. Repeated measure ANOVA was performed using commercially available software (StatView 5.0.1). Hormonal levels were correlated with ST height using simple linear regression. Analysis was performed for ST height at J-Point and 40 ms, and for the QRS amplitude corrected values J-Point/QRS and 40 ms/QRS. Differences among the five leads were assessed by using factorial ANOVA, within each menstrual cycle phase, separately for baseline and autonomic blockade conditions, with Fisher's protected least significant differences post hoc analysis to determine overall lead differences. A P-value < 0.05 was considered significant for all purposes.

RESULTS

Figure 1A and B shows ECG recordings from each of the three phases of the menstrual cycle and describe the measurement technique. Results for

Figure 1. (A) Example of ST height measurement at J-Point and 40 ms after J-Point. (B) ECG Examples during different phases of the menstrual cycle at baseline and after double autonomic blockade in Lead V2.

ST-height parameters and heart rate at both baseline and after DAB are shown in Table 1.

ST height in the limb leads was found to be generally lower compared to the precordial leads. Furthermore, values of the precordial leads V2–V4 all behaved in the same way, whereas limb leads I and II behaved in opposite directions, with follicular values at baseline reaching maximal values in lead II but minimal values in lead I (Table 1). The QTc in the limb leads was 0.433 ± 0.07 ms and 0.446 ± 0.07 ms in the precordial leads ($P = \text{ns}$). There were significant differences in T-wave amplitude between the different leads both at baseline and following DAB. At baseline it was highest in lead II (0.36 ± 0.13 mv) and V4 (0.337 ± 0.152 mv) as compared to leads I (0.192 ± 0.83 mv, $P < 0.0001$ vs lead II and V2), V2 (0.242 ± 0.146 mv, $P < 0.0001$ vs II and V4), V3 (0.294 ± 0.148 mv, $P < 0.01$ vs II). The T-wave amplitude was 0.249 ± 0.131 mv in the limb leads and 0.257 ± 0.143 mv in the precordial leads ($P = \text{ns}$).

Thus, analysis of the influence of menstrual cycle at both baseline and after DAB on ST height was performed on pooled data for the mid-chest precordial leads V2–V4, as well as for the limb lead I and limb lead II, separately, using repeated measure ANOVA.

At baseline, no significant differences were found for ST height at J-Point and at 40 ms, as well as for the QRS-corrected values J-Point/QRS and 40 ms/QRS in the chest leads (Table 1). Similarly, there were no significant differences in the QTc or

T-wave amplitude in the chest leads between the different phases of the menstrual cycle. Subanalysis of each precordial lead did not demonstrate any differences among the three phases of the menstrual cycle. Analysis of the limb leads showed similar results (Table 1).

After DAB, in the precordial leads, ST height at J-Point did not differ significantly among the three menstrual phases, but a trend toward higher values during the follicular phase was noticed (-0.046 ± 0.395 mm follicular vs -0.167 ± 0.448 mm luteal and vs -0.083 ± 0.492 mm menses, $P = 0.1014$). ST height at 40 ms after J-Point, J-Point/QRS, and 40 ms/QRS was significantly higher during the follicular phase compared to the luteal phase (0.152 ± 0.413 mm vs -0.007 ± 0.427 mm, $P = 0.0059$ at 40 ms; -0.001 ± 0.030 vs -0.015 ± 0.032 , $P = 0.0039$ at J-Point/QRS; 0.013 ± 0.031 vs -0.004 ± 0.032 , $P = 0.0005$ at 40 ms/QRS, respectively). ST height values were lowest during the luteal phase, and intermediate during the menses phase without showing any statistical significant differences among those two cycle phases (-0.007 ± 0.427 mm luteal, and 0.052 ± 0.442 mm menses at 40 ms; -0.015 ± 0.032 luteal, and -0.006 ± 0.045 menses at J-point/QRS; -0.004 ± 0.032 luteal, and 0.004 ± 0.032 menses at 40 ms/QRS). Subanalysis for the precordial leads had confirmed significantly higher values of ST height at 40 ms, J-Point/QRS, and 40 ms/QRS during the follicular phase to be particularly prominent in lead V2, and had furthermore shown trends toward higher values of ST height in lead V3 and V4. Figure 2 shows the results of ST height at J-Point and 40 ms after J-Point during menses, and follicular and luteal phases at baseline and after double autonomic blockade.

After DAB, the QTc was significantly longer in the follicular phase (0.476 ± 0.10 ms) than in the luteal (0.449 ± 0.04 ms, $P < 0.01$ vs follicular) or menstrual (0.455 ± 0.06 ms, $P < 0.05$ vs follicular) phases of the menstrual cycle. There were no significant differences in the T-wave amplitude between the follicular (0.224 ± 0.121 mv), luteal (0.30 ± 0.128 mv), and menstrual (0.210 ± 0.11 mv) phases after DAB although DAB significantly shortened the overall T-wave amplitude (0.221 ± 0.12 mv) compared to baseline (0.286 ± 0.148 mv, $P < 0.0001$).

Heart rate at baseline was significantly higher during the luteal phase compared to the menses phase (70.0 ± 9.7 bpm luteal vs 64.2 ± 10.4 bpm

Table 1. ST Height (mm), Mean of Lead I, Lead II, and Lead V2–V4 During Different Menstrual Phases in Young Women at Baseline (BL) and after Double Autonomic Blockade

	Heart Rate	J-Point Height (mm)	40 ms(mm)	J-Point/QRS	40 ms/QRS
Baseline (n = 22)					
Lead I					
Menses	64.2 ± 10.4	0.095 ± 0.328	0.043 ± 0.199	0.027 ± 0.068	0.012 ± 0.045
Follicular	67.1 ± 9.2	-0.038 ± 0.296	0.014 ± 0.206	-0.005 ± 0.076	0.005 ± 0.048
Luteal	70.0 ± 9.7*	0.076 ± 0.281	0.105 ± 0.196	0.014 ± 0.061	0.023 ± 0.045
Lead II					
Menses	64.2 ± 10.4	0.123 ± 0.417	0.086 ± 0.366	0.008 ± 0.030	0.007 ± 0.029
Follicular	67.1 ± 9.2	0.150 ± 0.555	0.200 ± 0.399**	0.010 ± 0.039	0.014 ± 0.029
Luteal	70.0 ± 9.7*	-0.064 ± 0.365	-0.064 ± 0.381	-0.005 ± 0.025	-0.006 ± 0.025
Lead V2–4					
Menses	64.2 ± 10.4	-0.005 ± 0.342	0.214 ± 0.325	-0.001 ± 0.027	0.018 ± 0.027
Follicular	67.1 ± 9.2	0.044 ± 0.463	0.251 ± 0.434	0.003 ± 0.037	0.020 ± 0.037
Luteal	70.0 ± 9.7*	-0.052 ± 0.334	0.162 ± 0.381	-0.004 ± 0.028	0.014 ± 0.031
Mean (n = 66)	67.1 ± 10.0	-0.005 ± 0.389	0.201 ± 0.381	-0.003 ± 0.031	0.014 ± 0.030
Double Autonomic Blockade (n = 22)					
Lead I					
Menses	102.1 ± 9.5	0.153 ± 0.382	0.121 ± 0.257	0.032 ± 0.078	0.023 ± 0.059
Follicular	100.9 ± 8.2	0.058 ± 0.239	0.074 ± 0.182	0.016 ± 0.074	0.016 ± 0.054
Luteal	100.6 ± 9.9	0.168 ± 0.229	0.137 ± 0.189	0.034 ± 0.051	0.034 ± 0.040
Lead II					
Menses	102.1 ± 9.5	0.060 ± 0.561	-0.030 ± 0.452	0.002 ± 0.044	-0.003 ± 0.033
Follicular	100.9 ± 8.2	-0.045 ± 0.570	-0.120 ± 0.414	-0.001 ± 0.040	-0.007 ± 0.027
Luteal	100.6 ± 9.9	0.230 ± 0.411	0.120 ± 0.375	0.014 ± 0.036	0.005 ± 0.031
Lead V2–4					
Menses	102.1 ± 9.5	-0.083 ± 0.492	0.052 ± 0.442	-0.006 ± 0.045	0.004 ± 0.032
Follicular	100.9 ± 8.2	-0.046 ± 0.395	0.152 ± 0.413**	-0.001 ± 0.030**	0.013 ± 0.031**
Luteal	100.6 ± 9.9	-0.167 ± 0.448	-0.007 ± 0.427	-0.015 ± 0.032	-0.004 ± 0.032
Mean (n = 66)	101.7 ± 9.4***	-0.115 ± 0.448***	0.037 ± 0.428***	-0.012 ± 0.038***	-0.001 ± 0.036***

*P < 0.05 compared to menstrual phase in same autonomic status group.

**P < 0.05 compared to luteal phase in same autonomic status group.

***P < 0.05 compared to baseline at same cut point.

menses, $P = 0.0107$). No significant differences were found between follicular and luteal, or follicular and menses phases (mean heart rate follicular: 67.1 ± 9.2 bpm). After autonomic blockade, the heart rate was found to be similar during the three menstrual phases with values ranging from

100.6 ± 9.9 bpm luteal, 100.9 ± 8.2 bpm follicular, and 102.1 ± 9.5 bpm at menses. After controlling for heart rate as covariate, comparisons of ST height among the three phases of the menstrual cycle were similar to those without the correction.

DISCUSSION

In the present study, ST height and QTc in the precordial leads was highest during the follicular phase of the menstrual cycle. Results under baseline conditions did not reach statistical significance, but after DAB, ST height at 40 ms, J-Point/QRS, J-Point 40 ms/QRS, and QTc were significantly higher during the follicular phase compared to the luteal phase.

It is well known that levels of estrogen, progesterone, as well as androgen vary during the female menstrual cycle. During menses, estrogen and progesterone are relatively low, and estrogen

Figure 2. ST height (mm) at J-Point and 40 ms after J-Point (40 ms), mean of Leads V2–V4 during menses, follicular, and luteal phase at baseline (BL) and after double autonomic blockade (DAB).

begins rising during the follicular phase, reaching its maximum level just before ovulation. Other hormones such as LH and androgens rise as well.^{21,22} During the luteal phase, estrogen decreases to a lower level and progesterone increases. Thus, the greater ST height during the follicular phase that was found in this study, may have been caused by elevated estrogen levels at that point of the menstrual cycle. Lower ST height during the luteal phase could be explained by higher levels of progesterone that might have antagonized a possible estrogen effect. Androgens also can rise during the midcycle, so it is also possible that they had a modulating effect on ST height during the follicular phase. Furthermore, since receptors for both testosterone and estrogen have been found in the heart, theoretically both male and female sex hormones may modulate cardiac repolarization and ST height.^{13–16}

Prior studies on ER and its gender differences have suggested that testosterone is an important modulating factor. Surawicz et al. have shown in 529 men and 544 women that the increase in ST height in men occurs predominantly in adolescent males after puberty.⁵ It has also been shown that ST height generally decreases with age. Bidoggia et al. found when comparing 250 males to 250 females that the decline in ST height with age occurs in men, and not in women. They concluded that the sex-dependent differences decreased as a function of age, mainly because of age-dependent changes in the men.⁶ Recently published data by Bidoggia et al. emphasized again the role of testosterone by showing that the ST segment (at the J-Point) was lower in both normal women and castrated men, as compared to normal men, and also that women with virilization syndrome had higher ST segments than normal women and castrated men.²³

A variety of cellular mechanisms have been shown to be the cause of ST elevation in experimental models. During acute ischemia, modulation of $I_{K(ATP)}$ appears to be responsible.²⁴ Antzelevitch's group has described in a canine model that regional differences in I_{to} may be responsible for ST elevation produced in the Brugada Syndrome ECG.^{25,26} Prominent I_{to} in the epi- but not endocardium of the right ventricle has been thought to be responsible for the ST segment elevation seen in Brugada Syndrome. Furthermore, Diego et al.²⁷ found more prominent I_{to} density in the epicardium of males versus females, which they postulated as

the cause of the gender difference in Brugada Syndrome. However, the ST-segment elevation seen in ER is different from that in the Brugada Syndrome. Unlike in Brugada, the ST elevation is not associated with QRS prolongation and is most prominent in V1 and V2 rather than the midprecordial leads. Thus the ionic mechanisms responsible for ST-segment elevation in the Brugada Syndrome may be different from those in the early repolarization syndrome.

The observation that differences in ST height were seen following autonomic blockade but not at baseline could have several possible explanations. Heart rates were clearly different following autonomic blockade than at baseline, and it is possible that the ionic mechanisms responsible for menstrual cycle variability in ST height are more prominent at faster heart rates. It is also possible that there is an interaction between sympathetic or parasympathetic tone and ionic currents that modulate their effect at baseline but are absent following autonomic blockade. A prior study from our laboratory on QT interval variability in the menstrual cycle also showed differences only following autonomic blockade that were subsequently shown to be important when women were exposed to antiarrhythmic drugs.

While the differences seen in the present study were small and may not have direct clinical implications, the finding that there is menstrual cycle variability in ST height suggests that repolarizing currents differ at different phases in the menstrual cycle. This suggests a possibility that sensitivity to antiarrhythmic drugs may be variable at different times in the menstrual cycle and could potentially have implications for therapy. A similar observation regarding the QT interval²⁸ was subsequently shown to affect sensitivity to the QT-prolonging drug, ibutilide.²⁹

LIMITATIONS

There are several factors that may have influenced the results of the present study. First, ST-height measurements were performed manually. This method has an inherent error factor in the subjectivity of determining the J-Point and ST height in the ECG. However, we attempted to diminish this potential error factor by emphasizing the training of ECG readers, and by validating our method and results with a second observer and intra-correlation studies. Furthermore, levels of sex

hormones were not included in our analysis. Finally, the effects of menstrual cycle on cardiac ion currents were not directly measured in this study.

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