Influence of Menstrual Cycle on P Wave Dispersion

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Summary

Female gender is an independent risk factor for some types of arrhythmias. We sought to determine whether the menstrual cycle affects P wave dispersion, which is a predictor of atrial fibrillation. The study population consisted of 59 women in follicular phase (mean age, 29.3 ± 7.7 years) (group F) and 53 women in luteal phase (mean age, 28.1 ± 6.8 years) (group L). The ECGs of 35 patients (mean age, 26.4 ± 4.5) were obtained in both follicular and luteal phase. Both groups underwent a standard 12-lead surface electrocardiogram recorded at 50 mm/s. Maximal (Pmax) and minimal P wave durations (Pmin) were measured. P wave dispersion (PD) was defined as the difference between Pmax and Pmin. PD was significantly higher in group L than group F (46.6 ± 18.5 versus 40.1 ± 12.7; P < 0.05). Pmin was significantly lower in group L than group F (51.6 ± 12.1 versus 59.1 ± 12.1; P = 0.002). When we compared ECGs in different phases of the 35 patients, PD was significantly higher in luteal phase than follicular phase (53.2 ± 12.3 versus 42.8 ± 10.2; P < 0.05). Pmin was significantly lower in luteal phase than follicular phase (47.6 ± 6.6 versus 56 ± 10.1; P = 0.05). We detected a significant correlation between the day of the menses and PD (r = 0.27; P < 0.05). PD was increased in luteal phase compared to follicular phase, and this difference was more prominent as the days of the cycle progressed. (Int Heart J 2011; 52: 23-26)

Key words: Menstrual cycle, P wave dispersion, Atrial fibrillation

It is well known that female sex hormones have proarrhythmic potential and female gender is an independent risk factor for some types of cardiac arrhythmias, such as congenital and acquired long QT syndrome and torsades de points. There are dynamic fluctuations in QT interval and torsade de points risk during the menstrual cycle and pregnancy.11 This hormonal flux that occurs during premenstrual, perimenopausal, and pregnancy periods could lead to ventricular tachycardia (VT) initiation in female patients with VT originating from the right ventricular outflow tract.23 P wave abnormalities, detected in the electrocardiogram (ECG), have been thought to reflect left atrial enlargement,4 left atrial hypertension5 and altered conduction.5 A simple ECG marker, P wave dispersion (PD), has been used to evaluate the intraatrial and interatrial conduction times and the inhomogeneous propagation of sinus impulses which are well known electrophysiologic characteristics of the atrium prone to fibrillation.6-5 Prolonged P wave duration and PD have been reported to represent an increased risk for atrial fibrillation (AF) in patients with no underlying heart disease.6-5

The relationships between menstrual cycle and different kinds of arrhythmias have been studied before, but there are no data on P wave abnormalities in the menstrual cycle. The aim of this study was to investigate the effects of the menstrual cycle on P wave dispersion.

Methods

A total of 112 female patients between 15-49 years old (mean age, 28.7 ± 7.3 years old) with regular menstrual cycles (28-31 days) were enrolled in this study. Patients with no underlying chronic disease were recruited. None of the patients were using oral contraceptives and there were no pregnancies. Echocardiography, chest x-rays, and serum electrolytes were normal. Patients were grouped as group F; 59 women in follicular phase at ECG assessment (7-12 days from the beginning of the menstrual cycle, mean age, 29.3 ± 7.7 years) and group L; 53 women in luteal phase at ECG assessment (18-26 days from the beginning of the menstrual cycle, mean age, 28.1 ± 6.8 years). The ECGs of 35 patients (mean age, 26.4 ± 4.5 years) were obtained in both follicular and luteal phase. Blood tests for serum estradiol, progesterone, and electrolytes (Na, K, Cl, Mg) were evaluated after 8 hours of fasting. The present study was approved by the Ethical Review Board of the University of Karaelmas. Patients and control participants provided oral and written informed consent according to the Helsinki Declaration.

Patients with a history of AF, left ventricular dysfunction, left ventricular hypertrophy, valvular heart disease, chronic obstructive pulmonary disease, ventricular preexcitation, atrioventricular conduction abnormalities, abnormal thyroid function, or serum electrolytes were excluded from the study.

All standard 12-lead ECGs were obtained using a recorder (Agilent, Andover, MA, USA) set at a 50 mm/second paper
speed and 20 mm/mV standardization. Recordings were performed during spontaneous breathing in the supine position. All measurements of P wave duration were calculated blindly by 2 observers. P waves on all derivations were measured on 12-lead surface ECGs. The onset of the P wave was defined as the point of first visible upward slope from baseline for positive waveforms and as the point of first downward slope from baseline for negative waveforms. The return to the baseline was considered as the end of the P wave. The Pmax measured in any of the 12 leads of the surface ECG was used as the longest atrial conduction time and Pmin as the shortest atrial conduction time. The difference between the Pmax and the Pmin was calculated and defined as PD (Figure 1).

All echocardiographic examinations were performed with a System Five (GE Vingmed Ultrasound, Horten, Norway) cardiac ultrasound scanner and 2.5-3.5 MHz transducers. All patients were examined in the left lateral and supine positions by precordial M-mode, two-dimensional echocardiography. One lead ECG was recorded continuously. Left ventricle end-diastolic, left ventricle end-systolic, and left atrial end-systolic diameters were measured from M mode in the parasternal long-axis views according to the standards of the American Society of Echocardiography. Ejection fractions were measured according to the Simpson method.

All statistical studies were carried out using an SPSS program (version 11.0, SPSS, Chicago, Illinois, USA). Data are presented as the mean ± SD. Statistical comparison of quantitative data concerning Pmax, Pmin, and PD were performed by the Wilcoxon test. The two-tailed unpaired Student t test was performed for reproducibility of P wave duration and PD. The parameters measured from the ECGs of group F and group L were compared with each other. We also compared the parameters of ECGs of 35 subjects in both phases. The association between PD with the day of the menstrual cycle the ECG was obtained and age was assessed using Pearson’s correlation test. A P level of < 0.05 was considered statistically significant.

**RESULTS**

Reproducibility was estimated by analyzing recordings on two separate occasions (intraobserver variability). The investigators were blinded when assessing interobserver variability. The intraobserver and interobserver coefficients of variation averaged 5%.

The demographic, clinical, and electrocardiographic findings are summarized in Table I. Serum sex hormone levels and electrolyte levels are summarized in Table II.

There were no differences in age, BMI, systolic blood pressures, or heart rate between the groups. Diastolic blood pressure was within the normal range in both groups, but was significantly higher in group F than in group L (Table I).

PD was significantly higher in group L than in group F (46.6 ± 18.5 versus 40.1 ± 12.7; P < 0.05). Pmin was significantly lower in group L than in group F (51.6 ± 12.1 versus 59.1 ± 12.1; P = 0.002) (Table I) (Figure 2).

When we compared the ECGs in the two phases in 35 patients, PD was significantly higher in the luteal phase than in the follicular phase (53.2 ± 12.3 versus 42.8 ± 10.2; P < 0.05). Pmin was significantly lower in the luteal phase than in the follicular phase (47.6 ± 6.6 versus 56 ± 10.1; P = 0.05) (Figure 3).

We detected a significant correlation between the day of the menses and PD (r = 0.27; P < 0.05). There was no correlation between age and PD. We could not find any significant correlation between estrogen, progesterone levels, and PD (r = -0.13, 0.21; P > 0.05).

No electrolyte imbalance was observed in the subjects in either the follicular or luteal phase. The levels of sodium, potassium, calcium, chloride, and magnesium were normal in both the follicular and luteal phases (Table II).

**Table I.** Characteristics and Electrocardiographic Findings of Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group F (n = 59)</th>
<th>Group L (n = 53)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.3 ± 7.7</td>
<td>28.1 ± 6.8</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.8 ± 9.8</td>
<td>23 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/minute)</td>
<td>75 ± 13</td>
<td>79 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>112 ± 17</td>
<td>105 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>72 ± 11</td>
<td>63 ± 8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Mean day of menses (days)</td>
<td>8 ± 3.1</td>
<td>22 ± 4.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pmax (msn)</td>
<td>98.4 ± 15.1</td>
<td>98.3 ± 17.5</td>
<td>NS</td>
</tr>
<tr>
<td>Pmin (msn)</td>
<td>59.1 ± 12.1</td>
<td>51.6 ± 12.1</td>
<td>0.002</td>
</tr>
<tr>
<td>PD (msn)</td>
<td>40.1 ± 12.7</td>
<td>46.6 ± 18.5</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

NS indicates not significant; PD, P wave dispersion; LA, left atrium; and EF, ejection fraction.

**Table II.** Left Atrial Diameter, Ejection Fraction, Serum Sex Hormone Levels and Electrolytes of the Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group F (n = 59)</th>
<th>Group L (n = 53)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA diameter (mm)</td>
<td>32.3 ± 3.6</td>
<td>30.1 ± 3.6</td>
<td>NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td>64.1 ± 2.2</td>
<td>62.8 ± 2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>138.6 ± 77.3</td>
<td>65.8 ± 16.7</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Progesterone (ng/mL)</td>
<td>1.05 ± 0.23</td>
<td>4.2 ± 2.5</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>140.6 ± 2.3</td>
<td>140.2 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.2 ± 0.4</td>
<td>4.3 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.5 ± 0.6</td>
<td>9.4 ± 0.53</td>
<td>NS</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>105.9 ± 2.8</td>
<td>107.1 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Magnesium (mg/dL)</td>
<td>2.1 ± 0.45</td>
<td>2.1 ± 0.27</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS indicates not significant; LA, left atrium; and EF, ejection fraction.
Increased P wave dispersion (PWD) is a noninvasive electrocardiographic marker for paroxysmal AF. AF is the most commonly observed arrhythmia in clinical practice and is associated with increased cardiovascular morbidity and mortality. PD has been shown to be influenced by autonomic nervous system activation, which induces changes in left atrial size and the velocity of impulse propagation. Prolongation of intra- and interatrial conduction times (marked by maximum P wave duration) and the inhomogeneous propagation of sinus impulses (marked by PWD) are electrophysiological characteristics of the atrium that is prone to AF.

It is well known that levels of estrogen, progesterone, and androgen vary during the female menstrual cycle. During menses, estrogen and progesterone are relatively low, and estrogen begins rising during the follicular phase, reaching its maximum level just before ovulation. Other hormones such as LH and androgens increase as well. During the luteal phase, estrogen decreases to a lower level and progesterone increases.

The balance between sympathetic and vagal effects is an important predictor for AF. Two studies have reported a sympathetic predominance several minutes before the initiation of AF in patients with no structural heart disease or paroxysmal atrial fibrillation. In a study by Nakagawa, et al. which investigated QT interval dynamics and heart rate variability during the menstrual cycle, plasma noradrenaline level was significantly higher in the luteal phase than in the follicular phase. On the other hand, measurements of heart rate variability, which are indices of vagal activity, were not significantly different between the two phases. In women, autonomic regulation of the heart fluctuates during the menstrual cycle and sympathetic activity is higher in the luteal phase than in the follicular phase. These results suggest that increased sympathetic activity during the luteal phase may result in a shorter QT interval compared to the follicular phase. Tupek, et al. reported that increased sympathetic activity caused a significant increase in PD in a study which investigated the effects of the Valsalva maneuver on P wave dispersion in patients with paroxysmal AF. We found PD was higher in luteal phase, which is a predictor of AF in women who have no structural disease. This effect may be related to increased sympathetic activity during luteal phase.

The increase in P wave duration is thought to be an accepted indicator of atrial conduction prolongation. The heterogeneity of electrophysiological and structural properties of the atrium may play a role in the genesis of unidirectional block of premature impulses. Also, intracellular and intercellular factors (regulatory proteins, ionic channels, etc.), and metabolic imbalance may lead to nonuniform anisotropic conduction of the atrial myocardium. Site-dependent inhomogeneous atrial conduction may result in increased variability of the P wave duration, and thus increase P wave dispersion. We know that electrolyte levels may change in different phases of the menstrual cycle and there are significant cyclic variations within physiological limits in all parameters. In a previous study, Dadlani, et al. found variations in sodium, potassium, and chloride that were found to be parallel with each other. They also concluded that their levels increase significantly from the follicular to the ovulatory phase and fall significantly during luteal phase. However, Gupta, et al. found increased calcium levels in the follicular phase and decreased calcium levels in the luteal phase. The changes in electrolyte levels between the menstrual cycle phases could be another reason for the increasing PD values in the luteal phase in our study. Although the electrolyte levels of the two groups were different in our study, the difference was not statistically significant. We are unable to explain the reason for this. Further detailed studies may provide more insight into this topic.

In an experimental study by Chen, et al. dogs pretreated with 17 beta estradiol were investigated for effective refractory periods (ERPs) after 800/minute atrial pacing. Atrial ERPs decreased after fast atrial pacing and this was more prominent in dogs pretreated by 17 beta estradiol and verapamil. They demonstrated that 17 beta-estradiol had a significant effect on atrial electrophysiology, which may decrease the occurrence of AF. We found a shorter PD in follicular phase compared to luteal phase. In our study, although there was an inverse relation between estrogen levels and PD, we found no statistically signifi-
cand correlation between estrogen and PD. High levels of estrogen in follicular phase might cause a decrease in the occurrence of AF.

**Study limitations:** Dilaveris, et al concluded that manual measurement of the P wave duration in standard 12-lead ECGs is feasible, more stable, and more reliable when performed on a high resolution screen of a digital EGG system than with more conventional methods involving paper printed EGGs. We measured P wave dispersion using paper printed ECGs.

We could not measure catecholamine levels (epinephrine and norepinephrine) in the study. It could be a more rational method to measure catecholamines for demonstrating the relation between sympathic activity and PD.

In conclusion, PD may vary in the two phases of the menstrual cycle. PD in the luteal phase seems higher than in the follicular phase, and this becomes more prominent as the menstrual cycle progresses. In the follicular phase, the decrease in AF risk may be dependent not only on an increase in sympathetic stimulation that resulted from high progesterone levels in luteal phase, but also on the protective effect of estrogen in follicular phase.

**References**