Concurrent Supplement of Estradiol and Progesterone Reduces the Cardiac Sensitivity to D,L-Sotalol-Induced Arrhythmias in Ovariectomized Rabbits

Jianhua Cheng, MD, PhD1, Dan Su, PhD1, Xiaohong Ma, MD2, and Hanyi Li, MD1

Abstract

Background: Although the difference in the modulation of estradiol and dihydrotestosterone on ventricular repolarization has been intensively studied, little information is available concerning the role of the different ovarian hormones in the modulation of repolarization in the female. Methods: The chronic modulation of female hormones, estradiol, and progesterone, on cardiac repolarization and the susceptibility to D,L-sotalol, a class III antiarrhythmic agent, were studied in female rabbits by ovariectomy and hormone replacement therapy (HRT) through recording and analyzing of electrocardiograms. Results: The corrected QT interval (QTc) measured 2 weeks after ovariectomy was not significantly different from that in the time-matched control rabbits. After 2 weeks of HRT, the QTc in the ovariectomized rabbits treated with estradiol alone (group E) was not significantly different from that in the control (group C); whereas in the ovariectomized rabbits treated with estradiol plus progesterone (group E + P), it was significantly shorter than those in groups E (P < .05) and C (P < .01), respectively. The corrected Tpeak-end interval (Tpec), an indicator of global dispersion of ventricular repolarization, was also significantly reduced in group E + P compared with that of group C (P < .01). In group E, D,L-sotalol-induced prolongation of QTc and the rate and the severity of arrhythmias were significantly higher, while the dose of sotalol to initiate arrhythmias was significantly lower than those in groups C or E + P, respectively (P < .05 or P < .01). Conclusion: Estradiol potentiates QTc prolonging effects of D,L-sotalol and increases the susceptibility to D,L-sotalol-induced arrhythmias without significantly altering QTc itself, whereas progesterone may accelerate the process of repolarization and protect the females from drug-induced arrhythmias, thus counteracting the effect of estradiol.

Keywords
Progesterone, estradiol, repolarization, menstruation, antiarrhythmic agents

Introduction

Accumulating evidence suggests that sex differences in ventricular repolarization exist in almost all species, ranging from human to mice, despite marked interspecies differences in the ionic currents underlying ventricular repolarization. Generally speaking, cardiac repolarization is prolonged and repolarization reserve is diminished in female animals and humans, compared to the male.1,2 The reduced repolarization reserve is demonstrated by a relatively greater increase in ventricular action potential duration (APD) or QT interval and a higher incidence of torsades de pointes (TdP) in the female in response to drugs that block repolarizing K+ currents.1,2 Many in vitro and in vivo experiments have suggested that the different modulation of cardiac ionic currents by estradiol and dihydrotestosterone (DHT) play a major role in the sex differences in repolarization.

Even though gender-specific differences in ventricular repolarization have gained wide recognition, little information is available concerning the role of the different ovarian hormones in the modulation of repolarization in the female. Several previously published clinical reports suggested a potential impact of estradiol and estradiol plus progesterone replacement therapies on ventricular repolarization in postmenopausal women. In healthy postmenopausal women, hormone replacement therapy (HRT) with estradiol alone usually produces a prolongation of QT interval, while estradiol plus progesterone does not significantly affect the QT interval.1,3-10 Furthermore, it is reported that the degree of QT prolongation in response to ibutilide, a class III antiarrhythmic agent, varies with the

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menstrual cycle phases: maximum increase in rate-corrected QT interval (QTc) after ibutilide is greater for women during menses and the ovulatory phase, compared with women during the luteal phase.11 These results suggest that estradiol and progesterone may have different modulating effects on cardiac repolarization which may give rise to a physiological variation in cardiac repolarization and a variable risk of drug-induced TdP in the female during the menstrual cycles. Thus, in the present study, the chronic modulation of female hormones on the repolarization and the susceptibility to class III antiarrhythmic agent was studied in rabbits by ovariectomy and HRT.

Methods

The experimental protocol was approved by the Ethical Committee for Biological and Medical Research in our university (the animal ethical approval document: No. 2009-093) and conforms to International Guiding Principles for Biomedical Research Involving Animals (CIOMS, 1985).

Ovariectomy of Rabbits and HRT

Female New Zealand white rabbits with body weights of 2.0 to 2.5 kg were anesthetized with 3% pentobarbital (30 mg/kg) and underwent ovariectomy under sterile techniques. Two weeks after the surgery, they were randomly divided into 3 groups: the control group (group C), the estradiol supplement group (group E), and the estradiol plus progesterone supplement group (group E + P), in order to mimic the ovarian hormonal states of the menses, follicular and luteal phases in women during the menstrual cycles.12 These 3 groups of animals were injected intramuscularly each day with vehicle, estradiol benzoate (100 μg/kg per d), or estradiol benzoate (100 μg/kg per d) plus progesterone (5 mg/kg per d), respectively, and the injections were continued for 2 weeks. A time-matched control group was also set up to evaluate the effect of ovariectomy on cardiac repolarization.

Recording and Analyzing of Rabbit Electrocardiogram

Limb-lead electrocardiograms (ECGs) were recorded with rabbits in anesthetized states. Electrocardiogram was recorded on paper at a speed of 50 mm/s using an ECG recorder (ECG-9130P, Nihon Kohden, Japan). The ECGs were coded and randomized to allow blinded measurement of QT interval and other parameters. All ECG recordings were analyzed manually using handheld caliper by a single observer who was unaware of the hormone state of the rabbits. The ECG recordings in which the end of the T wave could not be reliably determined were excluded from the analysis. Each measurement was given as the mean of 3 consecutive beats. The RR interval was measured as the time difference between the 2 consecutive R waves. The intervals from the onset of the QRS complex to the peak and the end of T wave were measured and indicated as QTp and QT, respectively. The Tpeak-end interval (Tpe), usually used as an indicator of the global dispersion of ventricular repolarization,13 was expressed as the difference between QT and QTp. The ECG parameters (QTp, QT, and Tpe) were corrected for heart rates using the formula described by other investigators14 (eg, QTc = QT − 0.704 × [RR − 250]) and were indicated as QTpc, QTc, and Tpec, respectively.

Influence of HRT on the Cardiac Sensitivity of Ovariectomized Rabbits to D.L-Sotalol

After 2 weeks of HRT, the rabbits were anesthetized with 3% sodium pentobarbital (30 mg/kg) and then intravenously infused with sotalol hydrochloride (d,L-sotalol), a class III antiarrhythmic agent, at a dose of 20 mg/kg and at a constant speed of 1 mg/kg per min through a microinfusion syringe pump (SP 200 Series; WPI, Sarasota, FL). The ECG during the infusion was constantly monitored and recorded. The ECG parameters (RR, QTp, QT and Tpe) at the end of the infusion were measured for analysis. The measured values were not rate corrected in this set of experiments, since no proper formula can be used due to the great difference in heart rates before and after the application of d,L-sotalol. Measurements were only taken when the animal was in sinus rhythm and when the end of the T wave could be reliably determined; therefore, there are some missing data owing to arrhythmia occurrence preventing accurate measurement. The d,L-sotalol-induced arrhythmias and the accumulative doses of d,L-sotalol initiating cardiac arrhythmias were also comparatively analyzed among the 3 groups with different HRT. The most severe ventricular arrhythmia in each animal that occurred during the 20-min infusion was identified and scored for analysis: 0 for no arrhythmia; 1 for single premature ventricular contraction (PVC); 2 for complex (including couplet, bigeminy, and trigeminy); and 3 for nonsustained ventricular tachyarrhythmia (NSVT).

Drugs

Estradiol benzoate injections, progesterone injections, and vehicle injections were purchased from Shanghai General Pharmaceutical Co., Inc (Shanghai, China). Sotalol hydrochloride injections were obtained from Yangtze River Pharmaceutical Group Co, Ltd (Taizhou, Jiangsu Province, China) and were diluted with normal saline to the desired volumes.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Analysis of variance (ANOVA) was used to calculate critical differences among multiple means, and Student t test was used for comparison between 2 means. Fisher exact test was used to analyze the incidence of sotalol-induced arrhythmias. A P value of less than .05 was considered statistically significant.
Table 1. Comparison of ECG Parameters in Rabbits 2 Weeks After Ovariectomy With Those of the Time-Matched Control Female Rabbits

<table>
<thead>
<tr>
<th></th>
<th>Control Rabbits</th>
<th>Ovariectomized Rabbits</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>202.5 ± 22.5</td>
<td>203.0 ± 16.1</td>
</tr>
<tr>
<td>QTp</td>
<td>94.8 ± 7.3</td>
<td>94.5 ± 8.7</td>
</tr>
<tr>
<td>QTpc</td>
<td>128.2 ± 20.9</td>
<td>127.7 ± 12.0</td>
</tr>
<tr>
<td>QT</td>
<td>128.3 ± 7.9</td>
<td>133.0 ± 9.9</td>
</tr>
<tr>
<td>QTc</td>
<td>161.7 ± 18.2</td>
<td>166.1 ± 14.1</td>
</tr>
<tr>
<td>Tpe</td>
<td>33.5 ± 6.9</td>
<td>38.4 ± 8.7b</td>
</tr>
<tr>
<td>Tpec</td>
<td>67.0 ± 13.5</td>
<td>71.5 ± 15.4</td>
</tr>
</tbody>
</table>

Abbreviations: ECG, electrocardiogram; RR, RR interval; QTp and QT, the intervals measured from the onset of QRS complex to the peak and the end of T wave, respectively; Tpe, T peak-end interval; SD, standard deviation.

The ECG parameters (QTp, QT, and Tpe) were analogously corrected for heart rates according to the formula: QTc = QT – 0.704 × [RR – 250] and expressed as QTpc, QTc, and Tpec, respectively. Data were expressed as mean ± SD. n = 12 and 45 in control rabbits and ovariectomized rabbits, respectively.

b P < .05 compared with the corresponding value in the control rabbits.

Results

Effects of Ovariectomy on ECG Parameters in Rabbits

To evaluate the possible influence of the variation of blood female hormones on cardiac repolarization, 45 female rabbits were ovariectomized, and their ECG parameters measured 2 weeks after the ovariectomy were compared with those of the time-matched control rabbits (Table 1). The parameters of ECG such as RR, QTp, QT, QTc, and Tpe intervals in ovariectomized rabbits were not significantly different from those in the control rabbits (n = 45 and 12, respectively). The value of Tpe in the ovariectomized rabbits was large than that of the control rabbits but the significance of difference disappeared after correction with heart rate.

Effects of HRT on ECG Parameters in Ovariectomized Rabbits

Two weeks after ovariectomy, the rabbits were randomly assigned to 3 groups receiving 2 weeks of treatment with vehicle, estradiol, and estradiol plus progesterone, respectively (n = 15 in each group). The comparison of the ECG parameters of the 3 groups was illustrated in Table 2. Most measured and rate-corrected ECG parameters for repolarization (QTp, QT, QTc, Tpe, and Tpec) in group E were not statistically different from those in group C, except that a significantly longer QTpc was observed in group E (P < .05). However, QT, QTc, Tpe, and Tpec in group E + P were significantly shortened when compared with those in group C (P < .05 or P < .01), and QTp, QTpc, and QTc were also significantly decreased in comparison with those of group E (P < .05). The RR intervals were not statistically different among the 3 groups.

Modulation of HRT on the Cardiac Susceptibility of Ovariectomized Rabbits to D,L-Sotalol

To investigate whether different HRTs can modulate the cardiac susceptibility of ovariectomized rabbits to D,L-sotalol, the rabbits were intravenously infused with D,L-sotalol after 2 weeks of HRT. The changes in ECG parameters induced by D,L-sotalol in ovariectomized rabbits with different HRTs were shown in Table 3. D,L-Sotalol significantly prolonged QTp and QT in 3 groups (P < .01, n = 7, 8, and 9 in groups C, E, and E + P, respectively) and also significantly increased Tpe in group E (P < .01) and group E + P (P < .05). RR intervals were also significantly lengthened in the 3 groups due to the β-blocking effects of D,L-sotalol (P < .05).

Table 2. Comparison of the ECG Parameters in Ovariectomized Rabbits After 2 Weeks of Hormone Replacement Therapies

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>E</th>
<th>E + P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>224.5 ± 16.3</td>
<td>217.2 ± 17.5</td>
<td>228.4 ± 31.0</td>
</tr>
<tr>
<td>QTp</td>
<td>99.9 ± 10.4</td>
<td>103.6 ± 10.2</td>
<td>95.7 ± 9.0d</td>
</tr>
<tr>
<td>QTpc</td>
<td>117.9 ± 11.6</td>
<td>126.7 ± 13.8b</td>
<td>110.9 ± 21.1c</td>
</tr>
<tr>
<td>QT</td>
<td>152.5 ± 19.5</td>
<td>149.1 ± 19.1</td>
<td>137.5 ± 14.1c</td>
</tr>
<tr>
<td>QTc</td>
<td>170.4 ± 15.5</td>
<td>172.2 ± 24.3</td>
<td>152.7 ± 15.7d</td>
</tr>
<tr>
<td>Tpe</td>
<td>52.5 ± 21.1</td>
<td>45.5 ± 17.9</td>
<td>41.8 ± 9.6b</td>
</tr>
<tr>
<td>Tpec</td>
<td>70.5 ± 20.1</td>
<td>68.6 ± 24.7</td>
<td>57.0 ± 15.9b</td>
</tr>
</tbody>
</table>

Abbreviations: ECG, electrocardiogram; RR, RR interval; QTp and QT, the intervals measured from the onset of QRS complex to the peak and the end of T wave, respectively; Tpe, T peak-end interval; SD, standard deviation.

C, E, and E + P indicate the groups treated with vehicle, estradiol, and estradiol plus progesterone, respectively. The ECG parameters (QTp, QT, and Tpe) were analogously corrected for heart rates according to the formula: QTc = QT – 0.704 × [RR – 250] and expressed as QTpc, QTc, and Tpec, respectively. Data were expressed as mean ± SD. n = 15 in each group.

b P < .05 and c P < .01 compared with the corresponding value in group C, respectively.

Table 3. Changes in ECG Parameters Induced by D,L-Sotalol in Ovariectomized Rabbits After 2 Weeks of Hormone Replacement Therapies

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>E</th>
<th>E + P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>218.4 ± 15.4</td>
<td>215.8 ± 15.3</td>
<td>224.9 ± 26.7</td>
</tr>
<tr>
<td>RR-s</td>
<td>341.0 ± 26.9c</td>
<td>348.7 ± 31.7c</td>
<td>363.1 ± 45.0c</td>
</tr>
<tr>
<td>QTp</td>
<td>93.8 ± 5.5</td>
<td>100.6 ± 9.1</td>
<td>93.2 ± 11.5</td>
</tr>
<tr>
<td>QTp-s</td>
<td>116.5 ± 7.2c</td>
<td>129.3 ± 9.2d</td>
<td>120.0 ± 13.8c</td>
</tr>
<tr>
<td>QT</td>
<td>145.1 ± 13.2</td>
<td>145.7 ± 19.8</td>
<td>132.1 ± 8.9d</td>
</tr>
<tr>
<td>QTc</td>
<td>176.6 ± 7.8c</td>
<td>191.5 ± 16.6d</td>
<td>169.7 ± 13.2#</td>
</tr>
<tr>
<td>Tpe</td>
<td>51.3 ± 16.1</td>
<td>45.1 ± 17.2</td>
<td>38.9 ± 8.8</td>
</tr>
<tr>
<td>Tpe-s</td>
<td>60.1 ± 7.6</td>
<td>62.2 ± 11.9d</td>
<td>49.7 ± 9.7d</td>
</tr>
</tbody>
</table>

Abbreviations: ECG, electrocardiogram; RR, RR interval; QTp and QT, the intervals measured from the onset of QRS complex to the peak and the end of T wave, respectively; Tpe, T peak-end interval; SD, standard deviation.

C, E, and E + P indicate the group of rabbits pretreated with vehicle, estradiol, and estradiol plus progesterone, respectively. The dose of D,L-sotalol was 20 mg/kg and was intravenously infused at a constant speed of 1 mg/kg per min. RR-s, QTp-s, QT-s, and Tpe-s indicate the corresponding values of RR, QTp, QT, and Tpe in the presence of D,L-sotalol. Data were expressed as mean ± SD. n equals 7 (C), 8 (E), and 9 (E + P), respectively.

b P < .05 and d P < .01 compared with the corresponding value before the application of D,L-sotalol in each group, respectively.

d P < .05 compared with the corresponding value in group C, respectively.

# P < .05 compared with the corresponding values in group E, respectively.
Table 4. Arrhythmias Induced by D,L-Sotalol and the Accumulative Dose of D,L-Sotalol for the Initiation of Arrhythmias in the Ovariectomized Rabbits With Different Hormone Replacement Therapies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Arrhythmia Incidence</th>
<th>PVC</th>
<th>Complex</th>
<th>NSVT</th>
<th>Average Arrhythmia Score</th>
<th>Arrhythmic Dose of Sotalol, mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>13%</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0.3 ± 0.7</td>
<td>5.6 ± 0.1</td>
</tr>
<tr>
<td>E</td>
<td>47%b</td>
<td>1</td>
<td>8</td>
<td>6</td>
<td>1.0 ± 1.2b</td>
<td>2.7 ± 1.2c</td>
</tr>
<tr>
<td>E + P</td>
<td>13%d</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0.3 ± 0.7d</td>
<td>10.5 ± 0.7e</td>
</tr>
</tbody>
</table>

Abbreviations: PVC, premature ventricular contraction; NSVT, nonsustained ventricular tachyarrhythmia; SD, standard deviation.

* C, E, and E + P indicate the groups pretreated with vehicle, estradiol, or estradiol plus progesterone, respectively. The dose of D,L-sotalol was 20 mg/kg and was intravenously infused at a constant speed of 1 mg/kg per min. The most severe ventricular arrhythmia in each animal occurred during the 20-minute infusion was identified and scored for analysis: 0 for no arrhythmia; 1 for PVC; 2 for complex (including couplet, bigeminy and trigeminy); 3 for NSVT. Data for the arrhythmic dose of D,L-sotalol and the average arrhythmia score were expressed as mean ± SD. n = 15 in each group.

b P < .05 and c P < .01 compared with the corresponding value in group C, respectively.

d P < .05 and e P < .01 compared with the corresponding values in group E, respectively.

The difference in the ECG parameters among the 3 groups was also enlarged by D,L-sotalol. Before the intravenous infusion of D,L-sotalol, only the difference in QT was significant between group E + P and group C. Whereas after the application of D,L-sotalol, QTp and QT in group E were significantly longer than those in group C (P < .05), and QT and Tpe in group E + P were significantly shorter than those in group E (P < .05).

The D,L-sotalol-induced arrhythmias during the infusion and the accumulative dose of D,L-sotalol for the initiation of arrhythmias are summarized in Table 4. Both the incidence of arrhythmias and the arrhythmia score (an indicator of the severity of ventricular arrhythmias) in group E were significantly increased compared with those in group C, whereas those in group E + P were significantly reduced in comparison with group E (P < .05, n = 15 in each group). No significant difference was observed in arrhythmic incidences and arrhythmia scores between groups E + P and C. A piece of ECG recording of sotalol-induced ventricular tachycardia in group E is illustrated in Figure 1. Moreover, the accumulative dose of D,L-sotalol to initiate arrhythmias in group E was significantly lower than that in group E + P or C (P < .01; Table 1), suggesting a higher sensitivity of estradiol-pretreated rabbits to D,L-sotalol-induced proarrhythmic effects. In group E, it is about 49% of that in group C; whereas in group E + P, it increased to 188% and 385% of those in groups C and E, respectively.

Discussion

In the present study, to evaluate the possible influence of ovarian hormones on cardiac repolarization during the different phases of the menstrual cycle, the effect of ovarian hormone deficiency as well as HRT with estradiol alone or with estradiol plus progesterone on ventricular repolarization was investigated in ovariectomized rabbits. It was found that the ECG parameters including RR, QTc, QTc, and Tpe in ovariectomized rabbits were not significantly different from those in the time-matched control rabbits. In the literature, the influence of ovariectomy on the ECG parameters of rabbits was rarely reported. Since the female rabbit is an induced ovulator, it has low circulating level of estradiol that is little affected by ovariectomy; thus, our observation that ovariectomy did not influence the ECG parameters is reasonable. After 2 weeks of HRT, estradiol alone had no significant influence on ECG parameters such as QTc and Tpe, except that it significantly increased QTc. However, when progesterone was included in the HRT, QTc and QTc were shortened, and Tpe, a
measurement that reflects the global dispersion of ventricular repolarization, was reduced. Those results suggested that progesterone may accelerate the process of ventricular repolarization and may play an important role in homogenizing the global heterogeneity of ventricular repolarization, whereas estradiol’s modulation of cardiac repolarization is minimal in this model.

Gonadectomy and HRT are the common methods employed in the study of the mechanisms underlying the gender differences in cardiac repolarization. Until now, most of these studies were conducted in ovariectomized or orchiectomized animals supplemented with either estradiol or DHT. It is found that DHT attenuated the QT interval compared with the placebo-treated controls in orchiectomized male rabbits. In ovariectomized rabbits, the ECG parameters did not differ among the placebo-, estradiol-, or DHT-treated group. Regarding the modulation of estradiol or DHT on the cardiac sensitivity to the repolarization-prolonging agents, it is found that both DHT-treated ovariectomized and orchiectomized rabbits displayed less QT prolongation in response to quinidine challenge compared with placebo controls. On the other hand, estradiol enhanced the sensitivity of the cardiac preparations isolated from the ovariectomized rabbits to class III antiarrhythmic drugs. Hara et al reported that in papillary muscles from ovariectomized rabbits, E-4031-induced prolongation of APD90 and the incidence of early afterdepolarization (EAD) were significantly greater in the estradiol-treated than the DHT- and placebo-treated groups. Different from the aforementioned studies, our study compared the HRT with estradiol alone or with estradiol plus progesterone on the modulation of the cardiac sensitivity to D,L-sotalol in ovariectomized rabbits. It has been found in our study that estradiol potentiated the QT prolongation and proarrhythmic effects of D,L-sotalol, as is indicated by longer QT interval, higher incidence as well as severity of ventricular arrhythmias, and lower accumulative dose of D,L-sotalol to initiate arrhythmias; and this result was consistent with the earlier studies aforementioned. Similarly, acute application of estradiol also increased the incidence of TdP, induced by clociflurin, in z1-adrenoceptor-stimulated, pentobarbital anesthesia-anesthetized rabbits of both sexes. These results strongly suggest that estradiol may predispose the female to a greater sensitivity to drug-induced QT prolongation and arrhythmias.

It is important to note that although the chronic treatment of estradiol potentiated the drug-induced QT prolongation associated with proarrhythmic effects, estradiol itself has little influence on baseline QT interval in the present study. This phenomenon was also observed in several previous studies aforementioned. Thus, it may be the nature of the process underlying repolarization (ie, repolarization reserve) rather than the baseline duration of ventricular repolarization itself that determines the hormone state-related differences in drug-induced effects. The ionic basis of repolarization reserve is supposed to be IKs and other outward potassium currents (ie, IK1 and IKA) contributing to ventricular repolarization. The chronic treatment with estradiol may mainly reduce the repolarization reserve and thus increase the susceptibility of female rabbits to D,L-sotalol-induced effects on cardiac repolarization.

Although it is well known that estradiol or the female gender may exacerbate the cardiac sensitivities to K+ channel-blocking agents in animal models, little information is available for progesterone. In the present study it has been revealed that in HRT with both progesterone and estradiol, the resulting shortening of QT interval and the decreased global dispersion of ventricular repolarization by progesterone may account for the lower sensitivity of the female rabbits to drug-induced repolarization prolongation and arrhythmias, thus counteracting the effect of estradiol. Since there is a physiological change in circulating levels of both estradiol and progesterone in women, with a high level of progesterone during the luteal phase, these findings may suggest a protective effect of progesterone against the drug-induced arrhythmias in women. Thus, our observation with progesterone on the risk of D,L-sotalol-induced effects may well explain the findings by Rodriguez et al obtained from study on humans: maximum increase in QTc after ibutilide was smaller for women during the luteal phase than menses and the ovulatory phase. Recently, it is reported that progesterone may enhance IKs in guinea pig ventricular myocytes. Thus, the observed protection against drug-induced arrhythmias by progesterone in our study may partially be attributed to an increase in repolarization reserve by IKs enhancement. Besides, progesterone has also been shown to significantly inhibit the incidences of ventricular tachycardia in female rats with myocardial ischemia/reperfusion injury; other possible mechanisms for the cardioprotective effect of progesterone cannot be excluded.

It is worth mentioning that in most in vivo and in vitro studies evaluating the drug sensitivities in rabbits, TdP is the most common form of arrhythmias induced by repolarization-prolonging drugs. However, the typical tachyarrhythmias induced by D,L-sotalol observed in our study is not necessarily TdP. One of the big difference between ours and the literature is that in their studies TdP was induced either in rabbits challenged with the z1-adrenoceptor agonist methoxamine or in Langendorff-rabbit hearts perfused with 50% reduced concentrations of Mg2+ and K+ in Tyrode’s solution through abrupt change in cycle length. Thus, under relatively physiological experimental conditions, TdP is not necessarily induced by class III antiarrhythmic drugs in rabbits, or there might be other mechanisms behind the induced arrhythmia than QT/QTc prolongation.

In summary, our study provided strong evidence for a different role of estradiol and progesterone in modulating ventricular repolarization and the cardiac susceptibility of the female rabbits to class III antiarrhythmic drugs. Estradiol can increase the susceptibility of female rabbits to D,L-sotalol-induced repolarization prolongation and the proarrhythmic effects, probably through a reduction in the repolarization reserve; whereas progesterone may counteract the effect of estradiol and prevent the excessive QT prolongation produced by D,L-sotalol through an increase in the repolarization reserve, thus protecting the females from drug-induced arrhythmias. Additional insight into the molecular and electrophysiological basis for the hormone-specific differences has to be gained from more detailed studies of animal models. Until now, there is comparatively
little information regarding the influence of the female sex hormones on drug-induced arrhythmias in women at different stages of the menstrual cycle. Several previous studies on female patients with congenital long QT syndrome showed that the arrhythmic events frequently occurred during the perimenstrual and the postpartum periods, when the blood progesterone was at very low levels.27-29 The clinical implications of our findings need to be further investigated. New knowledge on this topic may aid our understanding of the gender-related difference in cardiac repolarization and optimize the use of not only the cardiac drugs but also a range of noncardiac drugs with unwanted QT-prolonging effect.

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