Influence of endogenous oestrogens on QT interval duration

Jean-Sébastien Hulot, Jean-Louis Démolis, Rachel Rivière, Soraya Strabach, Sophie Christin-Maitre, Christian Funck-Brentano

Division of Clinical Pharmacology and Clinical Investigation Center, Saint-Antoine University Hospital, Paris, France
Department of Endocrinology, Saint-Antoine University Hospital, Paris, France

Aims

Women have a longer QT interval and a greater incidence of torsades de pointes than men. It has been suggested that oestrogens may influence the duration of cardiac repolarization. We thus investigated the influence of oestradiol (E2) on ventricular repolarization within the physiological concentration range of this hormone.

Methods and results

We studied QT interval duration in 21 healthy women aged 18 to 35 years with regular menstrual cycle (mean duration: 29±1 days) during two periods associated with a wide range of oestradiol plasma levels: low level during menses (105±34 pmol/l) and high level during the pre-ovulatory phase (750±277 pmol/l). We used heart rate-independent assessment of QT. QT–RR pairs were measured over a wide range of RR intervals obtained at rest and during a sub-maximal exercise test. Using a monoexponential nonlinear curve fitting for the QT–RR relation, the QT1000 ms during nadir and peak oestradiol periods was then determined for each subject. QT1000 ms interval was not different between both study periods: 382.1±18.4 ms at peak versus 382.2±19.4 ms at nadir oestradiol level (P=0.98).

Conclusion

No significant change in QT interval duration was observed within the large range of physiological E2 variations found during the menstrual cycle.

Introduction

Female gender is a known predisposing factor for 'torsades de pointes', a potentially lethal ventricular arrhythmia. The occurrence of this arrhythmia is increased by several factors such as the degree of QT interval prolongation. Thus, most drugs that prolong the QT interval duration (including antiarrhythmics but also others such as erythromycin, sparfloxacin, moxifloxacin) have been associated with a higher risk of torsades de pointes. However, the incidence in women is over-represented and drug-induced QT prolongation could be greater in women than in men at equivalent plasma concentrations of a drug.

The mechanisms responsible for this predisposition are unclear but may be related to gender-differences in baseline cardiac repolarization. In 1920, Bazett reported that baseline rate corrected QT interval was 15 to 20 ms longer in women than in men. More recently, it has been suggested that such difference was influenced by age in women, beginning at puberty and lasting until about age 50.

This finding suggests a potential role for sex hormones on the mechanisms involved in the duration of cardiac repolarization. Experimental data in animals show that oestradiol could decrease the expression of potassium rectifier channels which regulate the repolarization phase of the cardiac action potential reflected by the QT interval. Similarly, oestradiol could influence the QT response to drugs. Lastly, menstrual cycle
differences in QT responses to drug have been recently found in women.7

During the menstrual cycle oestradiol (E2) increases during the follicular phase and progesterone rises during the luteal phase. There is thus a physiological important change in circulating levels of oestrogens but also progesterone. These changes could possibly influence the baseline cardiac repolarization and thus momentarily predispose to greater drug-induced QT prolongation. However, the precise nature of hormone-dependent electrophysiologic effect, if any, remains to be determined in women for several reasons. Firstly, special methods to assess QT interval changes independently from heart rate changes are required. Indeed, the usual Bazett or Fridericia correction methods, which can be used when assessing the pronounced effect of a drug or a disease on QT interval duration, are not precise enough when investigating a small expected physiological effect as anticipated here.13 Secondly, no study selectively investigated the effect of dynamic changes in circulating levels of endogenous oestrogens on QT interval duration without fluctuation of circulating progesterone level.

Therefore, the purpose of this study was to examine the rate-independent changes of QT interval duration in healthy young women during the most extreme physiological variations of oestradiol level observed during two separate periods of the same menstrual cycle.

Methods

We studied 21 healthy women aged 18 to 35 years and with a body mass index between 18 and 28 kg/m^2 who were not taking any medication. All volunteers had had regular menstrual cycles (26 to 32 days) during the last 3 months, were neither pregnant nor taking hormonal contraceptives for at least 3 months. They were all evaluated on six separate periods of the same menstrual cycle: the evaluation was performed within 24 to 60 h after the onset of menses phase visit. For a given subject, all evaluations were made at the same clock time, in the same quiet room and under the same experimental conditions.

On each study day, several electrocardiographic recordings were obtained after a 10-min rest in the supine position in a quiet room and then with the participant in the sitting position and standing position. Additional recordings were obtained during the course of a submaximal exercise test performed on a bicycle ergometer (Siemens, Model EM840, Paris, France). The exercise test involved successive working loads of 3 min each, which increased by 30 W until a heart rate of 150 beats min⁻¹ was reached.

Electrocardiographic tracings were recorded every 30 s during the test. All recordings were made simultaneously in 12 leads at a paper speed of 50 mm s⁻¹ (amplitude, 1 mV=2 cm) with the use of a Case 15 recorder (Marquette Electronics, Inc, Milwaukee, Wis). The tracings were recorded as ‘median-linked complexes’ in order to obtain the best possible tracing quality, especially during exercise. All electrocardiographic recordings were read by the same investigator who was blinded to the results of oestradiol levels. The QT intervals were measured manually with a digitizing pad (SummaSketch II Professional MM II 1812, Summagraphics, Seymour, Conn) connected to a PC computer. The QT interval was measured in each subject in the anterior electrocardiographic lead where the T wave had the largest amplitude (anterior precordial). The position of the lead was marked on the skin with a pencil. The QT interval was measured from the onset of the QRS complex to the end of the T wave, which was defined according to the criteria of Lepeschkin and Surawicz.14

For each subject and each exercise test, a set of RR cardiac cycle length-QT interval pairs was obtained from all electrocardiographic recordings. For each subject and each study period, the QT versus RR relationship was analysed and the parameters of the monoeponential formula:

\[ QT = a - b \cdot \exp(-c \cdot RR) \]

where QT and RR are the observed data, a, b and c the regression parameters, were fitted to the data as described previously.15 These three regression parameters were then used to calculate the QT interval of each subjects during each study period corresponding to predetermined RR interval of 1000 ms (i.e. 60 beats min⁻¹), 900, 800, 700, 600, 500 and 400 ms. In this process, no extrapolation was done (i.e. all subjects had at least one QT/RR pair measured at a heart rate of 60 bpm).

Laboratory assays

For each participant, all oestradiol concentrations were performed at the end of the study using the same dosage kit. Oestradiol assays were all performed in duplicate at the department of biochemistry of Saint-Antoine University Hospital, Paris, France using a radioimmunoassay method (Schering, Cis Bio International). The inter-day coefficient of variability reaches 6.5% for an E2 concentration of 160 pmol/l. Kalemia, LH and progesterone concentrations were also measured for each evaluation. LH and progesterone concentrations were performed in the same department using a radioimmunoassay method (Vidas, bioMerieux, France). These assays are regularly validated by a national quality control system.
Statistical analysis

Sample size (21 subjects) was calculated to allow detection of a mean difference of 15 ms in the duration of QT 1000 ms interval between the peak and nadir oestradiol phases with (two-sided) of 0.05 and a power of 0.90. The SD of this difference was estimated from previous studies of our group to be 20 ms.

Because of the paired nature of the data, we used a paired t-test to assess a significant difference in mean QT 1000 ms interval duration between the peak and nadir oestradiol phases.

The relationship between QT 1000 and oestradiol concentrations was assessed using a mixed model analysis of repeated measures with an unstructured covariance modeling (PROC MIXED procedure of SAS software 8.1, SAS Institute Inc, Cary, NC, USA).

Results

Population characteristics

Main subjects characteristics are reported in Table 1. The mean menstrual cycle duration before inclusion was 29±1 days with a range of 27 to 31 days. Sex hormone levels fluctuated as expected during physiological menstrual cycles. Mean E2 plasma level was seven-fold higher at the peak period compared to the nadir period: 750±277 pmol/l during the pre-ovulatory phase versus 105±34 pmol/l at the beginning of the cycle (during menses) (P<0.0001). LH concentrations showed a slight increase at the peak E2 period compared to the nadir E2 period. However, LH concentrations did not reach the levels usually observed at ovulation and were consistent with an evaluation during the pre-ovulatory period (E2 peak period). As expected, mean progesterone levels were not different between both study periods. Similarly, the mean kalemia was not different between periods.

Table 1: Subjects characteristics and hormone levels in 21 women

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24±5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.7±7.6</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.0±2.6</td>
</tr>
<tr>
<td>Duration of menstrual cycle (days)</td>
<td>29±1</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>118±7</td>
</tr>
<tr>
<td>Diastolic</td>
<td>59±9</td>
</tr>
<tr>
<td>Oestradiol (pmol/l)</td>
<td></td>
</tr>
<tr>
<td>Nadir period</td>
<td>105±34</td>
</tr>
<tr>
<td>Peak period</td>
<td>750±277 a</td>
</tr>
<tr>
<td>LH (UI/l)</td>
<td></td>
</tr>
<tr>
<td>At oestradiol nadir period</td>
<td>3.0±0.9</td>
</tr>
<tr>
<td>At oestradiol peak period</td>
<td>13.7±12.2 a</td>
</tr>
<tr>
<td>Progesterone (nmol/l)</td>
<td></td>
</tr>
<tr>
<td>At oestradiol nadir period</td>
<td>3.2±4.1</td>
</tr>
<tr>
<td>At oestradiol peak period</td>
<td>2.9±2.0</td>
</tr>
<tr>
<td>Kalemia (mmol/l)</td>
<td></td>
</tr>
<tr>
<td>At oestradiol nadir period</td>
<td>3.8±0.2</td>
</tr>
<tr>
<td>At oestradiol peak period</td>
<td>3.8±0.3</td>
</tr>
</tbody>
</table>

*aP<0.0001 vs oestradiol nadir period.

Fig. 1 QT1000 ms evolution during the oestradiol nadir and the oestradiol peak periods.

Discussion

This study was conducted in order to detect a role of endogenous oestrogens on the duration of ventricular repolarization under physiological conditions and test the hypothesis that endogenous oestrogens explain the 15 ms to 20 ms difference in QT interval duration found between men and women.9,16 In spite of large oestradiol levels changes, of a sensitive rate-independent method of QT interval assessment and an adequately powered
study, no significant modifications of the QT1000 ms duration could be found. This result does not support a clinical influence of oestrogens on the duration of cardiac repolarization and on the gender differences in QT interval duration.

Oestradiol was suspected to decrease the expression of potassium rectifier channels\textsuperscript{10,11} therefore slowing the repolarization phase of the cardiac action potential and prolonging the QT interval. Despite these experimental data, a clinical electrophysiologic effect of oestradiol has never been established. In agreement with our results, Burke et al.\textsuperscript{17} and Rodriguez et al.\textsuperscript{7} found no difference in QTc interval duration in women evaluated at three different phases of the menstrual cycle (menses, end of the follicular phase and luteal phase). However both studies did not allow definite conclusions on the influence of oestradiol on cardiac repolarization to be drawn. Indeed, in the two studies the end of the follicular phase (where the oestradiol levels are the highest) was determined using a urinary ovulation predictor test detecting the LH peak which follows the oestradiol peak by 24 h.\textsuperscript{18} This method hardly identifies the hormonal phases.
Subsequent exclusion of volunteers from analysis was reported in the work of Burke et al.17 In the study of Rodríguez et al.,7 a concomitant increase of progesterone with oestradiol was observed at the end of the follicular phase. Since it has been suggested that progesterone could have a protective effect on drug-induced QT prolongation,7 it is important to assess QT interval duration in the absence of progesterone level changes. In our protocol, we studied volunteers on six consecutive days bracketing the expected date of ovulation in order to catch the maximal oestradiol level without progesterone level changes. We were able to avoid mixed hormonal effect on the duration of cardiac repolarization. Under these stringent experimental conditions, we found no influence of oestradiol on cardiac repolarization.

During our study, we investigated a wider range of oestradiol concentrations (from a minimal level of 53 pmol/l during menses to a maximal level of 1131 pmol/l at peak) as compared to others.7,10,17 Because of this large magnitude, our study invalidates the hypothesis that oestradiol explains the physiological gender differences in the duration of cardiac repolarization. Indeed, following the peripheral conversion of male hormones (testosterone and androstenedione), there is a slight secretion of oestradiol in men aged more than 17 years leading to a mean E2 level between 37–184 pmol/l.18 In women, in agreement with our results, minimal oestradiol levels are usually reported during menses in a slightly superior range of 74–370 pmol/l.18

In animal experiments, Drici et al.19 demonstrated the effect of oestrogens on cardiac repolarization using a high oestradiol concentration of 302±58 pg/ml (1117±214 pmol/l) in ovariec-tomized rabbits. This corresponds to the highest level we recorded in a few women during the pre-ovulatory period and to the upper range of expected levels during this period (367–1285 pmol/l).18 Consequently, we cannot exclude that oestradiol may have an effect on cardiac repolarization at very high concentrations. However, this situation is rare under physiological conditions, except during pregnancy, or even during hormonal treatment. Larsen et al.19 reported the lack of effect of equine oestrogen replacement therapy on the QTc interval in post-menopausal women. In a large observational study including 34 944 post-menopausal women, Kadish et al. (unpublished data, American Heart Association scientific sessions 2002) reported a statistically significant but small (1.8 ms) prolongation of QTc interval in women taking equine oestrogen alone as compared to women who were not taking hormone replacement therapy. This effect is thus inadequate to explain gender differences in cardiac repolarization and disappeared in women taking combined oestrogen and progesterin replacement therapy, suggesting a protective role for progesterone.

Rodríguez et al. reported differences in QT interval responses to drugs during menstrual cycle.7 Greater sensitivity to the potassium channel blockers ibutilide were observed during the first half of the menstrual cycle when oestradiol levels are high and progesterone levels are low. That oestrogens predispose to a greater sensitivity to drug-induced QT prolongation without changes of baseline QT interval duration cannot be excluded. This requires further investigation. We also cannot exclude that oestrogens may favor QT interval prolongation in genetically predisposed women with long-QT syndrome.

In conclusion, no significant changes in repolarization, as judged by QT interval duration, was observed within the large range of physiological oestradiol variations found during the menstrual cycle.

Acknowledgements

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References