Original Article

Effect of ovulation induction on QT dispersion in electrocardiography

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Aim: To investigate whether ovulation induction resulting in supra-physiological concentration range of ovarian hormones has an effect on interlead ventricular depolarization heterogeneity via QT dispersion measurements. Estrogens influence the duration of cardiac repolarization but there is no significant change in the QT interval duration within the range of physiological estradiol variations.

Materials and methods: Included in the study were 40 subjects, in whom ovulation induction was planned, and 20 volunteers. During the study, a 12-lead electrocardiogram of each woman was carried out 3 times: for the first time on day 2-3 of the menstrual cycle (menstrual day), for the second time 36 h after hCG administration (ovulatory day), and for the third time at 6-8 days following ovulation (mid-luteal day). The RR and QT wave distances were measured. The QT interval corrected for heart rate (corrected QT) was calculated for each derivation. The difference between the longest and shortest corrected QT intervals was determined as corrected QT dispersion.

Results: No difference was seen in the mean QT and corrected QT interval duration and the maximum corrected QT interval duration between menstrual phases. On the ovulatory day at peak estrogen level, the corrected QT dispersion was found to be lower than on mid-luteal and menstrual day.

Conclusion: QT dispersion demonstrates the regional repolarization heterogeneity of the myocardium, which reflects the propensity of ventricular arrhythmia decreases on the ovulatory day of the ovulation induction cycle.

Key words: Estrogen, ventricular repolarization, ventricular arrhythmia, ovulation induction

Ovulasyon indüksiyonunun elektrokardiyografide QT dispersiyonu üzerine etkisi

Amaç: Overyan hormonların suprafizyolojik düzeylerde olduğu ovulasyon induksiyon tedavilerinin QTdispersiyon ölçümü yoluyla ventrikül repolarizasyon heterojenitesi üzerine etkilerini araştırdık. Estrojenler kardiyak repolarizasyon üzerine etki ederler, fakat fizyolojik estradiol değişikliklerinde QT interval süresinde önemli bir değişiklik görülmemiştir.

Yöntem ve gereç: Ovulasyon indüksiyonu planlanan kırk infertil hasta ve 20 sağlıklı gönüllü çalışmaya alındı. Çalışma süresince kadınların 12 derivasyonlu elektrokardiyografi kayıtları 3 kez alındı; ilk olarak, menstrual siklusun 2-3ncü günü (menstrual gün); ikinci kez hCG uygulamasından 36 saat sonra (ovulasyon günü); üçüncü kez ovulasyonu takiben 6-8nci günde (midluteal gün) RR ve QT dalga mesafeleri ölçüldü. Kalp hızına göre düzeltilen QT intervali her derivasyon için hesaplandı. En uzun ve en kısa düzeltilmiş QT intervalleri arasındaki fark düzeltilmiş QT dispersiyonu olarak belirlendi.

Bulgular: Ortalama QT, ortalama düzeltilmiş QT interval süreleri ve maksimum düzeltilmiş QT interval sürelerinde menstrual siklusun fazları arasında fark yoktu. En yüksek estradiol düzeyinin olduğu ovulasyon gününde düzeltilmiş QT dispersiyonu midluteal ve menstrual günden daha düşük bulundu.

Sonuç: Myokardın bölgesel repolarizasyon heterojenitesini gösteren ve ventriküler aritmiye eğilimi yansıtan QT dispersiyonu ovulasyon indüksiyon siklusunun ovulasyon gününde azalmaktadır.

Anahtar sözcükler: Estrojen, ventriküler repolarizasyon, ventriküler aritmi, ovulasyon indüksiyonu

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Introduction

In infertility treatment, ovulation induction has been used for half a century. In treatment, numerous follicles are developed in the ovaries in order to increase the prospect of conception; hence, an exaggerated cycle is formed. As a consequence of multifollicular development, exposure to estrogen and other ovarian hormones occurs at high doses, albeit for a short time. During these treatments, follicular development and intra-cycle hormonal alterations may be followed closely.

Sex hormones are known to exert direct and indirect effects on cardiovascular function (1). Sex hormones also play a critical role in regulating cardiac repolarization. The female sex is considered to be a risk factor for ventricular arrhythmias. Furthermore, experimental studies have shown that estrogen has an impact on the electrophysiological properties of the heart. The female sex has been associated with a slower rate of cardiac repolarization, i.e. a longer ECG QT interval (2). It has been suggested that the resection of ovaries shortens the QT interval, while estradiol and dihydrotestosterone prolong it in the rabbit (3).

QT distance, which is defined as the time period from the beginning of the Q wave to the return of the T wave to the isoelectric line in an ECG, reflects the period passing during depolarization and repolarization of ventricles. QT interval refers to the overall duration of the electrical activation and resting of the ventricle, corresponding to the location of each lead, and is inversely correlated with the heart rate. QT dispersion is defined as the difference between the longest and shortest QT interval measured in a 12-lead ECG (4).

It is accepted that QT dispersion shows regional heterogeneity in myocardial repolarization. Nonhomogeneous myocardial repolarization time is explained by the delay in the action potential period due to the slowing of regional conduction or change in the conduction path. A higher QT dispersion means a higher heterogeneity in ventricular repolarization and, therefore, the higher the ventricular instability (5). Nonhomogeneous conduction velocity in different regions of ventricles, i.e. increase in QT dispersion, may lead to serious ventricular arrhythmias and, hence, sudden cardiac death (6). It is thought that homogeneity of overall duration of ventricular depolarization and repolarization (namely low QT dispersion) has a protective effect against arrhythmias. Prolongation of the QT interval and QT dispersion independently negatively affected the prognosis, cardiovascular mortality, and cardiac morbidity in a general population over 11 years (7).

The purpose of this study was to investigate whether ovulation induction brings about any changes in the QT interval and QT dispersion, which is considered a noninvasive method of measuring regional repolarization inhomogeneity, and to study their relation to circulating concentrations of sex hormones.

Materials and methods

Subjects

Included in the present prospective study were 40 infertile women, aged between 23 and 35, who were referred to the infertility clinic of Başkent University Obstetrics and Gynecology Department, from September 2008 to March 2009, in whom ovulation induction was planned and 20 age-matched healthy women with regular menstrual cycle. They had no cardiac or neurological symptoms nor did they smoke or take cardiovascular medications or any other drugs. All of the women gave written informed consent to the study protocol, which was approved by the local Ethics Committee. Patients with mild male factor or unexplained infertility and in whom ovulation induction and intrauterine insemination were planned were included in the study. Exclusion criteria were as follows: evidence or history of heart disease, hypertension, diabetes, thyroid disease, severe menstrual disorders (amenorrhea, anovulation, etc.) connective tissue disease, or renal disease.

Ovulation induction protocol

On day 2 or 3 of the natural cycle, all patients were examined with a transvaginal ultrasound and the total antral follicles were counted in both ovaries. Patients who did not have residue cysts over 10 mm and whose serum E2 levels were <60 pg/mL, FSH <8 mIU/mL, and LH <8 mIU/mL were instituted with the ovulation induction treatment on the same day. Stimulation with recombinant follicle-stimulating hormone (rec FSH) (Puregon, Organon, İstanbul, Turkey) at 50-100 IU/day was initiated and maintained for 8-10 days with adjustments made according to the response of the ovary to the dose. When at least one leading follicle reached a diameter of 18 mm, 250 μg of rhCG

(Ovitrelle; Serono, İstanbul, Turkey) was administered subcutaneously to trigger ovulation and the final stage of follicular maturation. Dominant follicles were counted ultrasonographically on the same day. On day 3 after the triggering of ovulation, micronized progesterone was initiated vaginally (Progestan; Koçak, İstanbul, Turkey) at the dose of 600 mg/day and administered for 12 days.

Experimental design

Each participant underwent a physical examination before participating in the study. Their ECG was recorded 3 times during the menstrual cycle. ECG records were taken for the first time on day 2-3 of the natural menstruation cycle (menstrual day), for the second time 36 h after hCG administration, when ovulation occurred and immediately before the insemination procedure (ovulatory day), and for the third time 6-8 days after ovulation (mid-luteal day). To minimize the instant varieties, 3 consecutive ECG records were also taken at half hour intervals, as mentioned above, on each day of the menstrual cycle. The average of measurements obtained from the 3 consecutive ECG records was considered as the measurement of that day of menstrual cycle. Serum E2 and progesterone levels of the patients were also measured on the 3 days of the menstrual cycle.

All patients underwent 12-lead ECG examinations following 10 min rest and holding their breath at 10 mm/mV amplitude and 25 mm/s rate. After the ECG records were transferred to digital media, they were magnified on a high resolution monitor and the heart rate, RR, and QT wave distances were measured.

All electrocardiograms were analyzed by a single observer blinded to the clinical data. The QT interval was manually measured by using hand-held calipers from the beginning of the QRS complex to the end of the T-wave. The end of the T-wave was defined as the intersection between a tangent to the terminal slope of the T-wave and the PR baseline. Only monophasic well defined T-waves were accepted for measurement. If the end of the T-wave could not be identified because of the low amplitude of the T-wave, then the lead was excluded from analysis. If a U-wave was present, then a tangential line was drawn on the terminal slope of the T-wave and the end of the T-wave was determined as the point of intersection of this line with the isoelectric base. The QT interval and the preceding RR interval were measured in 3 consecutive cycles. In each lead,

mean of the corrected QTc interval of 3 consecutive beats was considered as the QTc interval of that lead. Subjects with complete bundle branch block, atrial fibrillation, second or third degree atrio-ventricular block, or less than 9 measurable leads in the ECG were excluded.

The heart rate-corrected QT interval (QTc, millisecond (ms)) was calculated by using Bazett's formula $[QTc = QT/\sqrt{(RR)}]$ for each derivation (8,9). The QTc dispersion (QTcd) (ms) was defined as the absolute difference between the maximum (QTcmax) and minimum (QTcmin) QTc interval in any of the ECG leads. To determine the intraobserver variability of QTc interval measurements, 20 randomly selected electrocardiograms were analyzed by the same observer at a different time. These recordings were also analyzed by another observer to determine the interobserver variability.

Statistical analyses

Statistical analyses were performed using SPSS (version 13.0, SPSS Inc, Chicago, IL, USA). Numeric values are expressed as means ± SD. Comparisons study and control groups were done with the Mann-Whitney U-test. The difference between the electrocardiographic parameters within the study group was assessed by the paired-samples t test. When the parametric tests were not appropriate, the Wilcoxon signed rank test was used. $P < 0.05$ was considered statistically significant. Pearson's correlation analysis was used to assess the correlation between hormone levels and electrocardiographic parameters and to assess the intra- and interobserver variability in the measurement of the QTc interval.

Results

Demographic characteristics of the 40 infertile women and 20 healthy women at menstrual phase are demonstrated in Table 1. Both groups were similar in their mean age, BMI, AFC, and other biochemical parameters (Table 1). Blood pressure and heart rate did not differ between groups or between menstrual and ovulatory and mid-luteal day. No difference was seen in terms of ECG findings of the women between the control group and study group, who were all in the menstrual phase (Table 2). In the study group, there was a significant difference in terms of serum estradiol and progesterone levels in each of the 3 days of the menstrual

Table 1. Demographic characteristics and hormone levels of the study and control subjects.

Parameters	Study group N = 40	Control group N = 20	P value
Age (years)	27.6 ± 5.6	29.7 ± 4.9	ns
BMI (kg/m²)	25.5 ± 3.6	27.6 ± 6.1	ns
AFC	30.2 ± 16.5	20.4 ± 4.7	ns
DFC	3.1 ± 2.1		
Hemoglobin (g/dL)	12.5 ± 1.7	12.3 ± 1.3	ns
FSH (mIU/mL)	6.3 ± 2.3	7.8 ± 6.5	ns
LH (mIU/mL)	5.2 ± 2.5	6.5 ± 3.4	ns
TSH (mU/mL)	1.3 ± 0.7	1.7 ± 2.1	ns

AFC: Antral follicle count (on menstruation), DFC: Dominant follicle count (on ovulation), BMI: Body mass index, TSH: Thyroid stimulating hormone, FSH: Follicle stimulating hormone, and LH: Luteinizing hormone. All values are mean ± SD.

Table 2. Concentrations of sex hormones and electrocardiographic results of patients.

Parameters	Control group N = 20	Study group N = 40		
	Menstrual day	Menstrual day	Ovulatory day	Mid-luteal day
Estradiol (pg/mL)	86.6 ± 46.9	36.2 ± 15.6^o	684.1 ± 219.8^u	389.3 ± 242.7^m
Progesterone (ng/mL)	0.8 ± 0.5	0.5 ± 0.2	1.1 ± 1.2	35.1 ± 11.2$^{m\,o}$
QTc max (ms)	428.3 ± 21.1	427.6 ± 16.5	418.6 ± 16.3	417.2 ± 34.5
QTc min (ms)	361.1 ± 22.4	365.7 ± 18.5	371.3 ± 21.1^u	354.5 ± 20.9^m
QTc mean (ms)	396.3 ± 12.7	395.1 ± 14.4	395.7 ± 14.5	394.6 ± 14.3
QTc dispersion (ms)	53.1 ± 18.8	61.9 ± 14.2	47.7 ± 12.6$^{m\,u}$	62.8 ± 13.1
QT mean (ms)	347.6 ± 15.3	342.8 ± 14.6	346.7 ± 12.9	345.1 ± 11.9
Heart rate (beats/min)	69.8 ± 11.7	73.8 ± 9.4	74.6 ± 7.5	69.9 ± 8.5
Systolic BP (mmHg)	120.4 ± 4.8	119.4 ± 10.7	121.4 ± 9.6	118.5 ± 7.6
Diastolic BP (mmHg)	73.8 ± 12.9	69.5 ± 9.7	67.7 ± 11.5	71.2 ± 8.2

QTc: corrected QT interval, ms: millisecond, and BP: blood pressure. All values are mean ± SD.
^{o} vs. Ovulatory day $P < 0.05$
^{m} vs. Menstrual day $P < 0.05$
^{u} vs. Mid-luteal day $P < 0.05$

cycle. There was no difference between menstrual and ovulatory and mid-luteal day with regard to mean QTc interval duration and maximum QTc interval duration. On the ovulatory day with peak estrogen level, QTc dispersion was lower than that on the mid-luteal and menstrual days (Table 2). Minimum QTc interval duration was found to be longest on ovulatory day and shortest on mid-luteal day. When Pearson correlation analysis was carried out, no correlation was found between serum hormone levels at the 3 phases of

menstrual cycle and QTc interval and QTc dispersion. Both interobserver and intraobserver variabilities were <5% for all of the electrocardiographic variables. On each day, the intracycle variability was <7% for all of the measurements.

Discussion

This is the first study investigating the relation between QT dispersion, which reflects the tendency for arrhythmia, and the hormone levels of infertile women experiencing an exaggerated menstrual cycle with ovulation induction. At present, an increasing number of women demand infertility treatment without any hesitation. We do not have much information on the probable cardiac effects of ovulation induction treatments.

There are conflicting results regarding the alterations in the QT interval duration during the menstrual cycle with fluctuations in hormone levels. Hulot et al. observed no significant change in the QT interval duration within the large range of physiological estradiol variations found during the menstrual cycle (10). Nakagawa et al. found a shorter QT interval during the luteal phase than during the follicular phase, contrary to other investigations (11). They investigated the effects of the menstrual cycle on the QT interval dynamics but not the QT dispersion via holter ECGs and the autonomic tone in 11 healthy women (11). In the present study, in the ovulation induction cycle, during menstrual cycle when ovulation and luteinization is clearly shown, the QT interval and the QTc interval duration was investigated during an ECG. No change was seen in the QT and QTc intervals between different phases of the cycle.

The ovulation induction treatments with mild stimulation, in which mean 3 follicles are developed, are closer to the natural menstrual physiology. Follicular development can be clearly observed during the treatment and intra cycle hormonal alterations and peak hormone days can be also determined. Studies on ovulation induction cycles, when the cycle is closely monitored, as in our study, may show the effect of ovarian hormones on the heart better than studies carried out with spontaneous menstrual cycles.

Human studies have been insufficient in showing the effect of estrogen on ventricular repolarization. In

the present study, consistent with the findings of Saba et al. that HRT with estrogen significantly decreases the QT dispersion (12), the QTc dispersion was found to be decreased in the high estrogen level period. In the mid-luteal period, when estrogen partially decreases and progesterone peaks, the QTc dispersion was at the same level as that in the menstrual period, which may be a mechanism mediating the protective effect of estrogen on heart.

The most important advantage of the QT dispersion is that it shows the risk of ventricular arrhythmia with an easily applied noninvasive method. In manual measurements, interobserver and intraobserver differences may restrict the accuracy of measurements (6). Automated measurement methods have been developed for the QT interval with lower rates of error than manual measurements. However, in the automated measurements, there are also errors related to methodology and they are not much superior to the manual method (13). In the present study, measurements were made in a digital environment with high resolution, manually.

In many clinical studies investigating noncardiologic patients, the prognostic significance of the QT interval and QT dispersion was demonstrated. These studies examine patients with Type I DM (14), anorexia nervosa (15), CO poisoning (16), ankylosing spondylitis (17), electrolyte disturbances (18), undergoing dialysis (18) and renal transplant (19), severe burns (20), and professional athletes with left ventricle hypertrophy (21).

The present study has several limitations. First, although QT dispersion is a widely used index, its real predictive value remains questionable. The principal technical problem is the method used to identify the end of the T wave (6). Second, women with infertility problems constitute a patient group with high anxiety levels associated with the duration of infertility and the history of pregnancy loss. Therefore, electrocardiographic changes may be evaluated administering anxiety scales. The duration of ovulation induction and the number of repeated cycles may enhance anxiety and may lead to different results. Third, in this study, we found that the QT dispersion decreased in patients undergoing mild stimulation for planned ovulation induction. However, in different

populations such as in patients with an IVF cycle in which much higher estrogen levels are attained or in patients with ovarian hyperstimulation syndrome, the QT dispersion measurements may be found to be different from our results. Finally, in the present study, QT measurements were obtained from healthy subjects (no cardiovascular, metabolic, or neurologic disease) and need to be confirmed in other high risk population groups.

Conclusion

QT dispersion demonstrating the regional repolarization heterogeneity of the myocardium, which reflects the propensity to cardiac arrhythmia decreases in the ovulation phase of the cycle, with peak estrogen levels in the ovulation induction cycles with mild stimulation. Our results may show the safety of the elevation of sex steroids on ventricular repolarization heterogeneity.

References

1. Stumpf W. Steroid hormones and the cardiovascular system: direct actions of estradiol, progesterone, testosterone, gluco- and mineralocorticoids, and soltriol (vitamin D) on central nervous regulatory and peripheral tissues. Experientia 1990; 46: 13-25.

2. Merri M, Benhozin J, Alberti M, Locati E, Moss AJ. Electrocardiographic quantitation of ventricular repolarization. Circulation 1989; 80: 1301-8.

3. Drici MD, Burklow TR, Haridasse V, Glazer RI, Woosley RL. Sex hormones prolong the QT interval and downregulate potassium channel expression in the rabbit heart. Circulation 1996; 94: 1471-4.

4. Hantukova K, Malik M, Yi G, Camm AJ. Adjustment of QT dispersion assessed from 12 lead ECG's for different number of analysed electrocardiographic leads: comparison of stability of different methods. Br Heart J 1994; 72: 390-6.

5. Loo AV, Arendts W, Hohnloser SH. Variability of QT dispersion measurements in the surface electrocardiogram in patients with acute myocardial infarction and in normal subjects. Am J Cardiol 1994; 74: 1113-8.

6. Pye MP, Cobbe SM. Mechanisms of ventricular arrhythmias in cardiac failure and hypertrophy. Cardiovasc Res 1992; 26: 740-50.

7. Elming H, Holm E, Jun L, Top-Pedersen C, Kober L, Kircshoff M et al. The prognostic value of the QT interval and QT interval dispersion in all-cause and cardiac mortality and morbidity in a population of Danish citizens. Eur Heart J 1998; 19: 1391-400.

8. Bazett HC. An analysis of time relations of electrograms. Heart 1920; 7: 353-70.

9. Hodges M, Salerno Q, Erlien D. Bazett's QT correction reviewed. Evidence that a linear QT correction for heart rate is better. J Am Coll Cardiol 1983; 1: 694.

10. Hulot JS, Demolis JL, Riviere R, Strabach S, Christin-Maitre S, Funck-Brentano C. Influence of endogenous oestrogens on QT interval duration. Eur Heart J 2003; 24: 1663-7.

11. Nakagawa M, Ooie T, Takahashi N, Taniguchi Y, Anan F, Yonemochi H et al. Influence of menstrual cycle on QT interval dynamics. Pacing Clin Electrophysiol 2006; 29: 607-13.

12. Saba S, Link M, Homoud MK, Wang P, Estes III NAM. Effect of low estrogen states in healthy women on dispersion of ventricular repolarization. Am J Cardiol 2001; 87: 354-6.

13. Coumel PL, Maison-Blance P, Badilini F. Dispersion of ventricular repolarization: Realty? Illusion? Significance. Circulation 1998; 97: 2491-3.

14. Zdarska D, Peliskova P, Charvat J, Slavicek J, Mlcek M, Medova E, et al. ECG body surface mapping (BSM) in type 1 diabetic patient. Physiol Res 2007; 56: 403-10.

15. Nahshoni E, Weizman A, Yaroslavsky A, Toledano A, Sulkes J, Stein D. Alterations in QT dispersion in the surface electrocardiogram of female adolescents diagnosed with restricting-type anorexia nervosa. J Psychosom Res 2007; 62: 469-72.

16. Yelken B, Tanriverdi B, Cetinbas F, Memis D, Süt N. The assessment of QT intervals in acute carbon monoxide poisoning - Original Investigation. Anadolu Kardiyol Derd 2009; 9: 397-400.

17. Yildirir A, Aksoyek S, Calguneri M, Aytemir K, Kabakci G, Ovunc K. QT dispersion as a predictor of arrhythmic events in patients with ankylosing spondylitis. Rheumatology (Oxford) 2000; 39: 875-9.

18. Shugushev KhKh, Shugushev ZKh, Khamizova MM, Vasilenko VM. Effect of programmed hemodialysis on parameters of ventricular repolarization and cardiac rhythm disturbances in patients with terminal renal failure. Kardiologiia 2004; 44: 67-70.

19. Monfared A, Ghods AJ. Improvement of maximum corrected QT and corrected QT dispersion in electrocardiography after kidney transplantation. Iran J Kidney Dis 2008; 2: 95-8.

20. Osada M, Tanaka Y, Komai T, Maeda Y, Kohno Ii, Umetani K et al. QT dispersion in patients with severe burns in intensive care unit. Intensive Care Med 2000; 26: 1581.

21. Mayet J, Kanagaratnam P, Shahi M, Senior R, Doherty M, Poulter NR et al. QT dispersion in athletic left ventricular hypertrophy. Am Heart J 1999; 137: 678-81.