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Two markers in predicting the cardiovascular events in patients with polycystic ovary syndrome: increased P-wave and QT dispersion

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Abstract. – OBJECTIVE: Polycystic ovary syndrome (PCOS) is a prevalent disease with many potential long-term cardiovascular risks. P-wave dispersion (Pdis) and QT dispersion (QTdis) have been shown to be noninvasive electrocardiographic predictors for development of cardiac arrhythmias. In this study we aimed to search Pdis and QTdis parameters in patients with PCOS.

PATIENTS AND METHODS: The study included 82 patients with PCOS and 74 age- and sex-matched healthy controls. Baseline 12-lead electrocardiographic and transthoracic echocardiographic measurements were evaluated. P-wave maximum duration (Pmax), P-wave minimum duration (Pmin), Pdis, QT interval, heart rate-corrected QT dispersion and QTdis were calculated by two cardiologists.

RESULTS: Patients wirh PCOS had significantly higher QT dispersion (49.5 ± 14.1 vs. 37.9 ± 12.6 ms, $p < 0.001$), and P wave dispersion (54.2 ± 11.4 vs. 45.9 ± 10.1 ms, $p < 0.001$) than the controls. Serum testosterone and estradiol levels was correlated with the Pdis (r = 0.677, $p < 0.001$ and r = 0.415, $p < 0.001$ respectively) and QTdis (r = 0.326, $p < 0.001$ and r = 0.321, $p < 0.001$ respectively).

CONCLUSIONS: Pdis and QTdis are simple and useful electrocardiographic markers which may be used in the prediction of the risk of adverse cardiovascular events in PCOS patients.

Key Words:
Polycystic ovary syndrome, P-wave dispersion, QT dispersion.

Introduction

Polycystic ovary syndrome (PCOS) is the most frequent endocrinal disorder seen in women of reproductive age and characterized by chronic anovulation and hyperandrogenism[1]. PCOS affects 5-10% of the population and it is not only an endocrinopathologic disorder but also a metabolic syndrome associated with the subclinical markers of premature cardiovascular diseases including diabetes mellitus (DM), hypertension (HT), dyslipidemia, endothelial dysfunction, and atherosclerosis[2]. Decreased vagal and increased sympathetic activity have been reported in PCOS patients and PCOS has been found to be associated with cardiac conduction system disorders that may further increase the risk of cardiovascular events[3].

P-wave dispersion (P_{dis}) is defined as the difference between the longest and the shortest P-wave duration on 12-lead electrocardiography (ECG) and it is a noninvasive marker developed for the determination of the heterogeneity of atrial depolarization[4]. Patients with PCOS have prolonged P_{max} and P_{dis}. The increase in these parameters may be an indicator of patients at increased risk of atrial fibrillation (AF)[5]. QT dispersion (QT_{dis}), defined as the difference in QT interval among the different leads of the standard 12-lead ECG, is used for the assessment of the homogeneity of myocardial repolarization. Increased QT_{dis} has been reported in various cardiac pathologies including myocardial ischemia, heart failure, and left ventricular hypertrophy. Moreover, increased QT_{dis} is a risk factor for life-threatening ventricular arrhythmia, syncope, and sudden cardiac death[6].

In the present study, we aimed to compare P_{dis} and QT_{dis} in patients with PCOS and in healthy volunteers, as predictors of cardiovascular events.

Patients and Methods

Patients

The cross-sectional observational study included 82 women with PCOS and 74 age- and body mass index-matched healthy women. All the

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PCOS patients met the European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine diagnostic criteria for PCOS. The patients with known cardiovascular disease, thyroid disease, neoplasms, pregnancy or breast-feeding, smoking, chronic alcohol consumption, DM, HT, and renal impairment were excluded from the study. None of the patients were on any medication or undertaking oral contraceptives or other hormonal therapy, antihypertensive medication, or drugs that may have effects on conduction system for a minimum of 3 months prior to the study. A full physical examination and 12-lead ECG and transthoracic echocardiographic evaluation were performed in all the subjects. The subjects were studied during the early follicular phase (3-5 days) of their menstrual cycle, and in the PCOS group, 3-5 days after a spontaneous menses or independent of cycle phase in the presence of amenorrhea. The study complies with the Declaration of Helsinki and the experimental protocol was approved by the local Ethics Committee. All the subjects were informed regarding the purpose of the study and provided written informed consent.

Blood samples were collected after an overnight 12-h fasting to assess the levels of blood glucose, testosterone, estradiol, electrolytes, luteinizing hormone (LH), total cholesterol (TC), follicle-stimulating hormone (FSH), high-density lipoprotein cholesterol (HDL-C), and triglyceride. The calculation of low-density lipoprotein cholesterol (LDL-C) was achieved using the Friedewald equation.

All patients underwent a transthoracic examination. The echocardiographic examination was performed at rest, with the patient at left lateral decubitus position in accordance with the guidelines of the American Society of Echocardiography, by using a commercially available echocardiographic device (Vivid 3, General Electric, Milwaukee, WI, USA) with a 3-MHz transducer, by two experienced echocardiographers who were blinded to the study.

Analysis of the Electrocardiograms

Twelve-lead ECGs were received after a 10-minute resting period, with 20 mm/mV amplitude and 50 mm/s rate with standard lead positions in a supine position using a commercially available machine (Marquette Case, Hellige Medical System, Cardiosmart, Hellige Instrument Company, Freiburg, Germany). The assessment of ECGs was achieved manually by the use of a magnifying glass by two cardiologists who were blinded to the study. The start and end of the P-wave were defined as the points where the initial and final deflections of the P-wave crossed the isoelectric line, respectively. P_{dis} was defined as the difference between maximum and minimum P-wave duration. QT intervals were defined as the intervals between the start of the QRS complex and the end of the T-wave, which was identified as its return to the TP baseline. In the presence of U-waves, the QT interval was assessed to the lowest point of the curve between the T- and U-waves. The R-R interval was assessed and used for measuring the heart rate and to compute QT corrected (QTc) interval by using Bazett's formula. QT_{dis} was defined as the difference between the maximum and minimum QTc intervals in different leads.

Intra- and inter-observer mean percent mistake for P_{dis} and QT_{dis} measurements were determined in 100 randomly selected participants (50 patients/50 controls). Intra-observer mean percent mistake was smaller than 5% for P_{dis} and smaller than 4% for $QT_{dis.}$ Inter-observer mean percent mistake were smaller than 6% for P_{dis} and smaller than 5% for QT_{dis}.

Statistical Analysis

Data were analyzed using SPSS 17.0 for Windows (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD) and the categorical variables were shown as percentages. Chi-square test and unpaired *t*-test were used for comparing the categorical and continuous variables between the two groups, respectively. The Pearson and Spearman correlation test was used for the correlations between P-wave parameters and clinical parameters. A p value of <0.05 was considered significant.

Results

A total of 156 patients (82 patients with PCOS and 74 control subjects) were included in the present study. Baseline demographic, clinical, and laboratory characteristics of the study groups were presented in Table I. Both groups were matched according to age and BMI. There were no significant differences between the groups in terms of smoking status, heart rate, waist circumference, systolic and diastolic blood pressure, lipid levels, electrolyte levels and blood levels, fasting glucose, LH and estradiol levels. Patients

Table I. Clinical characteristics and laboratory findings of the study population.

	PCOS (n=82)	Controls (n=74)	p
Age (years)	25.9 ± 5.7	26.4 ± 6.8	0.577
BMI (kg/m2)	26.4 ± 4.1	25.9 ± 5.9	0.220
Waist circumference (cm)	86.7 ± 16.5	85.4 ± 14.6	0.329
Waist/Hip ratio	0.82 ± 0.04	0.80 ± 0.03	0.372
Heart rate (beat/min)	76.2 ± 13.4	74.9 ± 12.3	0.408
Systolic BP (mmHg)	121.1 ± 17.2	119.8 ± 14.5	0.399
Diastolic BP (mmHg)	81.5 ± 11.6	80.7 ± 12.3	0.543
Fasting glucose (mg/dL)	91.3 ± 9.8	88.6 ± 10.1	0.145
Cholesterol (mg/dL)	184.9 ± 38.7	179.6 ± 42.5	0.392
Triglyceride (md/dL)	121.9 ± 66.6	118.6 ± 71.8	0.745
LDL (mg/dL)	114.7 ± 36.9	108.8 ± 36.9	0.272
HDL (mg/dL)	45.8 ± 12.3	47.1 ± 15.1	0.260
FSH (IU/L)	5.5 ± 1.6	6,6 ± 1.4	0.013
LH (IU/L)	7.2 ± 4.4	6.4 ± 6.7	0.091
Estradiol (pg/mL)	51.3 ± 16.6	48.6 ± 18.2	0.075
Testosterone (ng/dL)	95.6 ± 55.9	49.6 ± 41.3	<0.001
Sodium (mEq/L)	138.2 ± 4.1	137.9 ± 4.3	0.780
Potassium (mEq/L)	4.6 ± 0.8	4.5 ± 0.9	0.702
Magnesium (mEq/L)	1.8 ± 0.6	1.8 ± 0.4	0.671
Calcium (mEq/L)	9.5 ± 0.6	9.4 ± 0.8	0.785

Data are presented as mean ± standard deviation. BMI: body mass index; BP: blood pressure; FSH: follicular stimulant hormone; HDL: high-density lipoprotein; LH: luteinizing hormone; LDL: low-density lipoprotein; PCOS: polycystic ovary syndrome.

Table II. Echocardiographic measurements of the study population.

	PCOS (n=82)	Controls (n=74)	p
LVEF (%)	65.5 ± 3.4	65.8 ± 3.1	0.296
LVEDD (cm)	4.68 ± 0.25	4.71 ± 0.31	0.484
LVESD (cm)	2.71 ± 0.21	2.74 ± 0.23	0.236
LA (cm)	3.0 ± 0.33	2.9 ± 0.28	0.282
E peak rate (m/s)	0.84 ± 0.11	0.82 ± 0.09	0.170
A peak rate (m/s)	0.73 ± 0.08	0.71 ± 0.07	0.152
E/A ratio	1.15	1.16	0.447
DT (ms)	171.8 ± 16.9	169.8 ± 14.6	0.316
IVRT (ms)	85.9 ± 8.4	83.7 ± 7.2	0.180

Data are presented as mean ± standard deviation. A: peak mitral valve flow velocity during atrial contraction; DT: deceleration time of early phase of mitral valve flow; E: the peak mitral valve flow velocity during the early rapid filling phase; IVRT: isovolumetric relaxation time; LA: left atrial diameter; LVEDD: left ventricle end-diastolic diameter; LVESD: left ventricle end-systolic diameter; LVEF: left ventricular ejection fraction; PCOS: polycystic ovary syndrome.

with PCOS had higher serum testosterone and estradiol levels (95.6 ± 55.9 *vs.* 49.6 ± 41.3 $p<0.001$ and 51.3 ± 16.6 *vs.* 48.6 ± 18.2 $p=0.075$, respectively) than the control subjects. However, serum follicular stimulating hormone (FSH) levels were lower in PCOS patients than in the control group (5.5 ± 1.6 *vs.* 6.6 ± 1.4 $p=0.013$).

The conventional echocardiographic measurements of the study population were shown in Table II. LV ejection fraction, LV end-diastolic and end-systolic diameters, left atrial diameter, E and A peak mitral valve flow velocity, deceleration time of early phase of mitral valve flow and isovolumetric relaxation time did not differ between the two groups.

The analysis of QT durations and P-wave measurements were presented in Table III. Patients with PCOS, P_{max}, P_{dis}, QT_{dis} and QTc_{max} were significantly increased compared to the control group (98.9 ± 17.3 *vs.* 94.8 ± 13.5 ms, $p=0.009$; 54.2 ± 11.4 *vs.* 45.9 ± 10.1 ms,

Table III. Electrocardiographic findings of the patients and controls subjects.

	PCOS (n=82)	Controls (n=74)	p
P_{max}	98.9 ± 17.3	94.8 ± 13.5	0.009
P_{min}	44.8 ± 9.8	48.8 ± 10.3	< 0.001
P_{dis}	54.2 ± 11.4	45.9 ± 10.1	< 0.001
QT_{max}	387.4 ± 32.4	384.4 ± 29.9	0.306
QT_{min}	339.1 ± 27.5	346.4 ± 24.6	0.002
QT_{dis}	49.5 ± 14.1	37.9 ± 12.6	< 0.001
QTc_{max}	448 ± 37.6	436 ± 32.5	0.008
QTc_{min}	392 ± 31.2	397 ± 27.8	0.064
QTc_{mean}	414± 33.7	417 ± 32.9	0.082

Data are presented as mean ± standard deviation. P_{max}: maximum P-wave duration; P_{min}: minimum P-wave duration; P_{dis}: P-wave dispersion; PCOS: polycystic ovary syndrome; QT_{max}: maximum QT; QT_{min}: minimum QT; QTdis: QT dispersion.

p<0.001; 49.5 ± 14.1 *vs.* 37.9 ± 12.6 ms, p<0.001, 448 ± 37.6 *vs.* 436 ± 32.5 ms, p=0.008, respectively). In contrast, P_{min}, QT_{min}, QTc_{min}, and QTc_{mean} were found to be decreased in patients with PCOS compared to the control group (44.8 ± 9.8 *vs.* 48.8 ± 10.3 ms, p<0.001, 339.1 ± 27.5 *vs.* 346.4 ± 24.6 ms, p=0.002, 392 ± 31.2 *vs.* 397 ± 27.8 ms, p=0.064, 414± 33.7 *vs.* 417 ± 32.9 ms, p=0.082, respectively).

Serum testosterone levels were correlated with the P_{dis} and QT_{dis} (r=0.677, p<0.001 and r=0.326, p<0.001, respectively) (Figures 1 and 2). Moreover, a positive correlation was found between the serum estradiol levels and P_{dis} and QT_{dis} (r=0.415, p<0.001 and r=0.321, p<0.001, respectively).

Discussion

In the present study, we demonstrated that patients with PCOS had significantly higher P_{dis} and Q_{dis} compared to the age- and sex-matched healthy volunteers. Moreover, increased P_{dis} and Q_{dis} were found to be correlated with serum testosterone and estradiol levels.

Women with PCOS presented an increased incidence of cardiovascular risk factors such as diabetes mellitus, hypertension, dyslipidemia, endothelial dysfunction, atherosclerosis, and hyperlipidemia[7]. Therefore, the incidence of long-term cardiac events and stroke is higher in women with PCOS compared to women without PCOS[8]. Furthermore, most of the risk factors for PCOS patients are also independent risk factors for the development of atrial fibrillation, which is the most common form of sustained cardiac tachyarrhythmia in clinical practice[9]. The risk of cardioembolic stroke is reported to be five times higher in patients with AF compared to patients without AF[10]. Groot et al[11] conducted a meta-analysis and demonstrated that the risk of coronary heart disease and stroke was twice higher in women with PCOS than in women without PCOS. Similarly, Wild et al[12] conducted a large-scale study on PCOS patients and reported that the risk of stroke was higher in those patients.

P_{dis} from the surface standard 12-lead ECG is a simple and noninvasive electrocardiographic marker used for evaluating the conduction disorders of sinus impulses between the atria and for measuring the heterogeneity of atrial depolarization[13]. Increased heterogenic electrical activity in atria is a trigger for the development of cardiac arrhythmias, particularly AF. Several studies have reported that the risk of AF is increased in PCOS[14]. The potential mechanism for this situation is as follows: impaired vascular endothelium of atrial tissue might trigger the remodeling in the atria and thus may result in atrial conduction abnormality. Zehir et al[15] demonstrated that atrial electromechanical delay was prolonged in PCOS patients. Tasolar et al[16] reported that P_{dis} was significantly higher in PCOS patients than in the control subjects. P_{dis} has been used in numerous studies in various clinical settings and mainly in the determination of the risk of AF[17]. Our study demonstrated that the patients with PCOS have increased P_{dis} and these patients may be at high risk for the development of reentrant cardiac arrhythmias, particularly AF.

QT_{dis} is a noninvasive electrocardiographic method that measures homogeneity in ventricular electrical activity[18]. Increased QT_{dis} has been

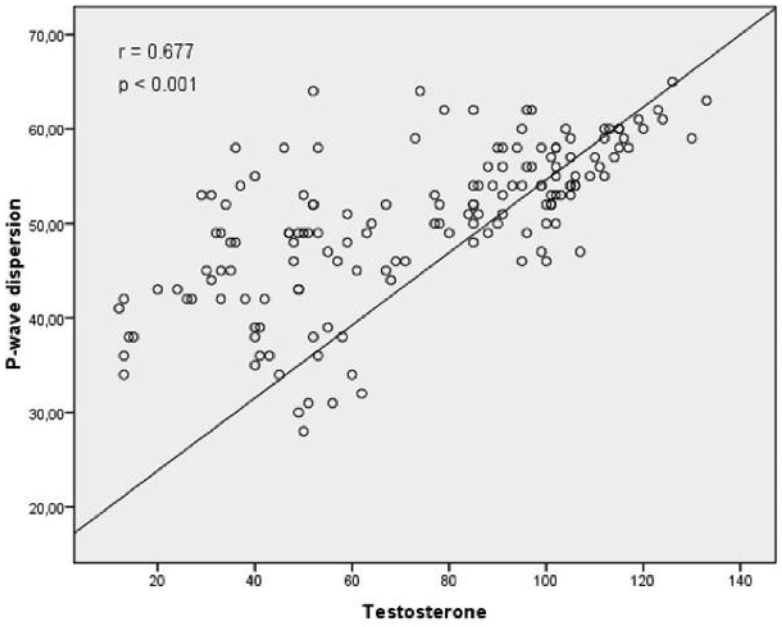

Figure 1. Correlation between testosterone levels and P-wave dispersion.

shown to be associated with ventricular arrhythmia in patients with cardiac diseases including heart failure, prolonged QT syndrome, dilated cardiomyopathy, HT, left ventricular hypertrophy, and postmyocardial infarction[19]. Moreover, several large-scale prospective studies[20] have reported the clinical and prognostic importance of prolonged QT_{dis} in various cardiac and noncardiac diseases. QT and QTc durations have been found to be longer in healthy women compared to healthy men[21]. Some other studies[22] have also shown that the QT interval is associated with both endogenous and exogenous sex hormones. Clinical data suggest that estrogen can cause prolonged QT_{dis}[23]. Experimental studies[24] in animals have revealed that estrogen leads to a prolongation in the QT duration and also in the repolarization phase of action potential by inhibiting the

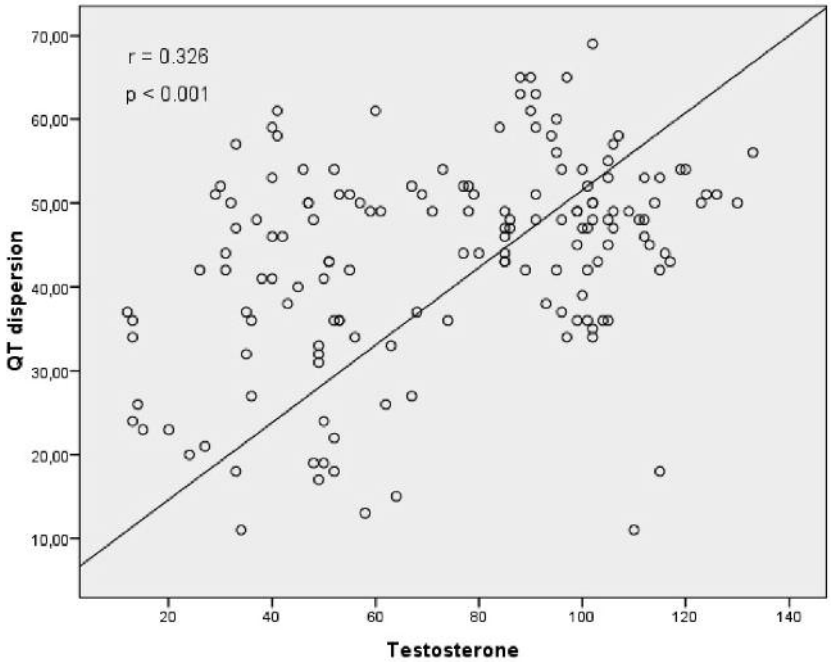

Figure 2. Correlation between testosterone levels and QT dispersion.

potassium current expression. A study[25] on healthy women reported that the QTc duration measured with an increased estradiol level in the follicular phase was higher than the QTc duration measured in the luteal phase. Moreover, Kadish et al[26] found that the postmenopausal women receiving estrogen hormone replacement therapy had a longer QTc interval compared to the women not receiving that therapy. These changes in QT interval and QTc durations have a direct effect on QT_{dis}. In our study, the PCOS patients had higher estradiol levels and longer QT_{dis} durations compared to the control subjects.

Observational and prospective studies have reported an association between testosterone levels and shorter ventricular repolarization. Zhang et al[27] demonstrated that the QT intervals were significantly shorter in middle-aged men with the highest quartile of endogenous total testosterone compared to the men with the lowest quartile. Charbit et al[28] revealed that the QTc interval was significantly shorter at high testosterone levels than at low levels and a negative linear association was found between QTc and testosterone levels. Another study[29] on PCOS patients reported that the QTc duration was shorter and this duration established a negative correlation with testosterone levels. In our study, serum testosterone levels were elevated in patients with PCOS and QTc_{min} and QTc_{mean} duration were lower in the PCOS group compared to the control subjects. Moreover, serum testosterone levels were correlated with QT dispersion.

Our findings suggest that increase in serum testosterone and estradiol levels may have an effect on atrioventricular electrical activity in patients with PCOS.

Conclusions

Our data showed that P_{dis} and QT_{dis} were increased in the PCOS patients and this increase established a positive correlation with serum estradiol and testosterone levels. Increased P_{dis} and QT_{dis} are risk factors for cardiovascular events such as atrial fibrillation, stroke, ventricular tachyarrhythmias, and sudden cardiac death. Thus, we suggest that P_{dis} and QT_{dis} may be used in the prediction of the risk of adverse cardiovascular events in PCOS patients. Furthermore, long-term prospective studies are needed to clarify the clinical utility and prognostic importance of P_{dis} and QT_{dis} in patients with PCOS.

Conflict of Interest

The authors report no conflicts of interest.

References

1) Zacur HA. Epidemiology, clinical manifestations and pathophysiology of polycystic ovary syndrome. Adv Stud Med 2003; 3: 733-739.
2) Paradisi G, Steinberg HO, Hempfling A, Cronin J, Hook G, Shepard MK, Baron AD. Polycystic ovary syndrome is associated with endothelial dysfunction. Circulation 2001; 103: 1410-1415.
3) Di Domenico K, Wiltgen D, Nickel FJ, Magalhaes JA, Moraes RS, Spritzer PM. Cardiac autonomic modulation in polycystic ovary syndrome: Does the phenotype matter? Fertil Steril 2013; 99: 286-292.
4) Perez MV, Dewey FE, Marcus R, Ashley EA, Al-Ahmad AA, Wang PJ, Froelicher VF. Electrocardiographic predictors of atrial fibrillation. Am Heart J 2009; 158: 622-628.
5) Erdogan E, Akkaya M, Turfan M, Batmaz G, Bacaksiz A, Tasal A, Ilhan M, Kul S, Sönmez O, Vatankulu MA, Tasan E. Polycystic ovary syndrome is associated with P-wave prolongation and increased P-wave dispersion. Gynecol Endocrinol 2013; 29: 830-833.
6) Glancy JM, Garratt CJ, Woods KL, De Bono DP. QT dispersion and mortality after myocardial infarction. Lancet 1995; 345: 945-948.
7) Thayer JF, Yamamoto SS, Brosschot JF. The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. Int J Cardiol 2010; 141: 122-131.
8) Zachurzok-Buczynska A, Szydlowski L, Gawlik A, Wilk K, Malecka-Tendera E. Blood pressure regulation and resting heart rate abnormalities in adolescent girls with polycystic ovary syndrome. Fertil Steril 2011; 96: 1519-1525.
9) Brand FN, Abbott RD, Kannel WB, Wolf PA. Characteristics and prognosis of lone atrial fibrillation. 30-year follow-up in the Framingham Study. JAMA 1985; 254: 3449-3453.
10) Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998; 82: 2-9.
11) De Groot PC, Dekkers OM, Romijn JA, Dieben SW, Helmerhorst FM. PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and meta-analysis. Hum Reprod Update 2011; 17: 495-500.
12) Wild S, Pierpoint T, Jacobs H, Mckeigue P. Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study. Hum Fertil (Camb) 2000; 3: 101-105.
13) Roithinger FX, Karch MR, Steiner PR, Sippens GA, Lesh MD. The spatial dispersion of atrial refractori-

ness and atrialfibrillation vulnerability. J Interv Card Electrophysiol 1999; 3: 311-319.

14) Kravariti M, Naka KK, Kalantaridou SN, Kazakos N, Katsouras CS, Makrigiannakis A, Paraskevaidis EA, Chrousos GP, Tsatsoulis A, Michalis LK. Predictors of endothelial dysfunction in young women with polycystic ovary syndrome. J Clin Endocrinol Metab 2005; 90: 5088-5095.

15) Zehir R, Karabay CY, Kocabay G, Kalayci A, Kaymaz O, Aykan AC, Karabay E, Kirma C. Assessment of atrial conduction time in patients with polycystic ovary syndrome. J Interv Card Electrophysiol 2014; 41: 137-143.

16) Ta olar H, Mete T, Balli M, Altun B, Çetin M, Yüce T, Ta olar S, Otlu Ö, Bayramo lu A, Pekdemir H. Assessment of atrial electromechanical delay in patients with polycystic ovary syndrome in both lean and obese subjects. J Obstet Gynaecol Res 2014; 40: 1059-1066.

17) Michelucci A, Giuseppe B, Colella A, Pieragnoli P, Porciani MC, Gensini G, Padeletti L. P wave assessment: statement of the art update. Card Electrophys Rev 2002; 6: 215-220.

18) Higham PD, Campbell RWF. QT dispersion. Br Heart J 1994; 71: 508-510.

19) Sani IM, Solomon DS, Imhogene OA, Ahmad AM, Bala GS. QT dispersion in adult hypertensives. J Natl Med Assoc 2006; 98: 631-666.

20) Cagli K, Ergun K, Lafci G, Gedik HS, Ulas M. QT and P wave dispersion; review. J Ankara Univ Faculty Med 2005; 58: 42-46.

21) Hii JT, Wyse DG, Gillis AM, Duff HJ, Solylo MA, Mitchell LB. Precordial QT interval dispersion as a marker of torsades de pointes. Disparate effects of class Ia antiarrhythmic drugs and amiodarone. Circulation 1992; 86: 1376-1382.

22) Saito T, Ciobotaru A, Bopassa JC, Toro L, Stefani E, Eghbali M. Estrogen contributes to gender differences in Mouse ventricular repolarization. Circulation Res 2009; 105: 343-352.

23) Yang PC, Clancy CE. Effects of sex hormones on cardiac repolarization. J Cardiovasc Pharmacol 2010; 56: 123-129.

24) Ebert SN, Liu XK, Woosley RL. Female gender as a risk factor for drug-induced cardiac arrhythmias: evaluation of clinical and experimental evidence. J Womens Health 1998; 7: 547-557.

25) Nakagawa M, Ooie T, Takahashi N, Taniguchi Y, Anan F, Yonemochi H, Saikawa T. Influence of menstrual cycle on QT interval dynamics. Pacing Clin Electrophysiol 2006; 29: 603-617.

26) Kadish AH, Greenland P, Limacher MC, Frishman WH, Daugherty SA, Schwartz JB. Estrogen and progestin use and the QT interval in postmenopausal women. Ann Noninvas Electrocardiol 2004; 9: 366-374.

27) Yiyi Z, Pamela O, Wendy SP, Darshan D, Dhananjay V, Elena BC, Elsayed ZS, Gordon FT, Eliseo G. Sex-steroid hormones and electrocardiographic QT-interval duration: Findings from the Third National Health and Nutrition Examination Survey and the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol 2011; 174: 403-411.

28) Charbit B, Christin-Maitre S, Demolis JL, Soustre E, Young J, Funck-Brentano C. Effects of testosterone on ventricular repolarization in hypogonadic men. Am J Cardiol 2009; 103: 887-890.

29) Vrtovec B, Meden-Vrtovec H, Jensterle M, Radovancevic B. Testosterone-related shortening of QTc interval in women with polycystic ovary syndrome. J Endocrinol Invest 2008; 31: 653-655.