Assessment of atrial electromechanical interval and P wave dispersion in patients with polycystic ovary syndrome

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ABSTRACT

Objective: Polycystic ovary syndrome (PCOS) is associated with increased cardiovascular risk, including ischemic stroke. Prolonged atrial electromechanical interval (EMI) is related to increased atrial fibrillation (AF) risk. The aim of the study is to evaluate atrial EMI and electrocardiographic P-wave indices related to increased AF risk in patients with PCOS.

Methods: Forty PCOS patients diagnosed on the basis of the Rotterdam criteria and 20 age-matched controls were prospectively included. Patients with atrioventricular or intraventricular conduction abnormalities, dysrhythmia or taking antiarrhythmic drugs, atherosclerotic heart disease, cardiomyopathies, valvular lesions, pericardial disease, a history of pulmonary emboli or pulmonary hypertension, and abnormal thyroid function were excluded. Intra and interatrial EMI were measured by tissue Doppler imaging and P-wave dispersion (Pd) was calculated on 12-lead electrocardiography (ECG). The Isovolumetric relaxation time was the interval between the aortic valve closure artifact at the end of the LV outflow envelope and the mitral valve opening artifact at the beginning of the mitral E wave.

Results: Patients with PCOS had significantly higher interatrial [38 (24-65) ms vs. 16 (9-19) ms p<0.001], left-sided intra-atrial (14.8±6.1 vs. 7±1.7 ms, p<0.001), and right-sided intra-atrial (22.3±8.1 vs. 8.6±3.6 ms, p<0.001) EMI compared with the control group. Pd was significantly greater in the PCOS group compared with control group [45 (27-60) ms vs. 30 (26–38) ms, p<0.001]. Echocardiographic parameters of atrial EMI were significantly correlated with body mass index, Pd, and isovolumetric relaxation time in patients with PCOS.

Conclusion: PCOS is associated with prolonged inter- and intra-atrial conduction times, which are related to increased AF risk.

Keywords: polycystic ovary syndrome, atrial conduction time, atrial electromechanical interval, P-wave dispersion

Introduction

Polycystic ovary syndrome (PCOS) is an endocrinological disorder seen in women in the reproductive age, with the frequency of 5-10%. PCOS is characterized by oligo or amenorrhea, anovulatory cycles, and hirsutism (1). PCOS was shown to be associated with cardiovascular risk factors such as hypertension, obesity, type 2 diabetes mellitus, and dyslipidemia (2). Additionally, elevated testosterone levels, insulin resistance, and metabolic syndrome are frequently observed in patients with PCOS (3). Markers of endothelial dysfunction and premature atherosclerosis, such as increased carotid intima-media thickness and coronary artery calcium, were also reported in premenopausal women with clinical features of PCOS (4, 5). Also, the rate of coronary artery disease and myocardial infarction is increased in women with PCOS (6, 7). As a major cause of mortality and morbidity, the rise in the stroke risk in patients with PCOS was also shown in several studies (8, 9).

Despite these findings, investigations concerning the possible relation between cardiac arrhythmias and PCOS are scarce. Previous studies dealing with the QT dispersion and duration in patients with PCOS suggest that the risk of ventricular arrhythmias is not increased in these patients and these results were attributed to elevated testosterone levels (10, 11). On the other hand, PCOS was associated with ECG markers of the inhomogeneous atrial conduction, which has a predictive value for the atrial fibrillation (AF) (12). AF is the most frequently sustained arrhythmia encountered in clinical practice and is a major cause of ischemic strokes (13). A well-known electrophysiological characteristic of the atrium prone to fibrillation consists of the delay in the intra- and interatrial conduction times and inhomogeneous propagation of sinus impulses. These conduction abnormalities of the atria can be evaluated by measuring atrial electromechanical delay by tissue Doppler investigation as well as P-wave dispersion by simple surface electrocardiography.
(ECG) (14-16). Thus far, limited information exits regarding atrial conduction times in patients with PCOS. Therefore, we aimed to evaluate intra- and interatrial conduction times and P-wave dispersion in patients with PCOS.

Methods

Study design

This study was designed as a prospective cross-sectional study and performed at Zekai Tahir Burak Hospital and Türkiye Yüksek İhtisas Hospital between May 2012 and August 2012. With a type I error (α) of 0.05 and a statistical power of 80%, 40 subjects were required for our study based on Pd values. We included 40 patients (mean age: 27.6±7.2 years) with PCOS and 20 healthy women (mean age: 26.3±6.1 years) in the study. PCOS was diagnosed on the basis of the Rotterdam criteria in the presence of at least two of the following three features: oligo or anovulation, hyperandrogenism, and polycystic ovaries (1). The control group included healthy women with regular menstrual cycles of at least 28 days without hirsutism and the absence of ultrasonographic findings of PCOS. All patients in the PCOS and control groups had not taken any medication for PCOS before they were enrolled into the study. During the study, all the patients were in sinus rhythm and had no documented AF episodes. We did not include patients with atrioventricular or intraventricular conduction abnormalities, dysrhythmia or who were taking antiarrhythmic drugs, atherosclerotic heart disease, cardiomyopathies, valvular lesions, pericardial disease, a history of pulmonary emboli or pulmonary hypertension, and abnormal thyroid function in the study.

Blood pressures were measured and body mass index (BMI) was calculated at the first evaluation. Blood samples were drawn after an overnight 12-h fasting to determine levels of blood glucose, serum electrolytes, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglycerides by autoanalyzer (Abbot Laboratories, Abbott Park, Illinois, USA) using commercial kits. All volunteers underwent standard 2D, M-mode, and Doppler echocardiography and standard 12-lead derivation electrocardiogram. The local Research Ethics Committee approved the study protocol and all patients gave informed consent.

Echocardiographic analysis

In all subjects, echocardiographic examinations were performed (Vivid 7 pro, GE, Horten, Norway, 2-4-mHz phased array transducer) by the same cardiologist, who was blinded to the clinical details of each patient and control subject. During echocardiography, a single-lead electrocardiogram was recorded simultaneously. All measurements were averaged from three cardiac cycles. 2D echocardiographic measurements were performed according to standards outlined by the American Society of Echocardiography (17). The left atrial (LA) dimensions and left ventricular (LV) diameters were determined. We calculated LV ejection fraction (LVEF) according to Simpson’s method. Pulsed-wave mitral flow velocities were obtained from the apical four-chamber view after placing the sample volume on mitral leaflet tips. Mitral early diastolic velocity (E, cm/s), late diastolic velocity (A, cm/s), the E/A ratio, the E deceleration time (DT, ms), and the isovolumetric relaxation time (IVRT, ms) were calculated from the apical view. Tissue Doppler echocardiography was performed with transducer frequencies of 3.5-4.0 MHz by adjusting the spectral pulsed Doppler signal filters until a Nyquist limit of 15 to 20 cm/s was reached and using the minimal optimal gain. The monitor sweep speed was set at 50–100 mm/s to optimize the spectral display of myocardial velocities. Atrial electromechanical coupling (PA) was described as the time interval from the beginning of the atrial electrical activity (P-wave on surface ECG) to the beginning of the mechanical atrial contraction (late diastolic A wave). PAs were measured from the lateral mitral annulus (lateral PA), septal mitral annulus (septal PA), and RV tricuspid annulus (tricuspid PA). Interatrial electromechanical delay (EMD) was calculated by subtracting the tricuspid PA from the lateral PA (lateral PA-tricuspid PA). Right-sided intra-atrial EMD was calculated by subtracting the tricuspid PA from the septal PA (septal PA-tricuspid PA). Left-sided intra-atrial EMD was calculated by subtracting the septal PA from the lateral PA (lateral PA-septal PA) (15).

Electrocardiographic analysis

All subjects underwent a 12-lead ECG (ECG-1350K Cardiofax M, Nihon Kohden Corporation, Tokyo, Japan) recording after a 20-min resting period in the supine position at a paper speed of 50 mm/s with 2-mV/cm standardization. One cardiologist, who was blinded to the clinical status of the patients, measured ECG intervals. The P-wave duration was measured manually with calibers and a magnifying glass to decrease the error in measurements. The onset of P-wave was defined as the junction between the isoelectric line and the beginning of the P-wave deflection. The offset was defined as the junction between the end of the P-wave deflection and the isoelectric line. The longest atrial conduction time measured on any of the 12 leads was defined as P maximum (Pmax) and the shortest time was defined as P minimum (Pmin). The difference between Pmax and Pmin was calculated and defined as P-wave dispersion (Pd=Pmax-Pmin).

Statistical analysis

Statistical analyses performed using IBM SPSS 17.0 (SPSS Inc., Chicago, IL, USA) statistical package. Continuous variables were presented as mean±standard deviation or median (minimum-maximum). Categorical variables were summarized as frequencies and percentages. Normality of the continuous variables was evaluated using the Shapiro-Wilk’s test. Differences between the two groups according to continuous variables were determined by the independent samples t-test or Mann-Whitney U test as appropriate. Categorical variables were compared by Pearson’s chi-square, or Fisher’s exact test. Pearson’s correlation coefficient was used to show the relation between continuous variables. A p value of <0.05 was considered statistically significant.
Table 1. Clinical and laboratory characteristics of the study groups

|                      | PCOS group | Control group | P    |
|----------------------|------------|---------------|------|
| Age, years           | 27.6±7.2   | 26.3±6.1      | 0.510|
| Heart rate, beat/min | 81.9±8.6   | 80.3±10.4     | 0.512|
| BMI, kg/m²           | 26.6±5.7   | 25.1±4.7      | 0.281|
| SBP, mm Hg           | 120 (110-130) | 120 (110-130) | 0.739|
| DBP, mm Hg           | 80 (70-85) | 80 (70-85)    | 0.577|
| Hypertension, n (%)  | 3 (7.5)    | 1 (5)         | 1.000|
| Smokers, n (%)       | 11 (27.5)  | 5 (25)        | 1.000|
| Fasting glucose, mg/dL | 78.9±5.8  | 79.0±5.6      | 0.936|
| Total cholesterol, mg/dL | 165.9±22.5 | 168.3±18.8  | 0.683|
| LDL cholesterol, mg/dL | 100 (57-119) | 95 (67-140) | 0.838|
| HDL cholesterol, mg/dL | 53 (35-78) | 57 (45-84)    | 0.174|
| Triglyceride, mg/dL  | 90 (49-167) | 79 (70-110)  | 0.019|

Value are presented as mean±SD, median (interquartile range), or the number or percentage of patients. *Student’s t-test, Mann-Whitney U test, and chi-square test. BMI - body mass index; DBP - diastolic blood pressure; HDL - high-density lipoprotein; LDL - low-density lipoprotein; PCOS - polycystic ovary syndrome; SBP - systolic blood pressure

Results

Clinical and laboratory characteristics of the study groups are given in Table 1. Age, BMI, heart rate, systolic and diastolic blood pressures, fasting blood glucose levels, and smoking status were similar in both groups. Also, the mean serum levels of HDL and LDL cholesterol did not differ between the two groups. However, the mean triglyceride concentration was significantly higher in the PCOS group compared with the control group. There were no significant differences regarding interventricular septum thickness, LV posterior wall thickness, LV end-diastolic dimension, LV end-systolic dimension, and LVEF between the PCOS and control groups. However, the E-wave velocity of mitral inflow and the E/A ratio were significantly lower and IVRT and LA diameter were significantly higher in the PCOS group compared with the control group. Pmax was significantly higher in the PCOS group compared with the control group. Although Pmin did not differ significantly between the groups, Pd was significantly higher in the PCOS group compared with the control group. In addition, lateral PA, septal PA, and tricuspid PA were significantly higher in the PCOS group than in the control group. Moreover, interatrial, left-sided intra-atrial, and right-sided intra-atrial electromechanical delays were significantly higher in the PCOS group compared with the control group (Table 2). In the PCOS group, no significant associations were noted between echocardiographic parameters of atrial conduction time (left-sided intra-atrial EMD, right-sided intra-atrial EMD, and interatrial EMD) and age. However, all these three parameters were significantly correlated with BMI, Pmax, Pd, and IVRT (Table 3). Figure 1 shows the correlation between Pd and EMDs.

Discussion

Our study provided two major findings. First, in patients with PCOS, interatrial electromechanical delay, left-sided electromechanical delay, and right-sided intra-atrial electromechanical delay were significantly longer compared with the women with a normal menstrual cycle. Second, Pmax and Pd were higher in patients with PCOS compared with the women without PCOS. Besides, there were significant associations between the aforementioned echocardiographic parameters of atrial conduction time and BMI, Pmax, and Pd as well as echocardiographic indices of diastolic function in women with PCOS.

AF is the most frequently sustained arrhythmia in clinical practice and is a major cause of ischemic stroke (13). The devel-
opment of AF is associated with a five-fold increase in stroke rate and a two-fold increase in mortality (18). Previous studies have demonstrated that the prolongation of atrial conduction time and a greater Pd are related to an increased risk of AF development (14-16). Besides, several morbidities such as paroxysmal atrial fibrillation, hypertension, mitral stenosis, obesity, and obstructive sleep apnea were shown to prolong the atrial electromechanical conduction times (19-23). Recently, prolonged Pmax and increased Pd were found in patients with PCOS compared with women with normal menstrual cycles (12). However, as far as we know, atrial conduction times have not been evaluated in patients with PCOS till date.

In our study, in addition to longer P-wave indices, we found significantly longer interatrial and both left and right intra-atrial conduction times in patients with PCOS compared with the control group. Our findings suggest heightened susceptibility for the development of AF in women with clinical and laboratory characteristics of patients with polycystic ovary syndrome.

The E-wave duration and E/A ratio were lower and IVRT was longer in patients with PCOS compared with the control group. Furthermore, LA diameter was found to be higher in patients with PCOS compared with the control group. These findings were in accordance with those of previous studies, which showed impaired diastolic function parameters in women with clinical features of PCOS (24). Therefore, all these data support the notion that prolonged P-wave indices and increased atrial electromechanical conduction time might be a consequence of relatively impaired diastolic LV function.

A higher prevalence of AF has been shown in patients with metabolic syndrome. In a recent study, patients with metabolic syndrome have been demonstrated to have a longer electromechanical atrial conduction time compared with those without metabolic syndrome (25). Similar to PCOS, obesity, abnormal glucose metabolism, dyslipidemia, and elevated cardiovascular risk are common features of metabolic syndrome. Previously, Yağmur et al. (22) revealed a longer atrial conduction time and higher LA diameter in obese patients. Obesity is frequently seen in women with PCOS (2). We also found a significant correlation between echocardiographic atrial conduction parameters and BMI in patients with PCOS despite a relatively lower range of BMI values in our study. Intriguingly, the waist-to-hip ratio has been shown to be significantly correlated with Pd in a recent study of Erdoğan et al. (12).

Insulin resistance and low-grade inflammation have also been implicated in the pathogenesis of PCOS. Insulin resistance is associated with abnormal autonomic nerve system tone, fluctuations of glucose levels, and microvascular flow abnormalities (26). These conditions result in myocardial fibrosis, atrial dilatation, and electrical instabilities, which promote AF formation. Besides, women with abnormal glucose metabolism had an increased tendency for atrial fibrillation compared with their male counterpart (27).

Several electrocardiographic distinctions between genders, such as tendencies to specific arrhythmias and differences in specific electrocardiographic intervals, have been documented. Sex hormones play an important role in this condition; for example, testosterone, which is higher in men and also in women with PCOS, inhibits inward calcium currents and increases inward rectifying potassium currents (28). Atrial fibrillation is more common in men and differences in sex hormones

### Table 3. Correlation between echocardiographic parameters of atrial conduction time and clinical as well as laboratory characteristics of patients with polycystic ovary syndrome

| Parameter   | Left-sided EMD, ms | Right-sided EMD, ms | Interalatrial EMD, ms |
|-------------|--------------------|---------------------|-----------------------|
| Age, years  | 0.035 0.832        | 0.175 0.281         | 0.150 0.356           |
| BMI, kg/m²  | 0.446 0.004        | 0.695 <0.001        | 0.770 <0.001          |
| Pmax, ms    | 0.665 <0.001       | 0.692 <0.001        | 0.892 <0.001          |
| Pd, ms      | 0.665 <0.001       | 0.684 <0.001        | 0.886 <0.001          |
| E/A ratio   | 0.368 0.019        | 0.024 0.885         | 0.226 0.162           |
| DT, ms      | 0.366 0.020        | 0.394 0.012         | 0.501 0.001           |
| IVRT, ms    | 0.366 0.020        | 0.394 0.012         | 0.501 0.001           |

Pearson’s correlation analysis. BMI - body mass index; DT - deceleration time; EMD - electromechanical delay; IVRT - isovolumetric deceleration time; LA - left atrium; LVEF - left ventricular ejection fraction; Pd - P-wave dispersion; Pmax - maximum P-wave duration.
may contribute to pathogenesis. Additionally, wave indices are higher in men compared with women (29). Hence, elevated testosterone levels may partially be responsible for proarrhythmic changes in women with PCOS.

**Study limitations**

There are some limitations of this study. Although the investigated electrocardiographic and echocardiographic parameters of increased AF susceptibility have all been addressed previously in clinical conditions associated with AF, the lack of long-term follow-up data regarding AF development is the main limitation of our study. Therefore, the relationship between these parameters and AF risk is not clearly known in patients with PCOS. In addition, we did not evaluate the hormone levels, markers of inflammation, and insulin resistance in the present study. Assessment of the relationship between these hormones, metabolic parameters, and possible AF risk markers would be more valuable.

**Conclusion**

Interatrial and intra-atrial conduction times were longer and Pd was higher in patients with PCOS compared with women without clinical and laboratory features of PCOS. Impaired diastolic function indices were also shown in patients PCOS. All these abnormalities may contribute to elevated cardiovascular and cerebrovascular event risk in women with PCOS.

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