

QT and corrected QT parameters in non-obese young Indian women with polycystic ovary syndrome

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Abstract

Background: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age group. The QTc interval duration, which is related to cardiac arrhythmia, sudden death, and a sign of cardiac autonomic neuropathy, has not been investigated thoroughly in PCOS population.

Aim and Objectives: The aim of the present study was to investigate the potential alterations in electrocardiographic (ECG)–QT parameters in lean and ideal weight young Indian patients with PCOS.

Material and Methods: Briefly, 24 classical PCOS diagnosed by Rotterdam 2003 Diagnostic criteria and were lean or ideal weight as per WHO criteria and 24 BMI matched, age matched normally menstruating women served as study participants. All of them underwent assessments clinically and by appropriate laboratory tests. Metabolic pattern was assessed and ECG analysis was performed for evaluating QT interval, minimum and maximum QT interval (QTmax and QTmin, respectively), QT dispersion (QTd), minimum and maximum QT interval corrected for heart rate (QTcmin and QTcmax, respectively), corrected QT dispersion (QTcd), and QT/QTc ratio.

Results: QT (388 ± 35 vs 431 ± 53 ms, P -value < 0.01); QTmax (427 ± 46 vs 467 ± 64 ms, P -value < 0.05); and QTmin (355 ± 4 vs 400 ± 48 ms, P -value < 0.001) were significantly different. QTd (65 ± 32 vs 67 ± 38 ms, P -value = 0.834); QTc (454 ± 34 vs 473 ± 56 ms, P -value = 0.103), QTc max (492 ± 37 vs 512 ± 69 ms, P -value 0.216), QTc min (417 ± 37 vs 439 ± 50 ms, P -value = 0.072), and QTcd (76 ± 34 vs 74 ± 44 ms, P -value = 0.808) were not significantly different between PCOS and healthy women.

Conclusion: Our data demonstrate no significant difference in QTc parameters in PCOS compared to healthy controls. This shows PCOS may not be under increased risk of developing cardiac arrhythmias compared to control population.

KEY WORDS: Polycystic ovarian syndrome, QT intervals, non-obese, cardiac autonomic neuropathy, metabolic pattern

Introduction

Infertility shows an increasing trend among Indian women. Polycystic ovary syndrome (PCOS), in which the ovaries

produce male hormones, is a leading cause of infertility problems. PCOS is featured by hyperandrogenism and chronic anovulation which has multifactorial causation, and the etiology is unclear^[1]. Autonomic dysfunction may be an under recognized cause of female fertility disorders.^[2]

In women of reproductive age group, the most common endocrine disorder is PCOS. Briefly, 5–10% of premenopausal women have hyper-androgenism, chronic anovulation, and polycystic ovaries.^[3]

Hyperinsulinism and insulin resistance are important risk factors concerned with PCOS. Decrease in insulin sensitivity is present in both obese and non-obese patients.^[4] Briefly, 50% of women with PCOS have insulin resistance and

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40% are obese.^[5,6] Insulin resistance is an important risk factor for coronary artery disease. PCOS, because of its association with the presence of insulin resistance have increased risk of diabetes mellitus, hypertension and adverse lipid profile.^[6] Studies of lipid profile in PCOS women have found raised triglycerides and decreased high density lipoprotein concentration.^[6] Therefore, PCOS may be related to an increased cardiovascular disease risk.

PCOS women are found to have several cardiovascular risk factors. The QTc interval duration, which gives ventricular repolarization is related to cardiac arrhythmia and sudden death,^[7] has not been investigated thoroughly in PCOS population with no obesity. Increased QTc interval is a major risk factor for the arrhythmias, coronary artery disease, and sudden cardiac death.^[8] Measuring QTc interval is an effective method for evaluating cardiac sympathetic innervation.^[9] QT interval prolongation could be an additional sign of cardiac autonomic neuropathy (CAN).^[10] Also data provide evidence of degree of QTc interval prolongation and severity of CAN are strongly related.^[9]

Gonadal steroid are important determinants of gender-related differences in ventricular repolarization.^[10–12] QT interval length is altered by cardiac calcium current and estrogens play an important role in modulating the length of action potentials.^[11,13] It is found that in postmenopausal women, a combination of estrogen-progestin replacement therapy decreases QT dispersion.^[14] QT dispersion is not affected by estrogen administration, but it increases QT intervals.^[14] Importance of these electrophysiological changes in the heart in PCOS is to be determined.

Few data are available on electrocardiogram (ECG) analysis in PCOS and are controversial.^[12,15] Women with virilization have exhibited shorter and faster repolarization than normal women.^[12] Alpaslan *et al.*'s work on 36 PCOS women reported non-significant prolongation of QT intervals and non-significantly increased QT dispersion, which could be explained in the context that accompanying coronary artery disease may be cause for these electrophysiological cardiac changes than the PCOS problem itself.^[15]

Hence, the present sectional case-control study was designed to investigate the potential alterations in ECG pattern in patients with PCOS. The objective of the present study was to know whether QT parameters were altered in lean and normal weight young Indian PCOS patients, which may reflect dysfunction in autonomic nervous system. It was hypothesized that the PCOS are associated with altered QT parameters.

Material and Methods

This cross-sectional case control study was conducted in the Department of Physiology, PSG IMS&R. Both study and control groups gave written informed consent. Also clearance from the Institute's Human Ethics Committee was obtained. The patient study group included women who presented to the infertility clinics, gynaecologists, and family physicians

with complaints of dysfunctional uterine bleeding, or infertility and diagnosed to have PCOS by the experts. PCOS was diagnosed with physical findings of hyperandrogenism, oligo/anovulation and ultrasonography, after exclusion of specific ovarian, adrenal and pituitary disorders, according to Rotterdam 2003 diagnostic criteria.^[16]

Sample size calculation

According to the disease prevalence in India the sample size was calculated.^[17] The required sample size calculated was 18. In total, 25 patients were analyzed of which one was excluded because of the presence of ectopic beats.

Subjects

The study groups were the same subject which were included for the previous work^[18]

- Patient group:** Briefly, 24 non-pregnant ideal and lean weight (measured by BMI – body mass index) women with PCOS. The patients were grouped as lean and normal as per the WHO criteria.^[19]
- Control group:** Briefly, 24 regularly menstruating (every 27–32 days) volunteer medical students, doctors, nurses, and staff of the hospital and who were matched for age and BMI were included.

Inclusion criteria for both groups included young women aged 16–35, they were lean or ideal weight according to BMI and W/H ratio, waist circumference less than < 80 cm, they were not on any medications affecting lipid or carbohydrate metabolism at least for past 2 months. Exclusion criteria included, women below 16 and above 35, pregnant and lactating women, those who had undergone hysterectomy and had attained menopause, women taking lipid lowering drugs for the past 2 months. Also women on oral hypoglycemic drugs or insulin sensitizing agents, oral contraceptives, and sex steroids for last 2 months and those patients on current infertility treatment were excluded.

Control group were in their follicular phase (6–8 days the start of menstruation) and PCOS were amenorrhic during data recording. The study group had their relevant laboratory investigation.

The anthropometric parameters included were

a. Body mass index (BMI)

The study group were measured for height and weight (wt). Height was measured in centimeters. Study participants stood in their upright position using the height measuring scale. The weight was measured using electronic weighing machine. From this BMI was obtained by dividing weight in kg by square of the height (in meters). They were selected according to World Health Organization obesity is graded as underweight (BMI < 18.5 kg/m²), normal (18.5–24.9 kg/m²), pre-obese (25.0–29.9 kg/m²), and class I obese (30.0–34.9 kg/m²).^[19]

b. Waist circumference

Waist circumference was taken by standard measures.^[20] The subject assuming a standing position and then the points were marked on the subjects. Waist circumference was measured half way between the lower border of the ribs and the iliac crest in the horizontal plane. Briefly, 2 measurements to the nearest 0.5 cm were measured. A third measurement was taken if the variation between the measurements were >2 cm. The mean of the 2 closest measurements was calculated. For females waist circumference 80–87.9 cm was graded as overweight and ≥ 102 cm as obese. For

c. Waist hip ratio (WHR)

We also obtained standard cut-off for WHR which denotes risk (> 0.85 in women) and lower cut-offs (0.80 in women).^[21]

Baseline cardiovascular parameters**a. Resting heart rate (RHR)**

After 5 min of sitting rest, by palpating the left radial artery at wrist the pulse rate was counted for complete 1min.

b. Resting blood pressure (RBP)

After 20 min of quiet supine rest, blood pressure was recorded. Subjects were in supine position, using a manual sphygmomanometer (a Novaphone make). Systolic and diastolic blood pressure was measured. Recorded from right arm to the nearest 2 mmHg. Blood pressure was defined as the points of the appearance and disappearance of Korotokoff sounds, respectively.

QT parameters

A continuous ECG was recorded after 20 min of complete rest in supine position, with eyes open, patient not falling asleep, using students Biopac system. The RR and QT intervals are to be measured from seven cardiac cycles from a recording of lead II of the resting ECG. All ECGs are to be evaluated blindly. The same well trained non-physician researcher to read all the ECGs. The QT interval was measured from the earliest onset of the QRS complex to the terminal portion of the T wave, where it met the baseline.^[22] The RR interval from the preceding cardiac cycle is to be measured from the peaks of the R waves to correct the QT interval for heart rate (QTc). The QT and the preceding RR intervals were measured manually from digital ECG signals. This data is to be used for calculating QTc interval using Bazett^[23] formula

$$QTc = \frac{QT}{(\sqrt{RR})}$$

Parameters to be obtained are

1. QTmax = Longest calculated QT interval.
2. QTcmax = Longest calculated corrected QT interval.
3. QTmin = Shortest calculated QT interval.

4. QTcmin = Shortest calculated corrected QT interval.
5. QTd = The difference between maximum QT interval and minimum QT interval.
6. QTcd = The difference between QTcmax and QTcmin.

Statistical Analysis

The statistical test used was unpaired Students 't'-test and P-value is to be estimated. Statistical significance of P-value is set at less than 0.05.

Results

Results were expressed as Mean \pm SD. The study group are the same subject we included for our previous work,^[18] hence their basic parameters were the same.

Basic parameters of the study group

PCOS and control group were young, (22.96 \pm 3.96 vs 24.21 \pm 4.69, $P = 0.324$), normal BMI (22.12 \pm 2.56 vs 20.86 \pm 2.73, $P = 0.104$) and of same weight (53.60 \pm 8.86 vs 51.09 \pm 9.31, $P = 0.344$).

Resting blood pressure of the study group

PCOS and controls had Systolic (107.67 \pm 10.66 vs 106.17 \pm 14.30) and Diastolic blood pressure (73.58 \pm 8.75 vs 71.08 \pm 9.14). Both showed lower values and there was no significant difference with P-value 0.682 and 0.338, respectively.

QT parameters of the study group

Mean RR interval of the PCOS and the control was highly significant (P -value: <0.001). Values are expressed in seconds. Of the QT parameters, QT (P -value < 0.001) was of highly significant where in PCOS was < 400 ms, QT max (P -value < 0.05) was significant. QTmin (P -value < 0.001) was highly significant and QTd (P -value 0.834) was not significant (Table 1).

Comparison of corrected QT parameters of the study group

Of the corrected QT parameters QTc interval (P -value = 0.103), QTcmax (P -value = 0.216), QTcmin (P -value = 0.072)

Table 1: Comparison of RR interval and QT parameters of the PCOS and control group

Parameter	PCOS	Control	P-value
RR	0.732 \pm 0.117	0.836 \pm 0.092	<0.001***
QT	0.388 \pm 0.035	0.431 \pm 0.053	<0.001***
QTmax	0.427 \pm 0.046	0.467 \pm 0.064	<0.05*
QTmin	0.355 \pm 0.039	0.400 \pm 0.048	<0.001***
QTd	0.065 \pm 0.032	0.067 \pm 0.038	0.834

RR – RR interval, QT – QT interval, QTmax – QT maximum, QTmin – QT minimum, QTd – QT difference.

Table 2: Comparison of corrected QT parameters of the PCOS and control group

Parameter	PCOS	Control	P-value
QTc	0.454 ± 0.034	0.473 ± 0.053	0.103
QTcmax	0.492 ± 0.037	0.512 ± 0.069	0.216
QTcmin	0.417 ± 0.037	0.439 ± 0.050	0.072
QTcd	0.076 ± 0.034	0.074 ± 0.044	0.808

QTc – corrected QT interval, QTcmax – corrected QT maximum, QTc min – corrected QT minimum, QTcd – corrected QT difference.

and QTcd (*P*-value = 0.808) were not significantly different (Table 2).

Discussion

PCOS is a clinical syndrome which requires complete evaluation. The major features are chronic anovulation, hyperandrogenism, hirsutism, obesity, subfertility, and insulin resistance. Alteration in the endogenous sex hormones found in these patients may increase their risk for cardiovascular adverse events. They have diastolic dysfunction, an early indicator of hypertension.^[24]

The cardiovascular parameters investigated in the patients showed conflicting results.^[25] This work was designed to analyze QT parameters in lean and ideal weight PCOS population compared to age- and BMI-matched healthy women.

Women with virilization exhibited a shorter and faster repolarization than normal women and castrated men.^[12] H. Meden-Vrtovec et al showed QTc interval in 56% PCOS patients was significantly shorter (< 400 ms).^[26] Other studies showed QT dispersion in young PCOS patients that there is no evidence for increased risk of ventricular arrhythmias or sudden cardiac death.^[15] Francesco et al^[27] observed in normal weight young PCOS women that resting ECG parameters were normal and they do not affect cardiac depolarization.

The receptors on cardiomyocytes are gonadal steroid receptors. They modulate gene expression in these cells. Estrogens influence activity of cardiac calcium currents^[11] which determines electrical cardiac cycle and the length of the action potentials and, thus, of the QT interval length.^[13] Estrogen receptor-mediated down-regulation of ventricular potassium channels is the cause. It was observed that estrogen level are low during menstruation and ovulation, therefore it is the progesterone-to-estrogen ratio determines the level of risk.^[28] Studies shows in postmenopausal women when given hormone replacement therapy (estrogen replacement therapies) decreased QT dispersion and prolonged QT intervals.^[14]

Sex hormones on cardiac depolarization

Hyperandrogenism is a feature of PCOS and the hyperandrogenic ECG pattern might be expected in PCOS women. Influence of androgen (specifically testosterone) in puberty, shortens QT interval male subjects. This may suggest

androgens rather than estrogens may be the cause for the gender differences in QTc. This is also supported by the absence of fluctuations in the baseline QTc interval duration in women during the menstrual cycle.^[29]

In our study significant differences in QT interval parameters were observed except in QTd and corrected QT parameters. In corrected QT parameters, all were increased than normal values in both patients and controls though not significantly altered. This shows hormonal changes per se may not be the cause for the prolonged corrected QT parameters seen in PCOS. Deep insight into altered progesterone to estrogen ratio and hyperandrogenism could give credit.

Conclusion

The present study focuses on cardiac autonomic activity in young and lean and normal weight PCOS patients. The results should be interpreted with the limitations of our study. It includes the small sample size, we were not able to do a comparative analysis between obese and lean PCOS, and serum sex hormone levels were not analyzed, if done would have paved the way for correlation analysis between QT parameters and hormone levels.

The result of the present study shows QT interval parameters were significantly shorter in PCOS than controls and QTc parameters prolonged though not significantly. This shows PCOS may not be under increased risk of developing cardiac arrhythmias compared to control population.

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