The importance of speckle tracking echocardiography in the early detection of left ventricular dysfunction in patients with polycystic ovary syndrome

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ABSTRACT

Polycystic ovary syndrome (PCOS) is characterized by hormonal and metabolic abnormalities and is thought to increase a risk for cardiovascular diseases. In this study we use speckle tracking echocardiography (STE) to evaluate left ventricular (LV) dysfunction in the early period of the disease. We enrolled 31 patients with PCOS and 32 healthy volunteers as a control group. The participants' ages ranged between 18 and 40 years. PCOS was diagnosed according to the Rotterdam criteria. LV strain (LS) and strain rate (SR) were evaluated using apical two-chamber (2C), three-chamber (3C), and four-chamber (4C) imaging. Global LS and SR were calculated as average of three apical views. The waist-to-hip ratio, homeostasis model assessment-insulin resistance (HOMA-IR), and fasting insulin and triglyceride levels were higher in the PCOS group than in the controls ($p = 0.001$, $p = 0.001$, $p = 0.001$, and $p = 0.005$, respectively). In the PCOS group, the mitral A wave, deceleration time (DT), and isovolumetric relaxation time (IVRT) were significantly higher than in the controls (all $p < 0.05$). The LV global longitudinal strain (GLS) and global longitudinal SR systolic (GLSRS) were significantly lower in the PCOS patient group (both $p = 0.001$). There were strong negative correlations between GLS and both fasting insulin ($r = -0.64$) and DT ($r = -0.62$) (both $p < 0.05$). The study demonstrated that PCOS patients had decreased LV function using STE. Therefore, STE imaging appears to be useful for the early detection of subclinical LV dysfunction in patients with PCOS.

KEY WORDS: Polycystic ovary syndrome; speckle tracking echocardiography; subclinical left ventricular dysfunction
DOI: http://dx.doi.org/10.17305/bjbms.2015.552 *Bosn J Basic Med Sci. 2015;15(4):44-49. © 2015 ABMSFBIH*

INTRODUCTION

Polycystic ovary syndrome (PCOS) is characterized by chronic anovulation and hyperandrogenism and is seen in 10% of the women of childbearing age. It is the most common endocrinopathy in women of this age group [1,2]. Left ventricular (LV) diastolic dysfunction is an early sign of cardiomyopathy in PCOS patients [3]. The etiology of the LV dysfunction is multifactorial and is associated with coronary artery disease, hypertension, autonomic neuropathy, microangiopathy, dyslipidemia, endothelium dysfunction, low-level inflammation, and oxidative stress [4-7]. Insulin resistance (IR) may also be a major risk factor for developing cardiovascular disease in PCOS patients [8].

Conventional and tissue Doppler echocardiography parameters are widely used for evaluating LV function. However, these measurements have major disadvantages, including angle dependence, limited spatial resolution, and deformation analysis in one dimension [9]. Two-dimensional (2D) speckle tracking echocardiography (STE) is a more effective method for objectively evaluating both the systolic and diastolic functions of the myocardium in detail [9-11]. STE assessment might be useful for identifying patients with subclinical LV dysfunction when the LV ejection fraction (LVEF) is normal on conventional echocardiography [12,13]. The aim of this study was to evaluate LV dysfunction in the early period in patients with PCOS at risk of developing LV dysfunction using STE.

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Submitted: 28 May 2015 / Accepted: 13 July 2015

MATERIALS AND METHODS

Study population

We included 31 consecutive patients with PCOS and 32 healthy volunteers as a control group. The participants were similar in terms of age, body mass index (BMI), and blood pressure and their ages ranged between 18 and 40. All of the subjects underwent a physical examination, 12-lead electrocardiography (ECG), transthoracic echocardiography, and chest X-ray. Height, body weight, and hip and waist circumference were measured at a clinical examination visit after an overnight fast. Brachial blood pressure was obtained using standard sphygmomanometry with the subject in the sitting position. Measurements were repeated three times after at least 5 minutes of rest and then averaged. Potential subjects were excluded if they had hypertension, coronary artery disease, congestive heart failure, systemic rheumatic disease, diabetes mellitus, thyroiditis, renal disease, hypercortisolism, or hyperprolactinemia; had used oral contraceptives, other hormone treatments, or any kind of medicine in the previous 3 months; were pregnant or breastfeeding; active smokers; or chronic alcohol consumers. The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Local Ethics Committee. Informed consent was obtained from each participant.

PCOS was diagnosed according to the Rotterdam criteria in the presence of at least two of the following three features: Oligo- or anovulation, hyperandrogenism, and polycystic ovaries [14]. The International Diabetes Federation diagnostic criteria were used to establish the presence of the metabolic syndrome [15]. According to the International Diabetes Federation definition, one has metabolic syndrome when she has central adiposity plus two or more of the following four factors: (1) Triglyceride (TG) concentration >150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality; (2) high-density lipoprotein (HDL) cholesterol concentration <50 mg/dL (1.29 mmol/L) or specific treatment for this lipid abnormality; (3) elevated blood pressure, with a systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg or treatment of previously diagnosed hypertension; and (4) raised fasting plasma glucose concentration >100 mg/dL (5.6 mmol/L) or previously diagnosed Type 2 diabetes.

At baseline, in the morning after an overnight fast, venous blood was sampled to determine the plasma concentrations of glucose, low-density lipoprotein (LDL), HDL cholesterol, TG, and insulin. After consuming a carbohydrate diet of 300 g for 3 days and a 10-14 h overnight fast, blood samples were taken from peripheral veins 60 min and 120 min after consuming 75 g glucose orally. The blood samples were analyzed using immunoassays.

In each subject, the degree of IR was estimated at baseline using the homeostatic model assessment (HOMA) according to the method described by Matthews et al. [16]. Specifically, an IR score (HOMA-IR) was computed with the formula: Fasting glucose (mg/dL) × fasting insulin (μU/mL)/405. BMI was calculated as body weight (kg)/height^2 (m).

Standard echocardiographic evaluation

All of the echocardiographic measurements were performed independently by two observers who were blinded to the clinical characteristics of the study population. The echocardiographic measurements were made in the left lateral position using a Vingmed ultrasound system (Vingmed System 7, General Electric, Horten, Norway) and a 2.5 MHz transducer with the assistance of ECG monitoring. The images were stored digitally and analyzed offline (EchoPAC PC, GE Vingmed). The frame rate for tissue Doppler imaging (TDI) measurements was >100/s. Using Simpson's formula, LVEF was calculated from measurements of the end diastolic and end systolic volumes on apical four-chamber (4C) views. The left atrial (LA) diameter, aortic diameter, and end-diastolic interventricular septum thickness (IVSTd) were measured from the parasternal long axis using M-mode echocardiography. TDI measurements were assessed in the apical 4C view. Early (E) and late (A) wave velocities ratio (E/A), deceleration time (DT), and isovolumetric relaxation time (IVRT) were measured from the mitral inflow profile. The myocardial systolic (Sm), early diastolic (Em), and late diastolic (Am) velocities were determined at the septal mitral annulus by placing a tissue Doppler sample volume. All calculations followed the standards laid down by the American Society of Echocardiography [17].

Two-dimensional (2D) echocardiography

2D echocardiographic images were obtained from apical 4C-, three-chamber (3C), and two-chamber (2C) views, as well as images of the LV. These images were stored digitally. All of the images were obtained while the subjects held their breaths and were stored in a cine loop format from three consecutive beats. The sample volume used for the velocity and strain measurements was positioned manually in the myocardium throughout the cardiac cycle. Then, the records were processed using acoustic tracking software (EchoPac PC; GE Vingmed, Horten, Norway). The frame rate was 60-90 frames/s. LV strain (LS) and strain rate (SR) were evaluated using apical 2C, 3C, and 4C imaging. The LV global longitudinal strain (GLS) and global longitudinal SR (GLSRS) were calculated as the arithmetic means of the three values.

Statistical analysis

Continuous variables are presented as a mean ± standard deviation (SD) while categorical variables are given as percentages. The Kolmogorov–Smirnov test was used to verify the normality of the distribution of continuous variables. Statistical comparison of clinical data between the two groups consisted of unpaired *t*-tests for parametric data and the Mann–Whitney *U*-test for non-parametric data. Correlations were assessed with the Pearson and Spearman correlation coefficients, and the Chi-square test was used for categorical variables. Analyzes were performed with PASW 18 (SPSS/IBM, Chicago, IL, USA), and a two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

In this study we included 31 patients with PCOS (mean age 24.6 ± 4.8 years) and 32 healthy volunteers as controls (mean age 22.5 ± 3.6 years). Demographic and baseline characteristics of the patients and control group are presented in Table 1.

There were no significant differences between the groups in terms of BMI, waist circumference, systolic and diastolic blood pressure, total cholesterol, LDL- or HDL-cholesterol, fasting glucose, and metabolic syndrome ($p > 0.05$). The waist-to-hip ratio was considerably higher in the PCOS group than in the controls ($p = 0.001$). In addition, the fasting insulin, HOMA-IR, and TG levels were notably higher in the PCOS group ($p = 0.001$, $p = 0.001$, and $p = 0.005$, respectively). Echocardiographic features of the groups are presented in Table 2. There were no significant differences between the groups in the LVEF, E, Am, Sm, LA, and IVSTd ($p > 0.05$). In the PCOS group, the A wave, DT, and IVRT were significantly higher than in the controls ($p < 0.05$), while Em and the E/A ratio were considerably lower in the PCOS group ($p = 0.001$ and $p = 0.001$, respectively).

The value of LS-2C was similar in both groups, while GLS, LS-4C, LS-3C, SRS-4C, SRS-3C, SRS-2C, and global longitudinal SR systolic (GLSRS) were significantly lower in the PCOS group compared to the controls (Table 3). There were strong, negative correlations between GLS, and both the fasting insulin ($r = -0.64$, $p < 0.05$) (Figure 1) and DT ($r = -0.62$, $p < 0.05$). There was a significant, moderate correlation between GLS and HOMA-IR ($r = -0.39$, $p < 0.05$). In addition, there was a significant, moderate, positive correlation between GLS and the waist-to-hip ratio ($r = 0.48$, $p < 0.05$), and a significant, weak, negative correlation between GLS and IVRT ($r = -0.27$, $p < 0.03$).

Inter-observer and intra-observer agreements were assessed by a Bland–Altman analysis. Ten patients were selected randomly to evaluate the intra- and inter-observer variability. The inter-observer variability for the strain and SR parameters was < 4.9% and < 5%, respectively. The intra-observer variability was <4.5%.

TABLE 1. Baseline characteristics of patients and controls

Parameters	PCOS (*n*=31)	Control (*n*=32)	*p* value
Age (years)	24.6±4.8	22.5±3.6	0.074
BMI (kg/m^2)	23.3±4.8	22.3±3.0	0.697
Waist circumference (cm)	82.6±14.8	78.9±13.0	0.729
Waist-to-hip ratio	0.86±0.03	0.83±0.04	<0.001
SBP (mmHg)	102.0±8.1	100.0±8.0	0.994
DBP (mmHg)	63.9±4.9	63.7±4.9	0.922
Total cholesterol (mg/dL)	176.6±27.3	159.4±31.8	0.119
LDL cholesterol (mg/dL)	104.7±23.6	93.5±26.0	0.260
HDL cholesterol (mg/dL)	54.9±12.5	55.8±13.3	0.724
TG (mg/dL)	112.3±48.5	77.1±32.6	0.005
Fasting glucose (mg/dL)	90.4±9.9	86.1±11.8	0.098
Fasting insulin (mIU/L)	18.14±5.23	8.90±4.90	<0.001
HOMA-IR	3.75±0.86	1.90±0.97	<0.001
Metabolic syndrome, *n*	7	5	0.751

BMI: Body mass index; DBP: Diastolic blood pressure; HOMA-IR: Homeostasis model assessment-insulin resistance; SBP: Systolic blood pressure; NS: Non-significant; PCOS: Polycystic ovary syndrome

TABLE 2. Comparison of standard echocardiographic parameters of the patients and the control group

Parameters	PCOS (*n*=31)	Control (*n*=32)	*p* value
LVEF (%)	67.8±3.8	67.3±2.4	0.666
E (cm/s)	91.7±14.1	99.7±8.5	0.072
A (cm/s)	70.4±9.3	62.4±7.0	<0.001
E/A	1.31±0.25	1.6±0.19	<0.001
Em (cm/s)	12.1±2.0	14.3±2.1	0.001
Am (cm/s)	9.2±2.3	7.8±1.1	0.085
DT (ms)	182.3±8.9	165.2±10.1	0.001
IVRT (ms)	76.3±7.0	71.8±5.0	<001
Sm (cm/s)	10.6±1.5	10.8±1.1	0.300
LA (mm)	29.0±3.1	27.6±1.6	0.057
IVSTd	8.4±1.6	8.6±0.7	0.890

LV: Left ventricular; LVEF: Left ventricular ejection fraction; E: Mitral early diastolic velocity; A: Mitral late diastolic velocity; DT: Mitral E-wave deceleration time; LA: Left atrium; IVRT: Isovolumetric relaxation time; $IVST_d$: Interventricular septum diastolic thickness; Sm: LV systolic myocardial velocity; Em: LV myocardial early diastolic velocity, Am: LV myocardial late diastolic velocity, NS: Non-significant; PCOS: Polycystic ovary syndrome

TABLE 3. Comparison of longitudinal and global strain-SR parameters of the patients and the control group

Parameters	PCOS	Control	*p* value
LS-4C (%)	–20.3±2.2	–22.9±1.6	0.001
LS-3C (%)	–21.3±2.0	–23.0±1.3	0.003
LS-2C (%)	–21.0±2.0	–22.8±1.7	0.120
GLS (%)	–20.8±3.7	–22.9±2.9	0.001
SRS-4C (1/s)	–1.25±0.17	–1.36±0.18	0.018
SRS-3C (1/s)	–1.30±0.17	–1.40±0.12	0.004
SRS-2C (1/s)	–1.25±0.14	–1.31±0.16	0.042
GLSRS (1/s)	–1.26±0.03	–1.40±0.07	0.001

Bold indicates statistically significant values. LS: Longitudinal strain; 4C-3C-2C: Apical four-, three-, and two-chamber views; GLS: Global longitudinal strain; SRS: Systolic longitudinal strain rate; GLSRS: Global longitudinal systolic strain rate

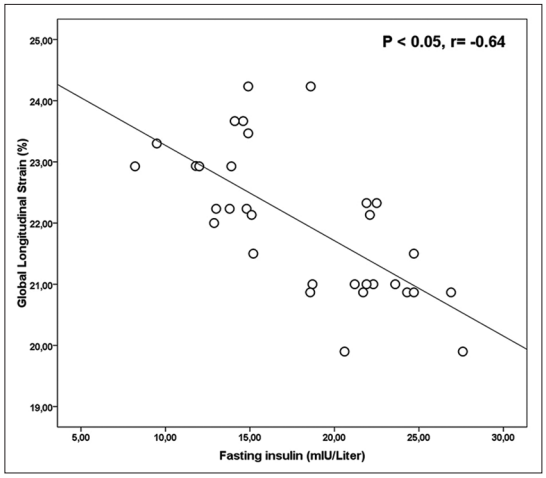

FIGURE 1. Correlation between global longitudinal strain and fasting insulin.

DISCUSSION

PCOS causes symptoms such as amenorrhea, hirsutism, and enlarged polycystic ovaries, and it is associated with a number of cardiovascular disease risk factors, such as dyslipidemia, impaired glucose tolerance, increased blood pressure, and IR [18]. A recent meta-analysis found an increased incidence of cardiovascular events in women with PCOS [19]. In this observational study, we identified an early decrease in LV function in the PCOS group compared to the control group using STE, which is a more objective method of evaluating both systolic and diastolic function.

In comparing PCOS patients to women with normal ovaries, many studies have reported that women with PCOS are seven 7 times more likely to have a myocardial infarction and common coronary artery disease [20]. This is not surprising as women with PCOS are often obese, with impaired glucose tolerance, apparent diabetes mellitus, IR, and metabolic syndrome. The cardiovascular disease risk increases in patients with metabolic syndrome and IR. Therefore, it is very important to detect early impairment in longitudinal LV functions in PCOS patients to prevent morbidity and mortality.

Cardiovascular abnormalities in PCOS patients including decreased cardiac systolic flow velocity, diastolic dysfunction, increased vascular stiffness, and endothelial dysfunction were previously reported [7,20]. In a previous case-control study, women with PCOS were found to have increased IVRT, index of early LV diastolic dysfunction, and lower ejection fraction compared to weight-matched healthy women [21]. LV systolic functions are frequently assessed using conventional echocardiography. However, conventional echocardiography has some limitations, such as imaging difficulties, dependence on operator experience, and obstacles related to LV geometry [22,23]. The introduction of the new STE method has enabled a more precise assessment of LV function [24] and enables regional and global assessment of the left ventricle. Previous studies have indicated that 2D STE is more sensitive than conventional echocardiography for detecting subclinical ventricular dysfunction in various clinical disorders [25,26]. Erdogan et al. [27] reported that the GLS values decreased considerably in PCOS patients. We also identified significant decreases in systolic function parameters such as GLS, LS-4C, LS-3C, SRS-4C, SRS-3C, SRS-2C, and GLSRS using STE in PCOS patients compared to the control group; this indicated that subclinical LV dysfunction starts early in PCOS patients.

In a study by Share et al. [28], they detected subclinical cardiac dysfunction in women with abdominal obesity. However, in our study there was no difference in BMI between two groups, however, waist-to-hip ratio was higher in PCOS group, suggesting that BMI is not the single factor in the pathogenesis impaired myocardial function in PCOS patients.

Diabetes and metabolic syndrome are the two best-known causes of coronary artery disease. We also found that the HOMA-IR showing IR, fasting insulin, and waist-to-hip ratio were higher in the PCOS patients. Metabolic syndrome was detected in seven patients in the PCOS group and in five of the controls. Wild et al. [29] found a significant correlation between an increased waist-to-hip ratio and coronary artery disease. In our study, PCOS patients had a high waist-to-hip ratio, which might be associated with the risk of coronary artery disease.

Heart failure risk is more common in obese women than in obese men. Obesity leads to LV dysfunction via increased production of cardio-inhibitory cytokines and some neurohormones, and by causing myocardial fibrosis [30,31]. In our study, there was no difference in the BMI of the two groups, while the waist-to-hip ratio was higher in the PCOS patients. Therefore, the waist-to-hip ratio might be associated with myocardial dysfunction in PCOS patients. Prelevic et al. [32] discovered that systolic blood flow velocity was lower in the PCOS group than the control group and that there was an inverse correlation between systolic outflow parameters and fasting insulin. In addition, they found that increased insulin levels were correlated with decreased LV systolic flow. In our study, fasting insulin was elevated in PCOS patients, and there was a significant, negative correlation between elevated fasting insulin and GLS.

LV diastolic dysfunction is an early indicator of cardiomyopathy and is correlated with IR, endothelial dysfunction, hypertension, cardiovascular disease, and oxidative stress. In our study, diastolic dysfunction parameters such as DT, IVRT, A, and the E/A ratio were considerably higher in the PCOS group. This implies that both systolic and diastolic dysfunction should be followed at an earlier period in PCOS patients. In addition, some studies have explored the important correlation between plasma insulin levels and IVRT [21].

This study had some limitations. The most important was that because it was a cross-sectional study, there was no long-term follow-up of cardiovascular morbidity and mortality. Another limitation was the small number of patients, which may prevent these results from being generalized to all PCOS patients. Nevertheless, our study detected important parameters that should shed light on the prediction of cardiovascular disease among PCOS patients. Further studies should be performed in the future to corroborate the findings from this study.

CONCLUSION

We show that both systolic and diastolic dysfunction can develop early in patients with PCOS. In addition to conventional echocardiography parameters, the decrease in GLS and GLSRS determined with the new STE method might be helpful in preventing the early progression of asymptomatic subclinical LV dysfunction.

ACKNOWLEDGMENTS

A summary of this study were presented as an oral presentation at the 64th ESCVS and 11th International Congress of Update in Cardiology and Cardiovascular Surgery, and the abstract was published in the American Journal of Cardiology, Volume 115, Supplement, 1 March 16, Pages S77-S78.

DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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