Subclinical left ventricular dysfunction in women with polycystic ovary syndrome: an observational study

Polikistik over sendromlu hastalarda subklinik sol ventrikül disfonksiyonu: Gözlemsel bir çalışma

Ercan Erdoğan, Mehmet Akkaya, Ahmet Bacaksız, Abdurrahman Tasal, Murat Turfan, Şeref Kul, Osman Sönmez, Mehmet Akif Vatankulu, Gökhan Ertaş, Gonca Batmaz, Mehmet Ergelen, Hüseyin Uyarel, Ömer Göktekin*

Departments of Cardiology, *Obstetrics and Gynaecology, Faculty of Medicine, Bezmialem Vakıf University, İstanbul-*Turkey*

ABSTRACT

Objective: Cardiac involvement has been increasingly recognized in patients with polycystic ovary syndrome (PCOS). Identification of the earliest asymptomatic impairment of left ventricular (LV) performance may be important in preventing progression to overt heart failure. Our aim was to investigate LV function with different echocardiographic techniques in patients with PCOS.

Methods: Thirty patients with PCOS and 30 age and body mass index matched healthy subjects were enrolled to this cross-sectional observational study. All subjects underwent echocardiography for assessment of resting LV function as well as two-dimensional speckle tracking echocardiography (2D-STE) and real-time three-dimensional echocardiography (3D-Echo). Global longitudinal strain (GLS) was calculated from 3 standard apical views using 2D-STE. Student t-test, Chi-square test, Pearson's, and Spearman's correlation analysis were used for statistical analysis.

Results: The early mitral inflow deceleration time (DT), isovolumetric relaxation time (IVRT) and E/Em ratio were increased in the PCOS group ($p<0.05$ for all). Waist-to-hip ratio, fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR) and low-density lipoprotein (LDL) levels were higher in PCOS group ($p<0.05$ for all). Significant correlation was observed between DT, IVRT and insulin value, HOMA-IR ($p<0.05$ for all). On 3D-Echo evaluation, none of the patients in both groups had LV systolic dysfunction with comparable LV ejection fraction and LV volumes. 2D-STE showed that GLS was significantly reduced in the PCOS group compared to control group (-16.78±0.56% vs. -18.36±1.04%, $p<0.001$). The GLS was found to be negatively correlated with waist-to-hip ratio and LDL values ($p<0.05$ for all).

Conclusion: These results indicate that PCOS may be related to impaired LV systolic function detected by 2D-STE. In addition, PCOS may lead to diastolic dysfunction. Reduced GLS might be an early indicator of cardiac involvement in this patient population.

(Anadolu Kardiyol Derg 2013; 13: 784-90)

Key words: Polycystic ovary syndrome, speckle-tracking echocardiography, left ventricular function

ÖZET

Amaç: Polikistik over sendromlu (PKOS) hastalarda kardiyak tutulumun olduğu kabul edilmektedir. Asemptomatik sol ventrikül (SV) fonksiyonlarındaki bozulmanın erken tespiti kalp yetersizliğine gidişatın önlenmesinde önemli olabilir. Amacımız PKOS hastalarında farklı ekokardiyografik teknikler kullanarak SV fonksiyonlarını araştırmaktır.

Yöntemler: Kesitsel ve gözlemsel çalışmamıza, polikistik over sendromlu 30 hasta ve demografik özellikleri benzer 30 sağlıklı kadın dahil edildi. İstirahat SV fonksiyonlarının değerlendirilmesinde standart transtorasik ekokardiyografi yanında, iki boyutlu benek izleme ekokardiyografi (2B-BIE) ve üç boyutlu ekokardiyografi (3B-Eko) bakıldı. SV hacimleri ve ejeksiyon fraksiyonu ölçümü 3B-Eko ile yapıldı. Apikal görüntülerden 2B-BIE tekniği kullanılarak global longitüdinal strain (GLS) değerleri hesaplandı. İstatistiksel analizde; Student t-testi, Ki-kare testi, Pearson ve Spearman korelasyon analizleri kullanıldı.

Bulgular: Polikistik over sendromlu hastalarda mitral E dalgası deselerasyon zamanı (DT), E/Em oranı ve izovolümetrik relaksasyon zamanının (IVRT) kontrol grubuna göre artmış olduğu görüldü (tümü için $p<0,05$). Bel-kalça oranı, açlık insülin, düşük dansiteli lipoprotein (LDL) ve insülin direnci (HOMA-IR) seviyeleri PCOS grubunda daha yüksek bulundu (tümü için $p<0,05$). DT ve IVRT ile açlık insülin düzeyi ve HOMA-IR arasında anlamlı korelasyon saptandı (tümü için $p<0,05$). 3B-Eko değerlendirmesinde her iki grubun SV sistolik fonksiyonlarının normal olmasına rağmen 2B-BIE ile bakılan GLS değerlerinin PKOS grubunda daha düşük olduğu (-16,78±%0,56 vs. -18,36±%1,04, $p<0,001$) gösterildi. GLS ile bel-kalça oranı ve LDL seviyesi arasında negatif korelasyon tespit edildi ($p<0,05$).

Sonuç: Polikistik over sendromunun asemptomatik SV sistolik fonksiyon bozukluğu ile ilişkili olabileceği 2B-BIE ile gösterildi. Ayrıca PKOS diyastolik fonksiyon parametrelerini de bozabilmektedir. Azalmış GLS, PKOS'lu hastalarda kardiyak tutulumun erken göstergesi olarak kullanılabilir.

(Anadolu Kardiyol Derg 2013; 13: 784-90)

Anahtar kelimeler: Polikistik over sendromu, benek izleme ekokardiyografi, sol ventrikül fonksiyonları

Address for Correspondence/Yazışma Adresi: Dr. Ercan Erdoğan, Bezmialem Vakıf Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Vatan Caddesi, 34093 Fatih, İstanbul-*Türkiye* Phone: +90 212 453 17 00 Fax: +90 212 621 75 80 E-mail: drercanerdogan@gmail.com

Accepted Date/Kabul Tarihi: 18.03.2013 **Available Online Date/Çevrimiçi Yayın Tarihi:** 28.08.2013

doi:10.5152/akd.2013.196

Introduction

Polycystic ovary syndrome (PCOS), characterized by chronic anovulation and hyperandrogenism, is a common diagnosis made in up to one in 15 of women of childbearing age (1, 2). Given the high prevalence of the metabolic syndrome (MetS) among women with PCOS, they are assumed to be at increased risk for cardiovascular disease (CVD) (3). It has been reported that women with clinical features of PCOS have lower 5-year cardiovascular event-free survival than women without clinical features of PCOS (4). Therefore, this group of patients need close and thorough follow-up.

Accurate determination of left ventricular (LV) volume and ejection fraction (EF) is important for clinical decision-making and follow-up. Conventional echocardiography (C- Echo) is a noninvasive, quick, inexpensive and radiation free method to assess EF and LV volumes, however, it does not provide reliable, reproducible, and accurate measurements. C-Echo has used the method of disks to calculate LV volumes based on areas in only 2 imaging planes. The three dimensional echocardiography (3D-Echo) calculates the actual left ventricular volume based on the actual shape, not the geometrical assumptions so that it has a good reproducibility, even if in the heart cavity has deformation, segmental wall motion abnormalities. It is more accurate than C-Echo, and is close to the gold standard magnetic resonance imaging MRI (5, 6).

Two-dimensional speckle tracking echocardiography (2D-STE) can assess global LV function and it is superior to EF measurement by being angle independent, less subject to artifact, and simpler to obtain than Doppler-derived tissue velocity imaging. Strain and strain rate imaging by a 2D-STE method is a novel echocardiographic technique for evaluation of regional and global myocardial function and is relatively free from angle dependency, frame-rate limitation of tissue Doppler imaging and is easier to calculate (7, 8). Based on 2D-STE, automated function imaging is used for reflection of systolic LV function by assessment of LV global longitudinal strain (GLS). Longitudinal tissue deformation is evaluated by frame-by-frame tracking of individual speckles throughout the cardiac cycle. This imaging technique discriminates between active and passive myocardial motion and enables angle-independent quantification of myocardial deformation in 2 dimensions (9, 10).

Since patients with PCOS are assumed to be at increased risk for CVD, there is a need in defining the presence or extent of myocardial dysfunction in this category of patients. The assessment using 2D-STE may be useful for identifying the patients with subclinical LV dysfunction although LVEF is normal on conventional echocardiography (11).

The aim of our study was to investigate and compare the changes in cardiac functions and myocardial contractility among the patients with and without PCOS who have preserved LV systolic function by 2D-STE.

Methods

Study design

This cross-sectional observational study was conducted by Cardiology Department at Bezmialem Vakıf University Faculty of Medicine Hospital between March and August 2012.

Patient population

Thirty patients with a diagnosis of PCOS aged younger than 40 year and 30 healthy women matched by age, BMI, heart rate and blood pressure were included in the study. All patients underwent physical examination, chest X-Ray, 12-lead electrocardiography (ECG) and transthoracic echocardiographic evaluation. Patients with any cardiovascular disorder including hypertension, diabetes mellitus, thyroid and renal diseases, hyper-cortisolism, use of oral contraceptives or other hormonal therapy within the prior 3 months, pregnancy or breast-feeding, hyper-prolactinemia, smoking, chronic alcohol consumption, or history of use of any medications in the last 3 months were excluded. Hypertension was excluded on the basis of a negative history, absence of antihypertensive treatment and normal blood pressure values (<140/90 mm Hg); diabetes mellitus was excluded on the basis of normal fasting glucose and a 75-g oral glucose tolerance test (OGTT); and subclinical hypothyroidism and renal impairment were excluded on the basis of normal TSH and creatinine levels, respectively. Women were studied in the early follicular phase (2-5 d) of the menstrual cycle or after 3 months of amenorrhea.

Subjects were informed regarding the purpose of the study and provided written informed consent. Investigations were in accordance with the Declaration of Helsinki and were approved by the local Ethics Committees.

Definitions

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 (12). The International Diabetes Federation (IDF) diagnostic criteria were used to establish the presence of the metabolic syndrome (MetS) (13). According to the IDF definition, someone has the metabolic syndrome if she has central adiposity plus two or more of the following four factors: 1) raised concentration of triglycerides (TG): >150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality; 2) reduced concentration of high-density lipoprotein (HDL) cholesterol: <50 mg/dL (1.29 mmol/L) or specific treatment for this lipid abnormality; 3) raised blood pressure: systolic blood pressure >130 mm Hg or diastolic blood pressure >85 mm Hg 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.

Laboratory data

At baseline, in the morning after an overnight fast, venous blood was sampled for the plasma concentration of glucose,

low-density lipoprotein (LDL) and HDL cholesterol, TG, and insulin. In each subject, the degree of insulin resistance was estimated at the baseline by homeostatic model assessment (HOMA) according to the method described by Matthews et al. (14). In particular, an insulin resistance (IR) score (HOMA-IR) was computed with the formula: fasting Glucose (mg/dL) x fasting Insulin(μU/mL) / 405.

Conventional echocardiography

C-Echo was performed on the subjects at rest in the left lateral decubitus position with synchronized electrocardiography by 2 professional cardiologists who were blinded to the clinical data with a commercially available system (Philips iE33, Bothell, WA, USA) equipped with a broadband S5-1 transducer (frequency transmitted: 1.7 MHz; received: 3.4 MHz). Complete 2D, color, pulsed and continuous-wave Doppler examinations were performed according to standard techniques. Parasternal long-axis views were used to derive the M-Mode measurements of left atrial (LA) size, LV end-diastolic septal (IVST) and posterior wall thickness (PWT), and LV end-diastolic (LVDd) and end-systolic (LVDs) dimensions. LV mass (LVM) was calculated from 2D echocardiographic measurements by using Devereux formula: $LVM=1.04\times[(IVST+PWT+LVDd)^3-(LVDd)^3]-13.6$ and was indexed to body surface area (15). LVH was defined as a left-ventricular mass index (LVMI) greater than 100 g/m^2. LV fractional shortening (FS) was calculated as [(LVDd–LVDs)/LVDd]×100. LVEF was calculated from LV volumes by the 3D-Echo. Body mass index (BMI) and body surface area were calculated according to standard formulas. Trans mitral pulsed-wave Doppler velocities were recorded from the apical four-chamber view with Doppler sample placed between the tips of the mitral leaflets. Early (E) and late (A) diastolic wave velocities, E/A ratio, E deceleration time (DT), and isovolumetric relaxation time (IVRT), isovolumetric contraction time (IVCT) were measured from the mitral inflow profile. The myocardial early diastolic (Em), and late diastolic (Am) velocities were obtained at the septal mitral annulus by placing a tissue Doppler sample volume. The E/Em ratio was calculated. All echocardiographic measurements used in the analysis were averaged from 3 heart beats.

Two-dimensional speckle-tracking echocardiography

The endocardial borders were traced in the end-systolic frame of the 2D images from the 3 apical views. Four consecutive end-expiratory cardiac cycles using the high frame rate (50 Hz or more) harmonic imaging in each echocardiographic view were acquired. Speckles were tracked frame by-frame throughout the LV wall during the cardiac cycle and basal, mid, and apical regions of interest were created. The operator manually adjusted segments that failed to be tracked. Any segments that subsequently failed to be tracked were excluded. Any view in which 2 or more segments could not be tracked was not included in the analysis, and the remaining apical views were averaged to calculate GLS; otherwise, GLS was calculated as the mean strain of all 17 segments. All measurements were made blinded to other results and clinical details.

Real-time three-dimensional echocardiography

Real-time 3D-Echo images were also obtained from (3D-Echo) an apical window with the patient in the same position as 2D-STE. Full-volume images were also gathered over 4 cardiac cycles using a matrix array transducer (×4 transducer, Philips iE33, Andover, MA, USA). Measurements of 3D-Echo volumes and 3D-EF were performed off-line. (QLAB workstation using 3D-Advanced Quantification, Philips).

Statistical analysis

Measured values are reported as mean±standard deviation, and statistical comparisons were performed using SPSS 15.0 statistics package (SPSS Inc, Chicago, IL, USA). The categorical and continuous variables between the two groups were compared using the Chi-square test and Student's t-test, respectively. GLS and velocities were compared using an independent two sample t-test. The correlation between variables (waist-to-hip ratio, insulin, HOMA-IR, LDL, GLS, DT, IVRT) was tested using correlation analysis. Differences were considered significant at a p value of <0.05.

Results

Demographic and clinical results

Clinical characteristics and laboratory findings of patients included in the study are shown in Table 1. Mean age of study population was 26.0±5.6 years with no difference between groups. There were no significant differences in the average heart rate, mean systolic and diastolic blood pressures. There were 6 patients with MetS in PCOS group and 4 in control group. The fasting glucose, HDL, TG, waist circumference and BMI were similar between two groups while waist-to-hip ratio, insulin, HOMA-IR and LDL levels were higher in PCOS group.

Echocardiographic results

The M-mode, 2D, 3D, pulse wave Doppler and tissue Doppler echocardiographic variables are shown in Table 2. LV dimensions, wall thicknesses and LA dimension were not different between two groups. 3D-EF, 3D-Echo volumes and FS were similar among the groups. The DT (169.8±5.7 msec vs. 163.6±5.6 msec; $p<0.001$), and IVRT (79±7 msec vs. 73±6 msec; $p=0.004$) were longer in the group of patients with PCOS whereas both groups had similar IVCT, E and A velocities and E/A ratio. Among the tissue Doppler parameters, patients with PCOS had lower Em and higher E/Em ratio (8.46±1.71 vs. 7.44±1.66; $p=0.04$) suggesting impaired diastolic function in this group. Significant correlation was observed between DT, IVRT and fasting insulin value, HOMA-IR (Table 3).

Table 1. Clinical characteristics and laboratory findings

Variables	PCOS (n=30)	Controls (n=30)	*p
Age, years	25.9±6.5	26.1±4.5	NS
Body mass index, kg/m^2	29.4±8.5	28.2±4.1	NS
Body surface area, m^2	1.83±0.2	1.92±0.1	NS
Waist circumference, cm	94.2±19.4	89.2±11.3	NS
Waist-to-hip ratio	0.85±0.03	0.81±0.02	<0.001
Systolic blood pressure, mm Hg	108±8	107±7	NS
Diastolic blood pressure, mm Hg	65±6	63±5	NS
Heart rate, bpm	81±12	77±10	NS
Fasting glucose, mg/dL	86±6	87±4	NS
High-density lipoprotein, mg/dL	50.1±15.3	51.0±10.4	NS
Low-density lipoprotein, mg/dL	113.9±33.1	96.1±23.6	0.04
Triglycerides, mg/dL	114.7±67.9	115.2±29.3	NS
Fasting insulin, mIU/Liter	22.67±23.12	10.08±3.26	0.02
HOMA-IR	4.83±4.74	2.18±0.76	0.02
Metabolic syndrome, n (%)	6 (%20)	4 (%13.3)	NS

Results are shown as mean±standard deviation and numbers/percentages
*t-test for independent samples and Chi-square test
HOMA-IR - homeostasis model assessment - insulin resistance, PCOS - polycystic ovary syndrome

Table 2. Left ventricular 2D, 3D, M-mode, Doppler and tissue Doppler echocardiographic parameters of the patients and the control group

Variables	PCOS (n=30)	Controls (n=30)	*p
LV end-diastolic dimension, cm	4.62±0.2	4.70±0.2	NS
LV end-systolic dimension, cm	2.63±0.1	2.67±0.2	NS
IVS thickness, cm	0.98±0.04	1.0±0.05	NS
LV posterior wall thickness, cm	0.97±0.04	0.98±0.03	NS
Left atrial dimension, mm	34.2±2	34.3±1.9	NS
Fractional shortening, %	43.1±2.1	43.2±2.4	NS
3D-LV ejection fraction, %	68±8	69±6	NS
LV mass, g	180±24	184±30	NS
LV mass index, g/cm^2	99.1±12.2	95±18.4	NS
E peak rate, m/s	0.85±0.08	0.84±0.17	NS
A peak rate, m/s	0.65±0.1	0.64±0.13	NS
Em peak rate, m/s	10.36±1.86	11.60±1.42	0.02
E/Em ratio	8.46±1.71	7.44±1.66	0.04
Mitral E/A ratio	1.33±0,25	1.35±0.36	NS
Deceleration time, msec	169.8±5.7	163.6±5.6	<0.001
Isovolumetric relaxation time, msec	79±7	73±6	0.004
Isovolumetric contraction time, msec	74±5	72±4	0.2

Results are shown as mean±standard deviation and numbers/percentages
*t-test for independent samples and Chi-square test
3D- three-dimensional, A- late diastolic inflow velocity, E- early diastolic inflow velocity, Em-myocardial early diastolic annular velocity, IVS - interventricular septum thickness, LV - left ventricle, PCOS - polycystic ovary syndrome

Speckle-tracking echocardiographic results and association of GLS with variables

GLS was significantly reduced in the PCOS group compared to control group (p<0.001; Table 4). In the correlation analysis, GLS was not correlated with fasting insulin, HOMA-IR, fasting glucose, HDL, TG, waist circumference and BMI. However, GLS was found to be negatively correlated with hip-to-waist ratio and LDL values (Table 5).

Feasibility, reproducibility of 2D-STE and 3D-Echo analysis

Speckle-tracking analysis was feasible in all our study population. Time required for speckle analysis was 133±24 seconds for PCOS group and 129±26 seconds for healthy subjects. Acquisition of 3D-Echo data and analysis took 126±37 seconds per patient.

Inter-and intra-observer variabilityies

Variability in the measurement of GLS was evaluated in 20 randomly selected patients. For intra-observer variability, the same observer measured GLS for each of the selected patients again 10 days later. The coefficients of variation of intra-observer variability for GLS were 3.5%, respectively. For the inter-observer variability, a second independent observer repeated the analysis. The coefficients of variation of inter-observer variability for GLS were 3.6%, respectively.

Discussion

In this observational study was to analyze the changes in LV systolic function in patients with PCOS. We found that patients with PCOS have impaired LV systolic longitudinal function as compared to individuals without PCOS.

LV systolic function is the most commonly assessed by LVEF using C-Echo. However, this technique provides limited data because of challenges related to image quality, assumptions of

Table 3. Correlation between deceleration time, isovolumetric relaxation time and fasting insulin value and HOMA-IR

Variables	Fasting insulin	HOMA-IR
Deceleration time	r=0.348	r=0.372
	p=0.02	p=0.01
Isovolumetric relaxation time	r=0.35	r=0.38
	p=0.02	p=0.008

Spearman and Pearson's correlation analyses
HOMA-IR - homeostasis model assessment - insulin resistance, PCOS - polycystic ovary syndrome

Table 4. Global longitudinal strain

Variable	PCOS (n=30)	Controls (n=30)	*p
Global longitudinal strain, %	-16.78±0.56	-18.36±1.04	<0.001

Results are shown as mean±standard deviation and numbers/percentages
*t-test for independent samples, PCOS - polycystic ovary syndrome

Table 5. The correlation between global longitudinal strain and clinical variables

Variables	Global longitudinal strain	
	r	p
Fasting insulin	0.271	0.06
HOMA-IR	0.277	0.06
Fasting glucose	0.05	0.75
High-density lipoprotein	0.175	0.24
Low-density lipoprotein	0.378	0.008
Triglycerides	0.02	0.89
Waist circumference	0.204	0.15
Waist-to-hip ratio	0.39	0.005
Body mass index	0.153	0.28

Spearman and Pearson's correlation analyses
HOMA-IR - homeostasis model assessment - insulin resistance, PCOS - polycystic ovary syndrome

LV geometry, and operator experience (7-8). 2D-STE is based on tracking of characteristic speckle patterns created by interference of ultrasound beams in the myocardium and its accuracy has been confirmed using sonomicrometry and MRI, tagging as reference methods (16). The development of speckle tracking has advanced the measurement of longitudinal function of the entire ventricle rather than basal segments alone. It is thought that longitudinal contraction is a particular marker of subendocardial function, which may be disproportionately involved in subclinical disease (17). In accordance to this, in the present study PCOS patients had normal LVEF on 3D-Echo, however impaired myocardial strain on 2D-STE, which might be an indicator of subclinical LV dysfunction in this population.

The HUNT study has investigated the normal strain value range in healthy subjects using tissue Doppler and 2D-STE (18). The normal GLS value was found -17.4% (2.3) in females and -15.9% (2.3) in males and strain values were reported to be decreased with the increasing age. In addition, this study showed that strain was overestimated by the 2D-STE method (18.4%) compared with the combined method (17.4%). The mean age of females in HUNT study was 47.8 (13.6) and the strain value in females below 40 years old was -17.9 (2.1). In our study, the average age was 26±5 and the GLS detected by 2D-STE was lower in PCOS group (-16.78±0.56% vs.-18.36±1.04%, p<0.001). As compared to HUNT study, lower GLS values by 2D-STE in a younger population may suggest a subclinical LV systolic dysfunction in this patient group.

There is severe evidence that patients with polycystic ovary syndrome (PCOS) have increased cardiovascular risk compared with age-matched controls. It has been estimated that myocardial infarction is seven times more likely in patients with PCOS (19), and cardiac catheterization studies have shown more extensive coronary artery disease in these patients than in women with normal ovaries (20). This association is actually not surprising because of the higher incidence of obesity, impaired glucose tolerance, overt diabetes mellitus and MetS in this patient population (21). MetS and diabetes mellitus are well known causes of CVD. In addition, obesity by itself is related to atherosclerosis, hypertension and prothrombotic complications (22, 23). Many studies have shown that LDL is increased in women with PCOS (24). Wild et al. (25) found that increased waist/hip ratio and hirsutism were associated with confirmed coronary artery disease. In our study, MetS was detected six patients in PCOS group and four in control group. The fasting glucose, HDL, TG, waist circumference and BMI were similar between two groups while waist-to-hip ratio, insulin, HOMA-IR and LDL levels were higher in PCOS group.

The relative risk of heart failure is greater in obese women than men (26). Obesity contributes to LV dysfunction in various mechanisms, including overproduction of cardioinhibitory cytokines, myocardial fibrosis via up-regulating some neuro-hormones (especially angiotensin II) and chronic volume overload through ventricles (27, 28). However, in the present study there was no difference in BMI between two groups while waist-to-hip ratio was higher in PCOS group, suggesting that the pathogenesis of impaired myocardial function in PCOS patients is not only dependent on BMI. Several previous studies have reported increased arterial stiffness in patients with PCOS related to higher prevalence of hypertension and endothelial dysfunction in these patients (29). Increased stiffness in the central arteries could lead an increase in wall stress in LV cavity and disrupt the structure of longitudinal myocardial fibers, which would result in myocardial dysfunction. Although myocardial strain was impaired in PCOS patients in our study, LVEF measured by 3D echo did not show difference between two groups. In contrast to our study, Prelevic et al. (30) measured LVEF by 2D echocardiography and found that PCOS patients have significantly lower LVEF than normal controls. This difference might have resulted from the different methods used for LVEF measurement in two studies.

Results of the echocardiographic studies were controversial in patients with PCOS. Some previous studies, did not find any significant differences in certain C-Echo and tissue Doppler echocardiographic measures of cardiac function between patients with PCOS and healthy control subjects. EF, mitral E/A ratio, DT, IVRT, tissue Doppler profiles of patients with PCOS were similar to controls (31, 32). However, detrimental effect of PCOS on the cardiovascular system is evident even in young women asymptomatic for cardiac disease. Orio et al. (33) reported that PCOS women had higher LA size, LVMI, lower LVEF and E/A ratio than controls. Also, subclinical impairment of LV systolic and diastolic function as indicated by lower peak strain, peak systolic strain rate, peak early diastolic strain rate, and peak early diastolic velocity was demonstrated in with PCOS and IR group (34). In addition, Prelevic et al. (30) reported that systolic flow velocity is lower in PCOS than in age-matched control women, and there is an inverse relationship between serum fasting insulin and LV systolic outflow parameters; fur-

thermore, increased insulin levels in PCOS are associated with decreased cardiac flow. In the present study, we found waist-to-hip ratio, insulin, HOMA-IR, LDL levels were higher in PCOS group and GLS correlation with the hip-to-waist ratio, LDL values. Insulin resistance plays an important role in the development of PCOS and hyperinsulinemia is a cardinal feature of PCOS (35). LV diastolic dysfunction is an early manifestation of cardiomyopathy and might be related to CVD, hypertension, IR, endothelial dysfunction and oxidative stress (36). Tıraş et al. (37) reported an IVRT were higher in patients with PCOS and significant correlation between IR and LV diastolic function. In our study, mitral E- and A-waves were similar in both groups, and DT, IVRT and E/Em ratio were significantly increased in PCOS group reflecting a trend for diastolic dysfunction. In addition, significant correlation was observed between DT, IVRT and fasting insulin value, HOMA-IR. One would expect that IR in this patient population is also a contributor for development of LV dysfunction

Study limitations

Our study has some limitations. The first limitation of our study was the relatively small number of patients. The limited number of patients in this study may not represent the whole PCOS population. Second, we did the measurements with only longitudinal strain and radial or circumferential strain was not assessed. Third, BNP level was not assessed in the present study. Final, in this study, long-term clinical outcome data, such as cardiovascular event rates and survival assessment, were not part of the present study. However our study leads way in furthering the efforts to understand the connecting links between PCOS and heart disease. Large control studies are needed to understand and validate our results.

Conclusion

PCOS may be related to impaired LV systolic function detected by 2D-STE. In addition PCOS may lead to diastolic dysfunction. Reduced GLS might be an early indicator of cardiac involvement in this patient population. Early detection of asymptomatic impairment of LV systolic function could provide physicians to prevent progression to overt heart failure with counseling the patients to alter the risk profile.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - E.E.; Design - M.A., M.T.; Supervision - E.E., A.B.; Resource - G.B., A.T., M.E., Ş.K.; Material-G.E., M.A.V.; Data collection&/or Processing - E.E., O.S.; Analysis &/or interpretation - H.U.; Literature search - M.A., M.T.; Writing-E.E.; Critical review - Ö.G., H.U.

References

1. Chang RJ, Nakamura RM, Judd HL, Kaplan SA. Insulin resistance in nonobese patients with polycystic ovarian disease. J Clin Endocrinol Metab 1983; 57: 356-9. [CrossRef]
2. Scarpitta AM, Sinagra D. Polycystic ovary syndrome: An endocrine and metabolic disease. Gynecol Endocrinol 2000; 14: 392-5. [CrossRef]
3. Legro RS. Polycystic ovary syndrome and cardiovascular disease: A premature association? Endocr reviews 2003; 24: 302-12. [CrossRef]
4. Shaw LJ, Bairey Merz CN, Azziz R, Stanczyk FZ, Sopko G, Braunstein GD, et al. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: Results from the national institutes of health--national heart, lung, and blood institute sponsored women's ischemia syndrome evaluation. J Clin Endocrinol Metab 2008; 93: 1276-84. [CrossRef]
5. Bauer F, Shiota T, Qin JX, White RD, Thomas JD. Measurement of left atrial and ventricular volume in real-time 3D echocardiography: Validation by nuclear magnetic resonance. Arch Mal Coeur Vaiss 2001; 94: 31-8.
6. Jenkins C, Bricknell K, Hanekom L, Marwick TH. Reproducibility and accuracy of echocardiographic measurements of left ventricular parameters using real-time three-dimensional echocardiography. J Am Coll Cardiol 2004; 44: 878-86. [CrossRef]
7. Marwick TH. Should we be evaluating the ventricle or the myocardium? Advances in tissue characterization. J Am Soc Echocardiogr 2004; 17: 168-72. [CrossRef]
8. Leitman M, Lysyansky P, Sidenko S, Shir V, Peleg E, Binenbaum M, et al. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. J Am Soc Echocardiogr 2004; 17: 1021-9. [CrossRef]
9. Reisner SA, Lysyansky P, Agmon Y, Mutlak D, Lessick J, Friedman Z. Global longitudinal strain: a novel index of left ventricular systolic function. J Am Soc Echocardiogr 2004; 17: 630-3. [CrossRef]
10. Delgado V, Mollema SA, Ypenburg C, Tops LF, Van der Wall EE, Schalij MJ, et al. Relation between global left ventricular longitudinal strain assessed with novel automated function imaging and biplane left ventricular ejection fraction in patients with coronary artery disease. J Am Soc Echocardiogr 2008; 21:1244-50. [CrossRef]
11. Barbosa JA, Mota CC, Simões E Silva AC, Nunes MD, Barbosa MM. Assessing pre-clinical ventricular dysfunction in obese children and adolescents: the value of speckle tracking imaging. Eur Heart J Cardiovasc Imaging 2013 Jan 4. [Epub ahead of print].
12. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004; 81: 19-25. [CrossRef]
13. International Diabetes Federation: The IDF consensus worldwide definition of the metabolic syndrome.
14. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-9. [CrossRef]
15. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation 1977; 55: 613-8. [CrossRef]
16. Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against

sonomicrometry and tagged magnetic resonance imaging. J Am Coll Cardiol 2006; 47: 789-93. [CrossRef]
17. Jones CJ, Raposo L, Gibson DG. Functional importance of the long axis dynamics of the human left ventricle. Br Heart J 1990; 63: 215-20. [CrossRef]
18. Dalen H, Thorstensen A, Aase SA, Ingul CB, Torp H, Vatten LJ, et al. Segmental and global longitudinal strain and strain rate based on echocardiography of 1266 healthy individuals: The HUNT study in Norway. Eur J Echocardiogr 2010; 11: 176-83. [CrossRef]
19. Dahlgren E, Janson PO, Johansson S, Lapidus L, Odén A. Polycystic ovary syndrome and risk for myocardial infarction.Evaluated from a risk factor model based on a prospective population study of women. Acta Obstet Gynecol Scand 1992; 71: 599-604. [CrossRef]
20. Birdsall MA, Farquhar CM, White HD. Association between polycystic ovaries and extent of coronary artery disease in women having cardiac catheterization. Ann Intern Med 1997; 126: 32-5. [CrossRef]
21. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2005; 90: 1929-35. [CrossRef]
22. Despres JP, Moorjani S, Lupien PJ, Tremblay A, Nadeau A, Bouchard C. Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. Arteriosclerosis 1990; 10: 497-511. [CrossRef]
23. Davi G, Guagnano MT, Ciabattoni G, Basili S, Falco A, Marinopiccoli M, et al. Platelet activation in obese women: Role of inflammation and oxidant stress. JAMA 2002; 288: 2008-14. [CrossRef]
24. Legro RS, Kunselman AR, Dunaif A. Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. Am J Med 2001; 111: 607-13. [CrossRef]
25. Wild RA, Grubb B, Hartz A, Van Nort JJ, Bachman W, Bartholomew M. Clinical signs of androgen excess as risk factors for coronary artery disease. Fertil Steril 1990; 54: 255-9.
26. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, et al. Obesity and the risk of heart failure. N Engl J Med 2002; 347: 305-13. [CrossRef]
27. Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH. Alterations of left ventricular myocardial characteristics associated with obesity. Circulation 2004; 110: 3081-7. [CrossRef]
28. Di Bello V, Santini F, Di Cori A, Pucci A, Palagi C, Delle Donne MG, et al. Obesity cardiomyopathy: Is it a reality? An ultrasonic tissue characterization study. J Am Soc Echocardiogr 2006; 19: 1063-71. [CrossRef]
29. Kelly CJ, Speirs A, Gould GW, Petrie JR, Lyall H, Connell JM. Altered vascular function in young women with polycystic ovary syndrome. J Clin Endocrinol Metab 2002; 87: 742-6. [CrossRef]
30. Prelevic GM, Beljic T, Balint-Peric L, Ginsburg J. Cardiac flow velocity in women with the polycystic ovary syndrome. Clin Endocrinol 1995; 43: 677-81. [CrossRef]
31. Tekin A, Tekin G, Çölkesen Y, Kılıcdağ EB, Başhan I, Sezgin AT, et al. Left ventricular function in patients with polycystic ovary syndrome: a Doppler echocardiographic study. Exp Clin Endocrinol Diabetes 2009; 117: 165-9. [CrossRef]
32. Selçoki Y, Yılmaz OC, Çarlıoğlu A, Onaran Y, Kankılıç MN, Karakurt F, et al. Cardiac flow parameters with conventional and pulsed tissue Doppler echocardiography imaging in patients with polycystic ovary syndrome. Gynecol Endocrinol 2010; 26: 815-8. [CrossRef]
33. Orio F Jr, Palomba S, Spinelli L, Cascella T, Tauchmanovà L, Zullo F, et al. The cardiovascular risk of young women with polycystic ovary syndrome: an observational, analytical, prospective case-control study. J Clin Endocrinol Metab 2004; 89: 3696-701. [CrossRef]
34. Kosmala W, O'Moore-Sullivan TM, Plaksej R, Kuliczkowska-Plaksej J, Przewlocka-Kosmala M, Marwick TH. Subclinical impairment of left ventricular function in young obese women: contributions of polycystic ovary disease and insulin resistance J Clin Endocrinol Metab 2008; 93: 3748-54. [CrossRef]
35. Dunaif A, Segal KR, Futterwei W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes 1989; 38: 1165-74. [CrossRef]
36. Brutsaert DL, Sys SU, Gillebert TC. Diastolic failure: Pathophysiology and therapeutic implications. J Am Coll Cardiol 1993; 22: 318-25. [CrossRef]
37. Tıraş MB, Yalçın R, Noyan V, Maral I, Yıldırım M, Dörtlemez O, et al. Alterations in cardiac flow parameters in patients with polycystic ovarian syndrome. Hum Reprod 1999; 14: 1949-52. [CrossRef]