Cardiac Functions and Peripheral Arterial Stiffness in Patients with Polycystic Ovary Syndrome: A Cross-Sectional Study

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Abstract

BACKGROUND/AIMS: Polycystic ovary syndrome (PCOS) patients have been described as having subclinical cardiac and vascular damage; nevertheless, research data is contradictory. We aimed to assess global cardiac functions, peripheral arterial stiffness (AS), and the relationships between echocardiographic and AS measurements in patients with PCOS.

MATERIALS AND METHODS: We enrolled 42 consecutive PCOS patients and 32 age- and body mass index (BMI)-matched healthy controls. All participants underwent a comprehensive two-dimensional echocardiographic examination. Applanation tonometry was utilized to determine peripheral AS [carotid-radial pulse wave velocity (PWV) and augmentation index (AIx)] in each participant. In addition, we evaluated the correlation between AS and echocardiographic parameters.

RESULTS: The PCOS and control groups had similar ages and BMIs. Right ventricular (RV) and left ventricular (LV) diameters, LV mass, and LV ejection fraction were similar between the groups. Considering the pulse wave and tissue Doppler parameters of the cardiac functions, the LV septal S', LV Tei index, RV S', RV Tei index, and E/E' ratio were comparable between the two groups. Peripheral AS parameters including, PWV and AIx were higher in those patients with PCOS [19.3±12.5 vs. 12.5±9.6; p=0.01 and 5 (4.7-5.5) vs. 4.4 (4.2-4.8); p=0.0001, respectively]. AS parameters were not correlated with echocardiographic parameters.

CONCLUSION: Despite normal echocardiographic LV and RV functions, women with PCOS had increased AS. There was no correlation between echocardiographic and AS parameters in these patients.

Keywords: Diastolic and systolic right ventricular functions, diastolic and systolic left ventricular functions, peripheral arterial stiffness, polycystic ovary syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most prevalent endocrinopathies in young females, characterized by excessive androgen levels, multiple cysts in the ovaries, and ovulatory failure.1,2 PCOS is associated with accelerated atherosclerotic cardiovascular (CV) disease due to the high incidence of CV risk factors, including elevated mean blood pressure, dyslipidemia, and impaired response to insulin.3 Nevertheless, the presently available data does not validate that PCOS independently increases the risk of a CV event.4,5 Several studies have
been conducted using various methods, such as echocardiography and the evaluation of arterial stiffness (AS), and it has been shown that these patients have both structural and functional abnormalities.\textsuperscript{3,14} It is generally supposed that these changes may be linked to CV risk factors rather than the presence of PCOS.

AS is a surrogate measure of early morphological and functional changes in vasculature and it is a powerful predictor of subsequent CV outcomes and death rates.\textsuperscript{15} PCOS has been linked with increased AS in various studies using AS measurements, including the common carotid artery stiffness index, carotid-femoral pulse wave velocity (PWV) and the augmentation index (Aix), the cardio-ankle vascular index, and brachial-ankle PWV.\textsuperscript{11-14} Data on the associations between PCOS and carotid-radial (peripheral) AS is limited.

Previous studies also demonstrated that PCOS is linked with left ventricular (LV) diastolic and systolic abnormalities.\textsuperscript{9,10} Echocardiographic findings suggest impaired LV relaxation and early remodeling in PCOS patients. However, there is not enough data on the global right ventricular (RV) functions in PCOS patients.

Thus, we aimed to assess the stiffness of peripheral arteries using applanation tonometry and compare the LV and RV echocardiographic findings of young women with PCOS with control subjects using comprehensive two-dimensional (2D) echocardiography, PW, and tissue Doppler (TD) imaging. We also aimed to determine correlations between echocardiographic measurements and AS parameters.

### MATERIALS AND METHODS

#### Subjects

The calculation of the number of subjects to be included in this study was performed using the G*Power 3.1 program. For 90% statistical power and $\alpha=0.05$ significance level, the smallest sample size required to determine the $d=0.50$ effect size for independent groups according to the t-test was calculated as 33 for the 1\textsuperscript{st} group and 15 for the 2\textsuperscript{nd} group, a total of 48. This study consisted of 42 consecutive PCOS patients and 32 healthy controls with normal menstrual cycles who were matched for age and body mass index (BMI). The exclusion criteria were: smoking; pregnancy; the previous or present use (up to the preceding 3 months) of combined hormonal contraceptives; smoking; pregnancy; the previous or present use (up to the preceding 3 months) of combined hormonal contraceptives, statins, anti-androgens, or hypoglycemic drugs; a history of to the preceding 3 months) of combined hormonal contraceptives, statins, anti-androgens, or hypoglycemic drugs; a history of

All participants provided their written informed consent. Our study was authorized by the Dokuz Eylul University Ethical Examination Board (approval number: 2022/33-11, date: 19.10.2022).

#### Echocardiographic Examination

An experienced cardiologist performed all echocardiographic examinations using a Philips Affinity 50 ultrasound system (Philips, Andover, MA, USA) using a 3.2 MHz transducer. The American Society of Echocardiography’s guidelines for standard 2D echocardiographic measures were followed.\textsuperscript{16} LV linear measurements were obtained using a parasternal long-axis view. Interventricular septum, posterior wall thickness, LV end-diastolic diameter, LV end-systolic diameter, and left atrium (LA) diameter were recorded. The Devereux formula was used for the LV mass calculation. LV volumes and ejection fraction (LVEF) were determined using the biplane summation-of-disks method. The left atrial (LAA) and right atrial (RAA) areas were calculated at end-systole from the apical four-chamber (4C) view. The RV-focused apical 4C view was used for the linear longitudinal end-diastolic dimension of RV (RVD), RV fractional area change (RVFAC) was calculated as (end-diastolic area-end-systolic area)/(end-diastolic area) x 100%.\textsuperscript{17} In the apical 4C view, an M-mode cursor was placed down the RV free wall to the lateral tricuspid annulus. The maximum length of tricuspid annulus movement during systole was specified as tricuspid annular plane systolic excursion (TAPSE).

PW Doppler was utilized for measuring the mitral flow velocities. The early diastolic peak E wave (E), atrial contraction wave (A), and E wave deceleration time (EDT) were measured and the E/A ratio was calculated. TD imaging was utilized to record the velocities of the mitral and tricuspid annulus. LV systolic (LV S') and LV diastolic (LV E') velocities were recorded. For diastolic LV filling performance, E/E' was calculated. RV systolic (RV S') and RV diastolic (RV E') velocity waveforms were also recorded.

TD velocity waveforms were also used to calculate the Tei indices. The RV Tei index was determined by dividing the ejection duration by the sum of the contraction time and isovolumetric relaxation duration.\textsuperscript{17} A similar method was also used for the determination of the LV Tei index.

#### Measurement of Arterial Stiffness

SphygmoCor applanation tonometry was used to measure the waveforms of the radial artery pressure (AtCor Medical, West Ryde, NSW, Australia). The apparatus automatically measured central aortic pressure, pulse pressure (PP), Aix, and aortic pressure augmentation.\textsuperscript{18} Aortic pressure augmentation was divided by PP to calculate Aix. By sequentially recording carotid and radial artery waveforms which were electrocardiography-gated, the same device determined the aortic pulse wave velocity (AoPWV). The length of the pathway was measured with a tape measure. The length pathway was measured as (the distance between the radial artery and the suprasternal notch) - (the distance between the carotid artery and the suprasternal notch). The AoPWV was calculated by dividing this length by the transit time. Echocardiographic examination and AS measurements were made consecutively in each participant during the morning fasting period.

#### Statistical Analysis

SPSS version 26 from SPSS Inc., Chicago, IL, was used for statistical analysis. Histograms and the Kolmogorov-Smirnov test were used for assessing normal distribution. Continuous variables are represented as means ± standard deviations and medians (interquartile range). To analyze between-group differences, the Mann-Whitney U test was used when the data were not normally distributed, and Student's t-test was used when the data were normally distributed. Correlations between echocardiographic data and AS parameters were determined by Pearson correlation analysis. All tests were two-sided, and $p<0.05$ was considered statistically significant.
RESULTS

The demographics and laboratory findings of the PCOS and control groups are shown in Table 1. Age, BMI, diastolic and systolic arterial pressure, and laboratory findings were similar between the two groups (p>0.05 for all).

The echocardiographic findings of the two groups are shown in Table 2. Among the conventional 2D echocardiographic parameters, LV diameters, LVEF, LV mass, LAA, RV diameter, RV FAC, and RAA were similar between the two groups (Table 2). Also, among the TD and PW Doppler findings; LV S’, RV S’, LV and RV Tei indices, and E/E’ were similar between the groups (Table 2).

Table 3 shows the AS parameters in the PCOS and control groups. AIx and AoPWV were elevated in the PCOS group compared to the controls [19.3±12.5 vs. 12.5±9.6; p=0.01 and 5 (4.7-5.5) vs. 4.4 (4.2-4.8); p=0.0001, respectively].

The correlation between the AIx and echocardiographic parameters in the PCOS group is presented in Figure 1. Among the global LV function parameters, no correlation was found between AIx and LVEF (r=0.14, p=0.37), LV Tei index (r=-0.27, p=0.07), E/A (r=-0.23, p=0.14) and E/E’ (r=-0.21, p=0.17). Similarly, AIx was not correlated with RV FAC (r=-0.02, p=0.88), TAPSE (r=0.08, p=0.61), RV S’ (r=0.19, p=0.22), and RV Tei index (r=0.03, p=0.81).

Table 1. Baseline clinical characteristics and laboratory findings

<table>
<thead>
<tr>
<th></th>
<th>PCOS, (n=42)</th>
<th>Controls, (n=32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age†</td>
<td>23 (21-25)</td>
<td>23 (21-27)</td>
<td>0.74</td>
</tr>
<tr>
<td>Body mass index*</td>
<td>23.3±5.3</td>
<td>23.7±5.2</td>
<td>0.77</td>
</tr>
<tr>
<td>Systolic blood pressure† (mmHg)</td>
<td>110 (98-125)</td>
<td>110.5 (104-129)</td>
<td>0.21</td>
</tr>
<tr>
<td>Diastolic blood pressure† (mmHg)</td>
<td>70.5 (68-80)</td>
<td>73 (70-80)</td>
<td>0.57</td>
</tr>
<tr>
<td>Glucose* (mg/dL)</td>
<td>93±5</td>
<td>91.7±6.8</td>
<td>0.07</td>
</tr>
<tr>
<td>Creatinine* (mg/dL)</td>
<td>0.8±0.12</td>
<td>0.78±0.12</td>
<td>0.54</td>
</tr>
<tr>
<td>AST† (U/L)</td>
<td>22 (16-29)</td>
<td>23 (16-30)</td>
<td>0.94</td>
</tr>
<tr>
<td>ALT† (U/L)</td>
<td>30 (25-35)</td>
<td>28 (25-31)</td>
<td>0.25</td>
</tr>
<tr>
<td>LDL-C* (mg/dL)</td>
<td>92.3±13.7</td>
<td>88.2±15.6</td>
<td>0.48</td>
</tr>
<tr>
<td>HDL-C* (mg/dL)</td>
<td>51 (45-60)</td>
<td>53.5 (48-62)</td>
<td>0.42</td>
</tr>
<tr>
<td>Total cholesterol* (mg/dL)</td>
<td>167±19</td>
<td>172±15</td>
<td>0.23</td>
</tr>
<tr>
<td>Triglyceride* (mg/dL)</td>
<td>117 (89-132)</td>
<td>122.5 (98-137)</td>
<td>0.16</td>
</tr>
<tr>
<td>Hemoglobin† (mg/dL)</td>
<td>12.8 (12.3-13.4)</td>
<td>12.7 (11.8-13.1)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

*: Mean ± standard deviation, †: Median (interquartile range). AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDL-C: Low-density lipoprotein-cholesterol, HDL: High-density lipoprotein-cholesterol, PCOS: Polycystic ovary syndrome.

Table 2. Comparison of echocardiographic parameters between PCOS and control groups

<table>
<thead>
<tr>
<th></th>
<th>PCOS, (n=42)</th>
<th>Controls, (n=32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD† (mm)</td>
<td>42 (41-44)</td>
<td>44 (40-47)</td>
<td>0.09</td>
</tr>
<tr>
<td>LVESD† (mm)</td>
<td>26 (25-28)</td>
<td>27 (25-31)</td>
<td>0.10</td>
</tr>
<tr>
<td>LVEF* (%)</td>
<td>64.7±6.3</td>
<td>62.7±7.8</td>
<td>0.21</td>
</tr>
<tr>
<td>LV mass* (g)</td>
<td>111.7±27.6</td>
<td>111.8±25.8</td>
<td>0.20</td>
</tr>
<tr>
<td>LV E/A*</td>
<td>1.4±0.2</td>
<td>1.5±0.2</td>
<td>0.08</td>
</tr>
<tr>
<td>LV EDT† (mson)</td>
<td>190 (177-217)</td>
<td>193 (165-217)</td>
<td>0.72</td>
</tr>
<tr>
<td>LV E/E’ ratio*</td>
<td>6.5±1.3</td>
<td>7.0±1.9</td>
<td>0.18</td>
</tr>
<tr>
<td>LV S† (cm/s)</td>
<td>10.9 (10.4-11.2)</td>
<td>10.8 (10.3-12)</td>
<td>0.77</td>
</tr>
<tr>
<td>LV Tei index* (%)</td>
<td>39±8</td>
<td>40±8</td>
<td>0.50</td>
</tr>
<tr>
<td>Left atrial area† (cm²)</td>
<td>16.1 (14.9-18.6)</td>
<td>18 (14.9-21)</td>
<td>0.20</td>
</tr>
<tr>
<td>RVd† (mm)</td>
<td>24 (23-26)</td>
<td>25 (24-26)</td>
<td>0.21</td>
</tr>
<tr>
<td>RV FAC* (%)</td>
<td>52.8±6.4</td>
<td>55.1±5.3</td>
<td>0.10</td>
</tr>
<tr>
<td>TAPSE* (mm)</td>
<td>22±2.7</td>
<td>22±2</td>
<td>0.94</td>
</tr>
<tr>
<td>RV S† (cm/s)</td>
<td>16.6±2.5</td>
<td>17.4±3.7</td>
<td>0.25</td>
</tr>
<tr>
<td>RV Tei index* (%)</td>
<td>30±10</td>
<td>28±6</td>
<td>0.38</td>
</tr>
<tr>
<td>RV E’ (cm/s)</td>
<td>17.6±3.3</td>
<td>16.9±3.7</td>
<td>0.23</td>
</tr>
<tr>
<td>Right atrial area† (cm²)</td>
<td>13.4±2.5</td>
<td>13.6±2.8</td>
<td>0.41</td>
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</table>

The correlation between the AoPWV and echocardiographic parameters in the PCOS group are presented in Figure 2. Among the LV parameters, AoPWV was not correlated with LVEF (r=0.06, p=0.69), the LV Tei index (r=0.24, p=0.12), E/A (r=-0.24, p=0.12) or E/E' (r=-0.15, p=0.34). Similarly, AoPWV was not correlated with RV FAC (r=-0.16, p=0.32), TAPSE (r=0.04, p=0.79), RV S' (r=0.008, p=0.96), or the RV Tei index (r=-0.01, p=0.50).

**DISCUSSION**

Our study revealed that PCOS patients have increased peripheral AS despite preserved echocardiographic LV and RV functions even without the frequently associated traditional CV risk factors. AS parameters and echocardiographic measurements were not correlated among the PCOS subjects.

Previous reports have suggested that PCOS is linked with larger LA diameter, increased LV mass index, increased EDT, and E/E' ratio. 7-10

<table>
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<th>Table 3. Comparison of arterial stiffness parameters between groups</th>
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<td></td>
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<tr>
<td>AIx (%)</td>
</tr>
<tr>
<td>AoPWV† (m/sn)</td>
</tr>
</tbody>
</table>

*: Mean ± standard deviation, †: Median (interquartile range), AIx: Augmentation index, AoPWV: Aortic pulse wave velocity, PCOS: Polycystic ovary syndrome.

**Figure 1.** Correlations between AIx and LV and RV systolic and functions.

AIx: Augmentation index, LV: Left ventricular, RV: Right ventricular, FAC: Fractional area change, RV S': RV systolic, A: Atrial contraction wave, E: The early diastolic peak E wave, E': Diastolic velocity.

**Figure 2.** Correlations between AoPWV and LV and RV systolic and diastolic functions.

AoPWV: Aortic pulse wave velocity, LV: Left ventricular, RV: Right ventricular, FAC: Fractional area change, RV S': RV systolic, A: Atrial contraction wave, E: The early diastolic peak E wave, E': Diastolic velocity.
These changes in echocardiographic findings suggest abnormalities in the diastolic filling of the LV and impaired LV relaxation. Wang et al.\(^9\) concluded that these women’s increased LV mass index may correspond to early remodeling before overt cardiac dysfunction. However, similar to our discoveries, Tekin et al.\(^19\) and Selcuki et al.\(^20\) demonstrated no significant discrepancies in LV and LA diameters, LVEF, EDT, or E/A ratio between patients with PCOS and controls. The discrepancies between these results may have been associated with the underlying differences in BMI and insulin resistance in the different studies.

Previous research has demonstrated that BMI is a reliable predictor of LV E’ dysfunction\(^1\) and a reduction in BMI is linked to a substantial decrease in E’ velocity and the LA volume index.\(^2\) As the mean BMI in the patients of our study is lower than in the previous reports,\(^3,10\) this may explain the conflicting results in impaired diastolic function in the PCOS group. We noted no differences in respect to LV mass between the PCOS and the control groups. Rashid et al.\(^7\) revealed that non-obese, normotensive PCOS patients had considerably larger LV mass and LV mass index than the control group, but they also found considerable overlap in the values of serum insulin and impaired response to insulin and LV mass index. They concluded that the elevated LV mass index values in PCOS patients might be explained by the direct mitogenic effect of insulin.\(^7\) The CARDIA Women’s study\(^8\) showed that LV mass index was increased in PCOS patients in comparison to controls, but the BMI values in that cohort were higher than in our population and the diagnostic criteria of PCOS were also different.

It has been shown that the Tei index is an easily measured and reliable method for evaluating both LV and RV S’ and diastolic myocardial performance.\(^17,21\) Unlike previous reports, we demonstrated that LV and RV Tei indices were similar between the PCOS and control groups. We also showed that RV functions in terms of RVFAC, RV S’, RV E’, and TAPSE were comparable between the two groups. To the best of our knowledge, this is the first preliminary report suggesting that both LV and RV E’ and systolic functions were similar in PCOS patients and control subjects.

Controversial data exist concerning whether PCOS raises CV disease risk. A meta-analysis including more than 100,000 individuals suggested that PCOS was linked to elevated CV disease risks.\(^4\) Additionally, a population-based retrospective analysis also showed that PCOS was associated with more ischemic heart disease.\(^5\) In contrast, a discrete meta-analysis proposed that PCOS were also different.

It is demonstrated that peripheral AS is an important CV risk factor.\(^11,35\) AS parameters including Axl and AoPWV were not correlated with CV and LV E’ and systolic functions in subjects with PCOS. A study conducted by Higashi et al.\(^36\) concluded that in atherosclerosis-free healthy subjects, AS measured by brachial-ankle PWV and carotid Axl was significantly associated with E’ in both males and females and E/E’ solely in females. The participants in our study were younger than those in the prior study, had lower values of Axl, and had lower diastolic and systolic blood pressures. These divergencies in baseline features and AS parameters might account for the differences in correlations.

**Study Limitations**

The limitations of this study were as follows; firstly, our study cohort had low BMI, younger age, normal diastolic and systolic blood pressures, and low plasma lipids, which may not represent an exact PCOS patient population. Secondly, as we used a cross-sectional sample, we could only establish an association between AS and PCOS. Thirdly, the echocardiographic data were limited to 2D, PW, and TD measurements and did not include more reliable speckle-tracking echocardiography and volumetric measurements. Fourthly, we could not demonstrate the effects of androgens, sex hormones, or ovulation time on AS parameters. Finally, the lack of assessment of insulin resistance and central AS may have affected our results. However, radial Axl was strongly correlated with carotid Axl in apparently healthy subjects, and radial Axl is a potential alternative marker of CV disease.\(^37\)

**CONCLUSION**

This research revealed that females with PCOS have normal LV and RV diastolic and systolic functions, specifically presented with LV and RV Tei indices. These women also have increased peripheral AS despite the lack of commonly associated traditional CV risk factors and obesity. Future research is warranted to determine if PCOS individuals with higher peripheral AS and no risk factors are at an elevated risk of future CV events.
MAIN POINTS

- This study demonstrated that both left ventricular and right ventricular global (both systolic and diastolic) functions are preserved in young, cardiovascular risk factors-free PCOS patients with respect to control subjects.
- This is the first study which applies both left and right ventricular myocardial work quantification by echocardiography through the Tei index in PCOS patients.
- The literature presents limited data on the associations between PCOS and carotid-radial (peripheral) arterial stiffness. We studied carotid-radial (peripheral) arterial stiffness in PCOS patients and compared both arterial stiffness and echocardiographic parameters with control subjects.
- We also revealed correlations between peripheral arterial stiffness and echocardiographic parameters.

ETHICS

Ethics Committee Approval: Our study was authorized by the Dokuz Eylül University Ethical Examination Board (approval number: 2022/33-11, date: 19.10.2022).

Informed Consent: All participants provided their written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions


DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study had received no financial support.

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