Alterations in cardiac flow parameters in patients with polycystic ovarian syndrome

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The aim of this study was to examine the echocardiographic profiles of patients with polycystic ovarian syndrome (PCOS). Serum concentrations of follicle stimulating hormone, luteinizing hormone, androstenedione, free testosterone, prolactin, DHEA-SO4 and 17-OH-progesterone, lipid profile (high and low density lipoproteins, triglyceride and total cholesterol) and basal and total insulin after a glucose tolerance test were measured in 35 patients with PCOS and 35 healthy controls matched for body mass index. Doppler, two dimensional M mode echocardiography was performed for the following indices: isovolumetric relaxation time (IVRT), E wave duration time (EVT), A wave duration time (AVT), E wave deceleration time (DT), peak early diastolic flow velocity (PEV), peak late diastolic flow velocity (PAV), E wave velocity time integral (FVI-E), A wave velocity time integral (FVI-A), atrial filling fraction (AFF), ejection fraction (EF), pre-ejection time (PEP), ejection time (ET) and aortic flow velocity time integral (FVI). Androstenedione, free testosterone, low density lipoproteins and cholesterol concentrations were significantly higher in patients with PCOS. There was no difference in basal and total insulin concentrations. IVRT, AVT, FVI-A, AFF and PEP were higher in patients with PCOS, while PEV, FVI-E, EF, ET, EVT and EVT/AVT were higher in the control group. There was a positive correlation between basal insulin values and IVRT, and between total insulin values and EF. These changes are consistent with a non-restrictive type of diastolic dysfunction and left ventricular stiffness. PCOS may lead to diastolic dysfunction via hyperinsulinaemia and male type dyslipidaemia.

Key words: cardiac flow/male type dyslipidaemia/PCOS

Introduction

Polycystic ovarian syndrome (PCOS) is a common endocrinological disorder affecting women of reproductive age. Its hallmarks are hyperandrogenism and ovulatory dysfunction. However, disorders such as non-classical adrenal 21 hydroxylase deficiency, hyperprolactinaemia and androgen secreting neoplasms should first be excluded (Barbieri, 1991; Dunaif, 1997). Hyperinsulinaemia and insulin resistance may also be present in both lean and obese women with PCOS (Wild, 1995).

Several lines of evidence suggest that women with PCOS have an increased risk of cardiac disease secondary to hyperandrogenism, insulin resistance or adverse lipid profiles (Wild, 1995). Insulin resistance is considered to be a risk factor for coronary heart disease as it is associated with non-insulin dependent diabetes mellitus, hypertension and dyslipidaemia (Conway et al., 1992). The presence of a male pattern of distribution of lipoprotein lipids in women with PCOS could potentially place them at greater risk for atherosclerotic vascular disease (Conway et al., 1992).

The concept of metabolic syndrome X, which has a characteristic metabolic profile, has also been proposed: hyperinsulinaemia, glucose intolerance, hypertriglyceridaemia, reduced high density lipoprotein (HDL) concentrations and hypertension (Reaven, 1988; Barbieri and Hornstein, 1988). Thus, PCOS and metabolic syndrome X may be variants of the same disease.

Hyperinsulinaemic women with PCOS have a significant risk of early cardiovascular disease. Atherosclerotic vascular disease and increased left ventricular mass may appear at an early stage in these patients (Conway and Jacobs, 1993).

The aim of the study was to compare the echocardiographic profiles of patients with PCOS with those of healthy subjects, to identify the presence of any abnormalities that may predispose them to cardiac disease.

Materials and methods

Study population

The study group consisted of 35 consecutive women with PCOS who presented at our clinic with infertility or hyperandrogenism. The control group consisted of 35 healthy volunteer female medical students. Institutional Review Board (IRB) approval was obtained before the study was commenced. All patients and control subjects provided informed consent for the study.

The diagnostic criteria for PCOS included hirsutism and biochemical evidence of androgen excess [i.e., elevated serum testosterone (free > 3.18 pg/ml) and/or androstenedione (>2.4 ng/ml) concentrations], menstrual cycle disturbances such as oligomenorrhoea and amenorrhoea (cycle length > 35 days) and ultrasonographic documentation of enlarged ovaries with multiple small subcortical follicles and increased stroma (Adams et al., 1985). Clinical hyperandrogenism was documented during the physical examination. The extent of hirsutism was quantified by the Ferrimann–Gallwey scoring system (Ferrimann and Gallwey, 1961). Cushing’s syndrome and non-classical 21 hydroxylase deficiency were excluded if clinically suspected by a
1 mg overnight dexamethasone suppression test and a 1 h adrenocorticotropic hormone (ACTH) stimulation test respectively. A transvaginal or transabdominal pelvic ultrasound examination was performed on each subject.

The control group included healthy women with regular menstrual cycles of 28 days, no hirsutism and no ultrasonographic findings indicative of PCOS.

The control group was matched for age and body mass index (BMI).

Biochemical analysis
Blood samples were obtained on the third day of the menstrual cycle, except in those with amenorrhoea, for measurement of follicle stimulating hormone (FSH), luteinizing hormone (LH), oestradiol, prolactin, dehydroepiandrosterone sulphate (DHEA-S), progesterone, androstenedione, 17-OH-progesterone (17-OH-P) and free testosterone concentrations. These tests were performed using standard radioimmunoassays.

Serum HDL, low density lipoprotein (LDL), triglyceride and total cholesterol concentrations were measured using standard enzymatic assays.

All participants underwent a 100 g oral glucose tolerance test (OGTT) at 08:00 or 09:00 h after having fasted for at least 12 h (Chang et al., 1983). After a venous blood sample was obtained for fasting glucose and insulin, 100 g glucose was ingested and further blood samples were obtained at 60, 120 and 180 min later. Total insulin concentrations were calculated as the sum of basal, 60, 120 and 180 min values (Antilla et al., 1993), and related to the results of the OGTT.

Echocardiographic and Doppler measurements
All participants underwent echocardiography, the cardiologists being unaware of the condition of the subject. This was performed using an imager system (General Electric 5600 KT®, Wisconsin, USA) with transducer frequency of 2.5 MHz. Doppler signals (two dimensional M mode) were recorded simultaneously. The aortic flow velocity profile was obtained from the apical four chamber view and transmural flow was obtained at the level of the mitral annulus.

Echocardiographic measurements included isovolumetric relaxation time (IVRT), E wave duration time (EVT), A wave duration time (AVT), E wave deceleration time (DT), peak early diastolic flow velocity (PEV), peak late diastolic flow velocity (PAV), PEV/PAV ratio, E wave velocity time integral (FVI-E), A wave velocity time integral (FVI-A), atrial filling fraction (AFF), ejection fraction (EF), pre-ejection time (PEP), ejection time (ET) and aortic flow velocity time integral (FVI).

IVRT was measured using continuous wave Doppler by aiming the Doppler beam at an intermediate position between inflow and outflow so that both velocities could be recorded.

Statistics
All parametric results are expressed as mean ± SD for each group. Differences between means were analysed by Student’s unpaired t-test using two-tailed tests of significance.

Correlation analyses of androgen, lipid and insulin values and echocardiographic parameters were performed using Pearson’s correlation coefficient (r). Linear regression analyses were performed in which each of the echocardiographic measures was tested separately against the independent variables androgen, lipid and insulin values to identify the optimal predictive model.

Results
The characteristics of the patient and the control groups are outlined in Table I. The groups were adequately matched for age and body mass index (BMI). The Ferrimann–Gallway score was significantly higher in women with PCOS. The basal FSH, LH, androstenedione and free testosterone concentrations were also significantly higher in women with PCOS. In contrast, no statistically significant differences were found in oestradiol, prolactin, DHEA-S, progesterone and 17-OH-P concentrations between the two groups. The mean concentrations of HDL and triglyceride did not differ between the two groups. However LDL and total cholesterol levels were significantly higher in the group with PCOS.

The results of the glucose tolerance test and insulin analysis are shown in Table II. Glucose intolerance was not observed in any woman. Basal insulin values were similar and there was no statistically significant difference in total insulin concentration between the groups.

The echocardiographic parameters of the patient groups are shown in Table III. IVRT, FVI-A, AFF and PEP were found to be significantly higher and peak E, FVI-E, EF and ET were found to be significantly lower in the women with PCOS.
Table III. Echocardiographic parameters of patients with PCOS and control subjects

<table>
<thead>
<tr>
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<th>PCOS (n = 35)</th>
<th>Control (n = 35)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>IVRT (ms)</td>
<td>119.02 ± 32.15</td>
<td>81.85 ± 14.50</td>
<td>0.001</td>
</tr>
<tr>
<td>EVT (ms)</td>
<td>231.08 ± 60.82</td>
<td>211.1 ± 28.18</td>
<td>NS</td>
</tr>
<tr>
<td>AVT (ms)</td>
<td>163.08 ± 58.10</td>
<td>169.11 ± 44.14</td>
<td>NS</td>
</tr>
<tr>
<td>DT (ms)</td>
<td>177.14 ± 51.95</td>
<td>172.85 ± 25.16</td>
<td>NS</td>
</tr>
<tr>
<td>PEV (cm/s)</td>
<td>78.88 ± 21.64</td>
<td>90.72 ± 17.75</td>
<td>0.015</td>
</tr>
<tr>
<td>PAV (cm/s)</td>
<td>55.64 ± 23.99</td>
<td>58.81 ± 22.36</td>
<td>NS</td>
</tr>
<tr>
<td>E/A</td>
<td>1.61 ± 0.62</td>
<td>1.73 ± 0.71</td>
<td>NS</td>
</tr>
<tr>
<td>FVI-E (cm)</td>
<td>9.28 ± 3.98</td>
<td>12.02 ± 2.94</td>
<td>0.002</td>
</tr>
<tr>
<td>FVI-A (cm)</td>
<td>6.58 ± 3.37</td>
<td>5.12 ± 2.05</td>
<td>0.032</td>
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<tr>
<td>AFF</td>
<td>0.40 ± 0.10</td>
<td>0.29 ± 0.70</td>
<td>0.001</td>
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<tr>
<td>EF (%)</td>
<td>74.31 ± 6.77</td>
<td>78.17 ± 4.70</td>
<td>0.007</td>
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<tr>
<td>PEP (ms)</td>
<td>60.74 ± 18.99</td>
<td>39.45 ± 4.85</td>
<td>0.001</td>
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<tr>
<td>ET (ms)</td>
<td>212.40 ± 88.25</td>
<td>243.54 ± 35.05</td>
<td>NS</td>
</tr>
<tr>
<td>Peak V (m/s)</td>
<td>1.02 ± 0.63</td>
<td>1.01 ± 0.47</td>
<td>NS</td>
</tr>
<tr>
<td>FVI (cm)</td>
<td>15.30 ± 5.30</td>
<td>16.70 ± 2.45</td>
<td>NS</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD.

NS = not significant; IVRT = isovolumetric relaxation time; EVT = E wave duration time; AVT = A wave duration time; DT = E wave deceleration time; PEV = peak early diastolic flow velocity; PAV = peak aortic flow velocity; FVI-E = E wave velocity time integral; FVI-A = A wave velocity time integral; AFF = atrial filling fraction; EF = ejection fraction; PEP = pre-ejection time; ET = ejection time; FVI = aortic flow velocity time integral; Peak V = peak aortic flow velocity; E/A = PEV/PAV.

Discussion

Our findings suggest that there are significant differences in certain echocardiographic measures between patients with PCOS and controls. This may reflect the fact that patients with PCOS are candidates for early cardiovascular disease. Although the risk of cardiovascular disease is increased in PCOS, data from cohort studies indicate that mortality is not increased (Pierpoint et al., 1998).

In a recent study of 16 premenopausal women >40 years old who had a history of clinical polycystic ovarian syndrome, it was found that their carotid artery mean intima-media thickness was significantly greater than those of controls. Hence, women with PCOS may have an increased risk of subclinical atherosclerosis (Guzick et al., 1996).

In addition to its association with hyperandrogenism, anovulation and infertility, PCOS is also associated with a number of cardiovascular disease risk factors including obesity, arteriolar nephrosclerosis, insulin resistance and dyslipidaemia (Wild, 1995). Insulin resistance was observed to be a prominent abnormality in both obese and lean patients with hyperandrogenism and PCOS (Jialal et al., 1987).

There is ongoing debate as to whether hyperandrogenism occurs before or after insulin resistance. Women with prolonged hyperinsulinaemia of exogenous source or those with insulinaemia do not develop hyperandrogenism (Bjorntorp, 1996). On the other hand, testosterone administration to normal, transsexual women or to female rats is followed by insulin resistance. Therefore, it seems likely that hyperandrogenism occurs first (Zimmerman et al., 1992; Bjorntorp, 1996).

Dyslipidaemia has also been reported in patients with PCOS, with higher mean serum triglyceride and lower mean serum HDL values (Wild, 1995). Insulin is a major positive regulator of lipoprotein lipase which is involved in the pathway of HDL production. A male type pattern of lipoprotein lipid concentrations is associated with an increased risk of coronary artery disease. Dyslipidaemia is thought to be secondary to insulin resistance, but it has been proposed that hyperandrogenism may affect lipoproteins and lipids independently of insulin concentration and body weight (Wild et al., 1985). Also various hormonal changes associated with PCOS may contribute to changes in blood lipid concentrations (Wild et al., 1985; Nader, 1991).
Recent studies suggest that leptin does not play a major role in the endocrine and metabolic aberrations of PCOS, serum leptin concentrations being almost exclusively determined by the total amount of body fat (Gennarelli et al., 1998).

To eliminate obesity as a factor in the evaluation of insulin secretion, the patient and control groups were matched for BMI. Both clinical and biochemical hyperandrogenism were present in the patients, who had both higher Ferrimann–Gallwexy scores and higher serum free testosterone and androstenedione concentrations.

LH/FSH ratios were not higher than in the control group (Antilla et al., 1991). The lipid profile demonstrated higher total cholesterol and LDL concentrations but, in contrast to earlier results, HDL and triglyceride concentrations were not statistically significantly different (Bjorntorp, 1996). There was no difference between basal and total insulin concentrations, but mean total insulin was a little higher in the patients with PCOS.

The echocardiographic parameters can be divided into two groups based on diastolic and systolic function. Long IVRT, high PAV, long AVT, short EVT, low FVI-E, high FVI-A, high AFF and ratio of E/A and FVI-E/FVI-A which are associated with systolic dysfunction (Stamm et al., 1982). The PCOS group had higher FVI-A, IVRT, AFF and lower FVI-E and FVI-E/FVI-A which are related to left ventricular stiffness and incomplete diastolic relaxation. These findings are consistent with a non-restrictive type diastolic dysfunction.

It is known that diastolic dysfunction might be one of the first echocardiographic abnormalities in patients with hypertension and atherosclerotic cardiovascular disease (Lin et al., 1988). Since patients with PCOS are known to be candidates for increased cardiovascular risk, it might be thought that the documented diastolic dysfunction may be an early finding for coronary heart disease in patients with PCOS.

In order to evaluate the causal relationship between PCOS and diastolic function disturbance we performed correlation and regression analysis of all mean hormone and lipid concentrations and basal and total insulin concentrations, separately with each echocardiographic parameter. We found a linear relationship between total insulin concentrations and IVRT. A further study will compare echocardiographic findings in women with PCOS and insulin resistance with those with PCOS and no insulin resistance.

Diastolic dysfunction may be related to physiological conditions including high salt intake, tachycardia, old age or other factors including aortic stenosis, pericardial tamponade, ischaemic cardiac disease and hypertension that may cause left ventricular hypertrophy (Choong et al., 1987; Lin et al., 1988). In patients with PCOS, diastolic dysfunction may be both a sign of future hypertension and a component of syndrome X together with hyperinsulinaemia, dyslipidaemia and hypertension.

In conclusion, echocardiographic findings suggest that patients with PCOS have diastolic dysfunction. Longitudinal follow-up studies are needed to clarify whether this dysfunction might be an early indicator of coronary heart disease or hypertension in these patients.

References


Received on January 7, 1999; accepted on April 29, 1999.