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PWV IN PCOS' PATIENTS (VOP EM PACIENTES COM SOP)

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Abstract: Introduction: Pulse wave velocity (PWV) is a simple, non-invasive and reproducible method of assessing arterial stiffness that is an independent cardiovascular risk factor and a predictor of morbidity and mortality in some groups. Patients with polycystic ovary syndrome form a heterogeneous group and are at risk of presenting risk factors for cardiovascular diseases. We evaluated the PWV in a group of women with PCOS in childbearing age using the values according to age group to determine the proportion of patients with altered exams and correlated with clinical characteristics and comorbidities of this population. **Materials and Methods:** A cross-sectional study at the endocrinology outpatient Clinic of the Clementino Fraga Filho University Hospital with women aged 18 - 45 years diagnosed with PCOS. Patients met the Rotterdam criteria for PCOS. Previous diagnosis of arterial hypertension, diabetes and dyslipidemia, as well as the use of medications for those were exclusion criteria. We evaluated PWV by the Sphygmocor-branded apparatus. We considered the value of PWV > 10 m/s as altered regardless and compared the values by the predicted for patients ages. **Results:** The study included 32 patients with PCOS. Seventeen patients had higher PWV values than predicted for their ages, making up 53% of our population, but all with PWV below 10m/s. The variables weight and BMI presented a tendency to statistical significance ($p = 0.06$ and $P = 0.09$). The other variables analyzed were similar in both groups. There was no positive correlation between altered PWV with the presence or absence of metabolic syndrome or with the phenotype of polycystic ovary syndrome. **Conclusion:** Our population presented with elevated PWV values compared to the predicted for their ages. Our results suggest that there is a possible correlation between the weight and

BMI of patients with PCOS with increased PWV values.

Keywords: PCOS, PWV, Cardiovascular risk, obesity, arterial stiffness.

INTRODUCTION

The role of arterial stiffness as an independent cardiovascular risk factor and predictor of morbidity and mortality has already been demonstrated in several groups such as patients with chronic renal failure(1), the elderly(2) and patients with diabetes(3).

Pulse wave velocity (PWV) is a simple, non-invasive and reproducible method, considered the gold standard for the evaluation of arterial stiffness. Its measurement is determined by the delay of time (t) between the beginning of the arterial pulse wave recorded at two distinct locations of the wave propagation path and the distance (D) between those two points with results given in meters/second (m/s). In the literature, PWV of 10 m/s is routinely used as the cutoff value to consider patients as having increased arterial stiffness. (4, 5)

As arterial stiffness increases with age, several studies have attempted to establish age-based cutoff points, which would be useful in assessing arterial stiffness in younger populations who could be at risk for cardiovascular disease. (6-8)

Polycystic ovarian syndrome (PCOS) is the most prevalent endocrinopathy in women of childbearing age, affecting 6% to 20 % of this population depending on the diagnostic criteria used.(9-11)

PCOS patients are at greater risk of presenting cardiovascular risk factors such as diabetes, hypertension and obesity, besides insulin resistance being a hallmark of this population. Despite the higher prevalence of cardiovascular risk factors in this population, to date there are no outcome studies showing a greater amount of cardiovascular events and long-term studies are still needed to determine patients who would benefit from primary prevention measures for cardiovascular diseases(12).

Studies involving PCOS' patients and PWV are scarce and results are conflicting, with some studies showing no differences in comparison to the general population (13) while others do(14). In our study, we evaluated women in childbearing age with polycystic ovarian syndrome using PWV's cut-off values according to their age to determine the proportion of patients with altered exams and attempted to correlate with clinical characteristics and comorbidities of that population.

MATERIALS AND METHODS

This cross-sectional cohort study was carried out in a group of women with polycystic ovarian syndrome ages between 18 – 45 years who voluntarily sought out the endocrinology outpatient clinic of Clementino Fraga Filho University Hospital (HUCFF). All patients who sought consultation at the outpatient clinic and fulfilled inclusion criteria were invited consecutively to participate in the study. We evaluated every patient that agreed to participate and signed the informed consent.

Patients were informed that they were free to withdraw their consent at any time during the follow-up. The Ethics and Research Committee of Clementino Fraga Filho University Hospital – medical school – Federal University of Rio de Janeiro approved study protocol.

We considered exclusion criteria patients below the age of 18 years or older than 45 years, previous diagnoses of hypertension, diabetes, dyslipidemia, angina pectoris, active neoplasms, chronic renal failure, obstructive pulmonary disease, as well as the use of treatment for these conditions. Patients who were taking medications that could interfere

with the test results were also excluded. The possibility of pregnancy was excluded in all patients.

The diagnosis of polycystic ovary syndrome was made using the Rotterdam criteria. (9) Patients were at least three months without contraceptives or other medications that could hinder the diagnosis. (9) According to these criteria, we divided patients into four possible phenotypes (table 1):

1. Hyperandrogenism (clinic and/or biochemical), chronic anovulation and ovaries with polycystic aspect on ultrasound.
2. Hyperandrogenism (clinic and/or biochemical) and chronic anovulation.
3. Hyperandrogenism (clinic and/or biochemical) and ovaries with polycystic aspect on ultrasound;
4. Chronic anovulation and ovaries with polycystic aspect on ultrasound.

The Sphygmocor brand apparatus (AtCor Medical Pty Ltd Head Office, West Ryde, Austrália) was used to measure pulse wave velocity

The same observer trained in the method performed PWV's measurement along the thoracic-abdominal descending aorta (central or aortic arterial stiffness) in all patients.

Patients, after at least five minutes of resting in a quiet room and with stable temperature, had their arterial pressure measured by a calibrated digital apparatus (HEM-907XL; Omron Healthcare, Kyoto, Japan) with correctly adjusted clamp. Two blood pressure measurements were performed in each patient and the mean of these measurements was used as a basis for the analysis of the PWV. The patients were fasting for at least 3 hours before the test was performed.

Another relevant data for PWV's evaluation is the measurement of the distance between the analyzed arteries. Distance was measured directly between right femoral and right carotid sites. We used the recommended scaling factor of 0,8 to convert PWV obtained into real PWV.(4)

Three measurements of the central pulse wave velocity were performed, and the mean value was calculated. Values above 10 m/s were considered pathological independent of the age. Besides that, values were compared with the predicted for age and considered normal when below and altered when above. We based age specific cut-off values in the reference values from *Blood Stiffness Collaboration Group* that counted with data from 13 centers in eight European countries with a database of 16,867 individuals (table 2). (7)

The criteria used for the diagnosis of metabolic syndrome were those of NCEP – ATPIII and three of the five criteria were required. (15)

Laboratory tests were collected in the laboratory of HUCFF between 7 am and 10:00 am after a 12-hour fasting. The following laboratory tests were done aiming to exclude other diagnostic hypotheses of ovarian dysfunction and hyperandrogenism: β-HCG, LH, FSH, total testosterone, TSH, free T4, prolactin and 17-OH-progesterone. Patients who had clinical suspicion of Cushing's syndrome were investigated according to current guidelines.

The lipid profile was evaluated using 12-hour fasting blood samples of total cholesterol, HDL-cholesterol and triglycerides. LDL cholesterol was calculated using the Friedewald formula (LDL = CT – (HDL + TG/5). None of the patients in the study had fasting triglyceride plasmatic values greater than 400 mg/dl.

The glycemic profile was done through the evaluation of fasting glycemia and glycated hemoglobin. In those with fasting glycemia and inconclusive glycated hemoglobin tests, oral glucose tolerance test was done after

overload with 75g of glucose with fasting glucose measurements and after 2 hours of the overload following the ADA guidelines.

RESULTS

This study has 32 consecutive patients who sought our endocrinology outpatient clinic with the diagnosis of PCOS and who agreed to participate in the study. The general characteristics of the population studied can be seen in table 3.

None of the patients in our sample reached a PWV value equal to or greater than 10 m/s. Considering the expected PWV for age, we divided the patients into two groups (patients who had PWV above the expected value and those who had value within the limits of normality) to perform the comparisons. (Table 4)

Seventeen patients had higher PWV values than predicted for their age. We consider these as belonging to the altered group. Fifteen patients presented values within normal limits. They were considered as normal group.

The variables weight and BMI presented a tendency to statistical significance ($p = 0.06$ and $P = 0.09$) with the patients in the normal PWV group presenting lower values of both variables. The other variables analyzed were similar in both groups. (Table 4)

In relation to PCOS, eleven patients presented phenotype 1 and 13 patients the phenotype 2, totaling 75% of the patients with the classical phenotype and there was no difference regarding the value of PWV between classical and non-classical phenotypes (averages 6.71 m/s ± 1.40 and 6.76 m/s ± 1.36 respectively with $P = 0.92$).

None of the patients had a previous diagnosis of diabetes, dyslipidemia, or hypertension. No patient was smoker, and none met criteria for arterial hypertension. Twenty-eight patients had HDL cholesterol below 50 mg/dl and of these two had triglycerides higher than 150 mg/dl. Initial exams evidenced 13 patients with altered fasting glycaemia and/or increased risk for diabetes. No diagnosis of diabetes was made in any of the 32 patients on admission.

Thirty four percent of the sample had metabolic syndrome by NCEP-ATPIII. No statistical significance was found between PWV values and the presence or absence of metabolic syndrome, however within the group of patients with PCOS and metabolic syndrome approximately 45% of the patients had altered PWV in relation to the predicted for their age and in the group of women without metabolic syndrome only 28.5% had altered PWV (table 5).

DISCUSSION

This cross-sectional study conducted in a group of patients with PCOS in childbearing age revealed that aortic arterial stiffness, assessed by carotid-femoral PWV, was altered in 53% of patients when compared with the age-predicted value.

No patient had a PWV greater than 10 m/s, the reference cut-off value used in the literature. However, the studies that characterized this value as reference evaluated populations older than ours. Our result suggest that the 10 m/s reference cut-off should not be used in young populations due to lack of sensitivity. It is noteworthy that none of the patients had arterial hypertension, even though blood pressure is one of the predictors of arterial stiffness.

The predicted PWV values for age were based on a European multicentric study, which may be different the Brazilian population. The Brazilian study ELSA Brazil tries to establish a standard of PWV by age group in the Brazilian population; however, the age range of the study population is higher than that of our patients, which precluded comparison. Because the only Brazilian population study

did not include patients in the same age-group as ours and we do not have a control group, we chose to use the values described in the European population as reference. (7, 8, 16)

Patients belonging to phenotypes 1 and 2 are considered to present the classic phenotype. Studies suggest that these groups have a worse metabolic profile with higher insulin resistance, obesity, and higher waist measurements. Similarly, groups 1 and 2 have a higher prevalence of cardiovascular risk factors. On the other hand, patients belonging to group 4, who do not have hyperandrogenism, have a better metabolic profile and a lower prevalence of cardiovascular risk factors. (17)

We did not find any difference in PWV's values when comparing the classical phenotypes with the least severe. We may not have found any difference due to the size of our sample and the higher proportion of patients with classical phenotype in our population. This is a characteristic evidenced in the literature probably representing that women with a greater number of symptoms are those who seek medical services for assistance and, by the fact that the study was carried out in a tertiary hospital, that has a characteristic of receiving more severe patients.(17)

Despite the frequent complaint of patients seeking medical attention, the prevalence of overweight and obesity in PCOS patients is variable with no population-based studies. Obesity has a role in the pathogenesis of the syndrome through increased insulin resistance, as well as increased serum levels of androgens. Patients with PCOS tend to present greater abdominal obesity with increased abdominal circumference and tend to have a higher degree of insulin resistance and a greater proportion of them have dyslipidemia, hypertension and endothelial dysfunction, exacerbating the characteristics of the syndrome.(18, 19) Our population of patients had a high prevalence of overweight and obesity with only six patients presenting BMI within the normal range. Mean BMI in our entire population was 29,21 kg/m^2 (± 9,21) while mean BMI in the group of patients with altered PWV was 30,77 Kg/m^2 (± 4,51) and in the control group was 27,44 Kg/m^2 (± 6,21).

High blood pressure and loss of vascular complacency, resulting in increased arterial stiffness, apparently have a bidirectional behavior. The increase in blood pressure can cause vascular injury, accelerating the process of vascular stiffening. Similarly, the increase in aortic stiffness raises the pulsatile component of the pulse wave causing an increase in both the systolic component of the blood pressure and the pulse pressure (difference between the systolic and diastolic components of blood pressure).(20) Data on hypertension and patients with PCOS showed no difference when compared to control patients; however, it was evidenced that patients with PCOS and obesity had higher blood pressure values. (21) In our study, previous arterial hypertension was an exclusion criterion. In this group of women without arterial hypertension, we found 53% of the patients with PWV altered when compared to the predicted for their ages, a data that draws attention to the underlying disease itself as a possible risk factor for increased arterial stiffness.

No statistical significance was found between PWV values and the presence or absence of metabolic syndrome, however within the group of patients with PCOS and metabolic syndrome approximately 45% of the patients had altered VOP in relation to the predicted for their age groups. On the other hand, in the group of 21 women without metabolic syndrome, only 28.5% of the patients had increased pulse wave velocity. This data may represent that the subgroup of patients with metabolic syndrome has a higher cardiovascular risk, but due to the size of the

sample we did not find statistical significance.

Studies evaluating endothelial function by arterial stiffness in young patients with PCOS show that the presence of obesity would be a more reliable marker of increased cardiovascular risk than the presence of the syndrome itself. These data are compatible with ours that evidenced a tendency to statistical significance for increased weight and BMI and PWV. (13, 14, 22)

Our study presents as a strong point its homogeneous population, representative of patients with PCOS, with well-defined inclusion and exclusion criteria. As a weak point, we can cite lack of a control group resolved using a reference value proposed by a population study.

CONCLUSION

Our population presented with elevated PWV values compared to the predicted for their ages. Our results suggest that there is a possible correlation between the weight and BMI of patients with PCOS with increased PWV values.

TABLES

Phenotypes	Hyperandrogenism	Anovulation	Ultrasound aspect
Phenotype 1	**Present**	**Present**	**Present**
Phenotype 2	**Present**	**Present**	**Absent**
Phenotype 3	**Present**	**Absent**	**Present**
Phenotype 4	**Absent**	**Present**	**Present**

Table 1 – POS patient's phenotypes

Age	Expected average PWV	Expected maximum PWV
< 30-year-old	6,2 m/s	7,6 m/s
30- to 39-year-old	6,5 m/s	9,2 m/s
40- to 49-year-old	7,2 m/s	9,8 m/s

Table 2 – PWV predicted values by age

Age (years)	29,78 (± 6,34)
Weight (Kg)	78,42 (± 16,07)
Height (m)	1,63 (± 0,06)
BMI (Kg/m2)	29,21 (± 9,21)
Waist (Cm)	94,58 (± 13,99)
HDL (mg/dL)	39,53 (± 8,99)
TG (mg/dL)	100,03 (± 30,14)
SBP (mmHg)	117,81 (± 9,93)
DBP (mmHg)	75,91 (± 8,74)
HbAc (%)	5,54 (± 0,38)
Glucose (mg/dL)	88,31 (± 9,04)
Testosterone (ng/dL)	35,66 (± 17,20)
LH (mUI/mL)	7,05 (± 4,54)
FSH (mUI/mL)	5,06 (± 3,97)
Prolactin (ng/mL)	11,70 (± 4,53)
PWV (m/s)	6,73 (± 1,37)

Phenotype 1	11 (34,37%)
Phenotype 2	13 (40,62%)
Phenotype 3	2 (6,25%)
Phenotype 4	6 (18.75%)

BMI= body mass index; HDL= HDL cholesterol; TG =triglycerides; SBP = systolic blood pressure; DBP = Diastolic blood pressure; HbAc = glycated hemoglobin; LH = luteinizing hormone; FSH = follicle stimulating hormone; PWV = pulse wave velocity

Table 3 - Features of study population

Variable	Normal group (n=15)	Altered group (n=17)	P value
Age (years)	28,3 (DP ± 6,5)	31,1 (DP ± 6,0)	0,21
Weight (Kg)	72,8 (DP ± 19,2)	83,4 (DP ± 11,0)	0,06
Height (m)	1,62 (DP ± 0,08)	1,63 (DP ± 0,04)	0,65
BMI (Kg/m2)	27,44 (DP ± 6,21)	30,77 (DP ± 4,51)	0,09
Waist (Cm)	93,21 (DP ± 17,05)	95,80 (DP ± 11,02)	0,61
HDL (mg/dL)	39,0 (DP ± 8,19)	40,0 (DP ± 9,87)	0,76
TG (mg/dL)	106,26 (DP ± 27,57)	94,53 (DP ± 32,03)	0,28
SBP (mmHg)	115,53 (DP ± 7,20)	119,82 (DP ± 11,68)	0,23
DBP (mmHg)	73,67 (DP ± 7,67)	77,88 (DP ± 9,37)	0,18
HbAc (%)	5,59 (DP ± 0,39)	5,50 (DP ± 0,38)	0,50
Glucose (mg/dL)	89,06 (DP ± 8,93)	87,64 (DP ± 9,35)	0,66
Testosterone (ng/dL)	37,08 (DP ± 17,08)	34,48 (DP ± 17,73)	0,68
LH (mUI/mL)	6,25 (DP ± 4,16)	7,72 (DP ± 4,86)	0,38
FSH (mUI/mL)	3,96 (DP ± 2,04)	5,96 (DP ± 4,92)	0,17
Prolactin (ng/mL)	12,49 (DP ± 4,45)	11,05 (DP ± 4,64)	0,39

Values described above are the means found in each group for the analyzed variable

BMI= body mass index; HDL=HDL cholesterol; TG =triglycerides; SBP = systolic blood pressure; DBP = diastolic blood pressure; HbAc = glycated hemoglobin; LH = luteinizing hormone; FSH = follicle stimulating hormone; PWV = pulse wave velocity

Table 4 - Comparison between patients with normal and altered PWV

Variable	MS group (n=21)	Without MS group (n=11)	P value
Age (years)	28,7 (± 6,5)	31,2 (± 5,3)	0,26
Weight (Kg)	73,7(± 16,4)	87,4 (± 11,3)	0,015
Height (m)	1,63(± 0,06)	1,63 (± 0,05)	0,45
BMI (Kg/m2)	27,28(± 5,40)	32,89 (± 3,78)	0,0009
Waist (Cm)	91,12 (± 14,81)	101,2 (± 9,72)	0,03
HDL (mg/dL)	39,3 (± 10,3)	39,9 (± 5,97)	0,84
TG (mg/dL)	100,04 (± 30,45)	100,00 (± 31,00)	0,99
SBP (mmHg)	116,85 (± 9,45)	119,63 (± 11,02)	0,49
DBP (mmHg)	75,43 (±9,59)	76,82 (±7,16)	0,65
HbAc (%)	5,3 (± 0,24)	5,94 (±0,26)	0,31
Glucose (mg/dL)	88,2 (± 9,44)	88,45 (±8,66)	0,95
Testosterone (ng/dL)	38,8 (±16,7)	29,91 (± 17,4)	0,18

LH (mUI/mL)	7,09 (± 4,31)	6,99 (±5,15)	0,95
FSH (mUI/mL)	4,23 (±2,45)	6,55 (±5,66)	0,22
Prolactin (ng/mL)	11,47 (± 4,78)	12,12 (±4,25)	0,70
PWV (m/s)	6,90 (± 1,39)	6,40 (±1,35)	0,17
Percentage of altered PWV	28,5 %	45,4%	

Values described above are the means found in each group for the analyzed variable

BMI= body mass index; HDL=HDL cholesterol; TG =triglycerides; SBP = systolic blood pressure; DBP = diastolic blood pressure; HbAc = glycated hemoglobin; LH = luteinizing hormone; FSH = follicle stimulating hormone; PWV = pulse wave velocity

Table 5 – Comparison between patients with and without metabolic syndrome

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