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Impaired Carotid Viscoelastic Properties in Women With Polycystic Ovaries

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Background—The purpose of this study was to assess the elastic properties of the carotid arteries in women with polycystic ovarian syndrome, asymptomatic women with polycystic ovaries, and healthy controls.

Methods and Results—We recruited the following 60 subjects: 20 symptomatic women with polycystic ovaries attending the reproductive endocrinology clinics, 20 asymptomatic women with polycystic ovaries attending the family planning clinic, and 20 staff volunteers as healthy controls with normal ovaries on transvaginal scan. Compliance and stiffness index were assessed in the common and internal carotid arteries using duplex ultrasound equipped with an echo-locked arterial wall–tracking system. Compliance was significantly lower in the common carotid artery in symptomatic and asymptomatic women with polycystic ovaries than in the controls (10.7, 14.1, and 19.2 %mm $Hg^{-1}\times10^{-2}$, respectively). The arterial stiffness index was correspondingly increased (12.3, 10.2, and 6.7, respectively). Similar results were obtained in the internal carotid artery for compliance (10.1, 11.0, and 16.9 %mm $Hg^{-1}\times10^{-2}$, respectively) and stiffness index (14.8, 16.2, and 8.7, respectively).

Conclusions—The results of this study provide additional evidence of vascular dysfunction in women with polycystic ovaries and are compatible with the hypothesis that they are at increased risk from coronary artery disease and stroke. **(*Circulation*. 2002;106:81-85.)**

Key Words: carotid arteries ■ cardiovascular disease ■ stroke ■ elasticity ■ hemodynamics

Polycystic ovary syndrome (PCOS) is an important condition whose prevalence and significance is not generally appreciated. At least 20% of women of reproductive age have polycystic ovaries (PCO),[1] and up to three fourths of these have one or more of the classical symptoms described by Stein and Leventhal,[2] making this one of the commonest endocrinopathies in the human.[3] The significance of the syndrome derives from a range of endocrine and metabolic abnormalities, at the center of which is insulin resistance.[3] Not surprisingly, therefore, these women are at increased risk of developing type II[4,5] and gestational diabetes.[6] Aside from insulin resistance and obesity,[3] they also have several cardiovascular risk factors, including hyperlipidemia,[4,5] hypertension,[7] and an increased waist to hip ratio.[3] On the basis of these risk factors, it has been estimated that they have a 7.4-fold increased risk of myocardial infarction.[4] Evidence in support of this hypothesis was provided by an analysis of coronary angiograms, in which women with PCO were found to have more arterial segments with significant occlusion.[8] Using ultrasound, Guzick et al[9] reported increased intima media thickness in the common carotid bulb and the internal carotid artery (ICA), which is indicative of early atherosclerosis before the formation of plaque and alteration in blood flow.[10] In a more recent cohort study,[11] the prevalence of type II diabetes and coronary artery disease was increased in women with PCOS. Surprisingly, however, in the only study of mortality in women with PCOS, the number of deaths from cardiovascular disease was not increased.[12] However, it is not clear whether this surprising finding resulted from selection bias or some as yet unidentified protective factor.

Hemodynamic studies in PCOS have concentrated almost exclusively on the pelvic vessels and have shown decreased vascular resistance within the ovarian stroma,[13] and although the mechanism responsible is not known, this may relate to increased synthesis of vascular endothelial growth factor.[14]

The results of those few studies in vessels outside the pelvis suggest decreased flow over the aortic arch[15] and increased resting forearm flow, and in a previous study we reported lower pulsatility index (vascular resistance) and back pressure, suggestive of reduced vascular tone in the ICA in women with PCOS,[16] whereas asymptomatic women with PCO exhibited similar changes of lesser magnitude. In a recent study, we investigated vascular responses in women with PCOS and observed a paradoxical constrictor response to hypercapnia in the ICA.[17] Similar findings have been reported in the uterine artery in PCOS in response to glyceryl trinitrate.[18] These findings would suggest an abnormality in endothelial function in these women.

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As has already been discussed, PCOS is associated with insulin resistance[3] and non–insulin-dependent[4,5] and gestational diabetes.[6] Because these conditions are also associated with decreased vascular compliance, we undertook the present study to assess arterial elastic properties in women with PCO or PCOS.

Methods

Study Design

In this cross-sectional pilot study, the following 3 groups of women aged 18 to 30 years were recruited from the North Middlesex Hospital, London: (1) 20 women attending the Reproductive Endocrinology and Gynaecology clinics with PCOS confirmed by the presence of bilateral polycystic ovaries on transvaginal scan[19] and clinical features of menstrual irregularity, infertility, oligomenorrhea (intermenstrual interval >35 days), or hirsutism (Ferriman and Gallwey score >7[20]); (2) 20 asymptomatic women attending the family planning clinic with polycystic ovaries on scan (the PCO group); and (3) 20 healthy control women (staff members) with normal ovaries, no evidence of hyperandrogenemia (hirsutism or acne), and regular menstrual cycles (intermenstrual intervals of 21 to 35 days) and who had not sought treatment for menstrual disturbance, infertility, or hirsutism at any time.

Women who smoked, had respiratory or cardiovascular disease, or were taking medication, including oral contraceptives or aspirin, that could influence vascular resistance were excluded. Vascular measurements were performed 6 hours postprandially, at 5 PM, between days 4 and 7 of the menstrual cycle in oligomenorrheic and control women; there was no special timing for amenorrheic women. The study was approved by the Local Research Ethics Committee, and written consent was obtained from each subject.

Vascular Viscoelasticity Assessments: Theoretical Considerations

Many indices have been derived to describe and quantify the physical behavior of vessels in response to an intraluminal force. This has lead to a debate among investigators as to the most appropriate index of change in arterial distension with respect to intraluminal pressure.[21]

In 1960, Peterson et al[22] defined the elastic modulus E_p as an index of arterial stiffness, which describes the relationship of strain to intraluminal pressure in an open-ended vessel. The original description referred to the change in vessel volume, but because the arterial lumen is generally circular in cross-section, the equation has been modified to the following:

$$E_p(\text{mmHg}) = (P_s - P_d)/\text{Strain}.$$

Strain is the fractional pulsatile diameter change that occurs in an artery exposed to a given change in intraluminal pressure, and is defined as follows:

$$\text{Strain} = (D_s - D_d)/D_d\ .$$

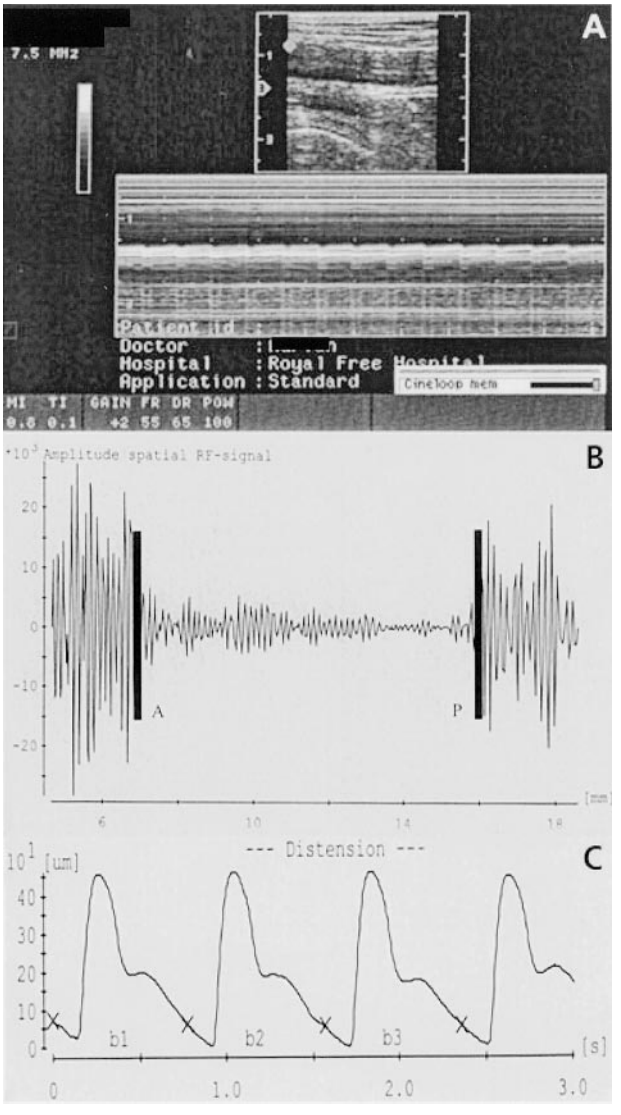
where *D* and *P* are diameter and pressure and *s* and *d* denote systole and diastole, respectively.

The inverse of the elastic modulus of Peterson et al[22] is known as cross-sectional or diametrical compliance (C) and is given by the following:

$$C(\%\text{mmHg}^{-1}\times 10^{-2}) = \frac{(D_s - D_d)}{D_d(P_s - P_d)} \times 10^4.$$

Both E_p and C are useful indices of vascular distensibility and describe the relative change vessel diameter in the presence of a change in blood pressure.

However, Kawasaki et al[23] recommended the stiffness index (β) as a useful parameter when comparing physiological changes in vessel wall between individuals, because it is less dependent on quantitative pressure change.[24]



B-mode and M-mode image of CCA in healthy subject (A); typical radiofrequency (RF) signal acquired from artery is analyzed to locate and mark anterior (A) and posterior (P) luminal surfaces (B). Vessel distension over 2 cardiac cycles is displayed (C).

$$\beta = \frac{[\log_e(P_s - P_d)].D_d}{(D_s - D_d)}$$

In this study, the arterial compliance C and stiffness index β were used to assess the vessel wall properties in the PCOS, PCO, and control subjects.

Technique

All women were examined in the supine position, with the head hyperextended and turned away from the side being scanned. Scans were performed by an experienced ultrasonographer (K.L.) using a color Doppler Pie 350 machine (Pie Medical Systems) with a 7.5-MHz linear probe and the RF signal output to a high-resolution wall-tracking system (Wall track, Pie Medical Systems).[24] This system allows the measurement of vessel wall movement over time by automatically tracking assigned points of the induced radio frequency signal deemed to be representative of the anterior and posterior vessel wall. With the M-mode cursor positioned perpendicularly and midway to the long axis of the common carotid artery (CCA) and 2 cm distal to the carotid bulb for the ICA, the change in induced radio frequency signal from the vessel was sampled (Fig-

TABLE 1. Subject Characteristics for the 3 Groups

Variable	Control	PCO	PCOS	*P* Value Between Groups
No. of subjects	20	20	20	
Age, y	27.5±4.0	27.7±4.6	29.2±4.0	NS
Height, m	1.68±0.06	1.64±0.07	1.65±0.07	NS
Weight, kg	68.1±11.6	61.0±11.3	85.5±25.3	0.008
BMI, kg/m^2	24.2±3.4	22.5±3.8	31.3±8.2	0.003
Systolic blood pressure, mm Hg	108.2±9.6	103.1±9.7	118.7±18.2	0.03
Diastolic blood pressure, mm Hg	59.5±8.4	56.3±6.8	68.9±14.6	0.04
Insulin, m-units/L	10.43±4.60	16.41±7.12	23.83±10.31	0.02
Total cholesterol, mmol/L	4.42±0.52	5.41±2.49	4.59±1.89	NS
HDL, mmol/L	1.38±0.20	1.36±0.21	1.33±0.43	NS
LDL, mmol/L	2.72±0.44	3.61±2.51	3.69±1.43	NS
Triglycerides, mmol/L	0.70±0.17	0.91±0.32	1.27±0.95	NS

Values are mean (SD).
HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

ure). The data were transferred to a personal computer for real-time display of the anterior and posterior arterial walls.

Pulse and blood pressure were measured on the left arm in all women using an automatic Dinamap device (Critikon Inc) at 2-minute intervals until the pulse rate varied by >5 beats/min and the systolic and diastolic blood pressures by less than 5 mm Hg over 2 readings. Because carotid blood flow is influenced by noise, we first determined the hearing threshold for each subject and then delivered 50-dB wide-band frequency noise (20 HZ to 20 KHz; Kamplex Diagnostic Audiometer; P.C. Werth Ltd) above this threshold via occlusive headphones that were worn throughout the procedure. Ambient light and temperature were controlled throughout the procedure.

Height and weight measurements were used to calculate the body mass index (BMI). The minimum waist measurements between the pelvic brim and the costal margin and the maximum hip measurement at the level of the greater trochanters were used to calculate the waist to hip ratio.

In addition, peripheral blood was obtained before the ultrasound examination from all women. Serum levels of cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, and fasting insulin were measured.

Statistical Analysis

The average vessel wall movement was obtained over 3 cardiac cycles, and the diametrical compliance and stiffness index were calculated using the blood pressure measured at the corresponding time and site. The average of 3 sets of compliance and stiffness index data at a given site was then calculated to obtain mean values for each site along the vessel in each subject. Intraobserver variability was determined separately for each site by determining the coefficient of variation of repeated measurements. Coefficients of variations below 10% were considered to indicate good reproducibility.

The following confounding variables were known a priori to differ between PCOS and healthy women and also to be associated with hemodynamic disturbances: age, BMI, and systolic and diastolic blood pressures. Intergroup differences in parameters were compared by one-way ANOVA and, if significant, followed by multiple regression analysis. All confounders were controlled for within regression models. Intergroup comparisons of were performed between PCOS versus controls and PCO versus controls. Adjusted means were calculated from general linear model procedure. This was achieved by including in the general linear model command the mean values of the confounding factors calculated for the control group. Statistical tests were considered significant if $P \leq 0.05$. All analyses were performed using the statistical package SPSS for Windows (Version 10.05).

Results

Arterial compliance and stiffness index were correlated between the right and the left sides ($r=0.901$, $P<0.001$), and, therefore, only the right side is reported. The coefficients of variations for ultrasound parameters were between 3.5% and 7.0% for the CCA and between 7.6% and 10% for the ICA, indicating good reproducibility for the CCA and a reasonable reproducibility for the ICA.

Table 1 summarizes the physical characteristics in the study sample. There was no significant difference with respect to age between the 3 groups. There was a significant difference in BMI ($P=0.003$) and systolic blood pressure ($P=0.03$) and diastolic blood pressure ($P=0.04$) between women with PCOS compared with healthy controls. The BMI

TABLE 2. Adjusted Comparison of Compliance (C) of the CCA and the ICA Between Control, PCO, and PCOS Groups

	Adjusted Mean			Adjusted Difference (95% CI)*	
Variable	Control	PCO	PCOS	Control–PCO	Control–PCOS
Number of women	20	20	20	...	...
C_{CCA} (% mm Hg$^{-1}\times10^{-2}$)	19.2	14.1	10.7	5.1 (8.1 to 2.6)*	8.5 (10.2 to 4.8)*
C_{ICA} (% mm Hg$^{-1}\times10^{-2}$)	16.9	11.0	10.1	5.9 (8.7 to 1.4)*	6.8 (9.2 to 0.4)*

Estimated marginal means were calculated from the general linear models using the following mean values of the confounding factors for the control group: age, 27.5 years; BMI, 24.2 kg/m^2; systolic blood pressure, 108.2 mm Hg; diastolic blood pressure, 59.5 mm Hg; and insulin, 10.43 m-units/L. Adjusted differences are given with 95% CIs.
*$P<0.05$.

TABLE 3. Adjusted Comparison of Stiffness Index (β) of the CCA and the ICA Between Control, PCO, and PCOS Groups

	Adjusted Mean			Adjusted Difference (95% CI)*	
Variable	Control	PCO	PCOS	Control–PCO	Control–PCOS
No. of women	20	20	20	...	...
β_{CCA}	6.7	10.2	12.3	−3.5 (−1.1 to −4.7)*	−5.6 (−2.8 to −6.2)*
β_{ICA}	8.7	16.2	14.8	−7.5 (−0.9 to −15.2)*	−6.1 (−4.5 to −13.1)*

Estimated marginal means were calculated from the GLM model using the following mean values of the confounding factors for the control group: age, 27.5 years; BMI, 24.2 kg/m^2; systolic blood pressure, 108.2 mm Hg; diastolic blood pressure, 59.5 mm Hg; and insulin, 10.43 m-units/L. Adjusted differences are given with 95% CIs.
*$P<0.05$.

and systolic and diastolic blood pressures just failed to reach the levels of significance between asymptomatic women with PCO compared with controls.

On multiple regression analyses, there was significant reduction in compliance in PCOS and PCO compared with the healthy controls (Table 2) in both CCA and ICA. Conversely, the stiffness index was significantly increased in both PCO and PCOS compared with control (Table 3).

Discussion

This is the first time that vascular elasticity has been assessed in women with PCOS, and the results demonstrate decreased compliance and increased stiffness of the CCA and ICA when compared with age-matched healthy controls. This is significant in view of the relationship between functional properties of the arterial wall and cardiovascular morbidity and mortality.

Arterial elasticity diminishes with smoking, coronary artery disease, age, and hypertension.[25] Aging is also associated with arterial dilatation and increased arterial wall thickness. However, all of the subjects in this study were young adults, and none smoked or had symptoms or signs of coronary artery disease, so the results are unlikely to be confounded by these factors. Similarly, whereas blood pressure was higher in women with PCOS than in the controls, the lower compliance remained after adjusting for this and other confounding variables. Furthermore, because BMI and fasting insulin levels are on average higher in women with PCO/PCOS than in control women and because BMI and fasting insulin are themselves associated with decreased vascular compliance, it is reasonable to expect that BMI or insulin could account for part of the relationship between PCO/PCOS and the measures of macrovascular dysfunction. However, the failure to detect differences on all lipid variables between PCOS and controls may reflect the small sample size and the age of the women studied; the mean ages of our group of PCOS subjects and those of Talbott et al[5] were 28.7 and >45 years, respectively.

Decreased vascular compliance is also a feature of subclinical atherosclerosis, arterial elasticity being reduced during fatty-streak formation before other pathological changes occur.[26] The results of this study are therefore in keeping with the previous report of increased intima media thickness at the carotid bulb and in the ICA in women with PCOS[9] and would suggest that these women may be at increased risk not only for coronary artery disease but also for stroke.

The mechanism responsible for the decreased arterial elasticity in PCOS is not known. However, similar findings in non–insulin-dependent diabetes have been attributed to nonenzymatic glycation of elastin and collagen in the tunica.[27] It would seem reasonable to suggest that this mechanism may be relevant in PCOS, given the association with hyperglycemia and hyperinsulinemia. The parallel with diabetes may also extend to an alteration in endothelial function.[28] The finding of an abnormal response to glyceryl trinitrate[18] together with our previous observation of a paradoxical response to carbon dioxide add weight to the concept of endothelial dysfunction in women with PCOS.

In summary, our results provide additional evidence of significant vascular dysfunction in women with polycystic ovaries and highlight the need to confirm or refute the present discrepancy between cardiovascular risk and mortality in these women. Studies are also required to determine the mechanisms responsible for the wide range of vascular abnormalities and potential cardioprotective factors associated with this condition, which affects at least 20% of the female population.

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