Is polycystic ovary syndrome associated with high sympathetic nerve activity and size at birth?

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Sverrisdóttir YB, Mogren T, Kataoka J, Janson PO, Stener-Victorin E. Is polycystic ovary syndrome associated with high sympathetic nerve activity and size at birth? Am J Physiol Endocrinol Metab 294: E576–E581, 2008. First published January 15, 2008; doi:10.1152/ajpendo.00725.2007.—Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disturbance among women of reproductive age and is proposed to be linked with size at birth and increased prevalence of cardiovascular disease. A disturbance in the sympathetic nervous system may contribute to the etiology of PCOS. This study evaluates sympathetic outflow in PCOS and its relation to size at birth. Directly recorded sympathetic nerve activity to the muscle vascular bed (MSNA) was obtained in 20 women with PCOS and in 18 matched controls. Ovarian ultrasonographic evaluation, biometric, hormonal, and biochemical parameters were measured, and birth data were collected. Women with PCOS had increased MSNA (30 ± 8 vs. 20 ± 7 burst frequency, \( P < 0.0005 \)) compared with controls. MSNA was positively related to testosterone \(( r = 0.63, \ P < 0.005)\) and cholesterol \(( r = 0.55, \ P = 0.01)\) levels in PCOS, which, in turn, were not related to each other. Testosterone level was a stronger predictor of MSNA than cholesterol. Birth size did not differ between the study groups. This is the first study to directly address sympathetic nerve activity in women with PCOS and shows that PCOS is associated with high MSNA. Testosterone and cholesterol levels are identified as independent predictors of MSNA in PCOS, although testosterone has a stronger impact. The increased MSNA in PCOS is associated with high MSNA. Testosterone and cholesterol levels are identified as independent predictors of MSNA in PCOS, although testosterone has a stronger impact. The increased MSNA in PCOS may contribute to the increased cardiovascular risk and etiology of the condition. In this study, PCOS was not related to size at birth.

birth weight; testosterone; insulin resistance; metabolic syndrome; cardiovascular disease; autonomic nervous system

POLYCYSTIC OVARY SYNDROME (PCOS), the most common female endocrine disorder, is a complex and heterogenic disease with unknown etiology (28). PCOS is characterized by reproductive disturbances including chronic anovulation, hyperandrogenism, and polycystic ovaries (28). Although ovarian hyperandrogenemia, which is the most consistent endocrine feature of PCOS, probably plays a key role in its etiology (1, 12), hyperinsulinemia and insulin resistance, as well as abdominal obesity and cardiovascular disease, all factors hypothesized to be associated with increased activity of the sympathetic nervous system (8). Furthermore, PCOS is associated with disturbances in the somatotropic axis, i.e., the growth hormone (GH)/insulin growth factor (IGF)-I axis (53), which plays a central role in the regulation of central sympathetic outflow (42–44).

Low size at birth, proposed to be more common among women with PCOS (19), has been shown to be associated with perturbations in sympathetic nerve activity (3, 52). Furthermore, an involvement of the sympathetic nervous system in PCOS is further strengthened by the finding of greater density of catecholaminergic nerve fibers in polycystic ovaries (16) and altered peripheral catecholamine secretion in adolescent PCOS (11).

Although it is known that activation of the sympathetic neurons innervating the ovary precedes the development of cystic ovaries in rats (22), there are no data on sympathetic activity in women with PCOS. There is one previous study investigating heart rate variability (HRV), an indirect method for measuring cardiac autonomic control, in young women with PCOS (54). This study showed that young PCOS women exhibited an adverse cardiovascular profile compared with controls. Even if the primary etiology of the complex disorder of PCOS remains a hen-and-egg mystery, a perturbation in the activity in the sympathetic nervous system may be relevant to its pathophysiology. Against this background, the primary aim of this study was to investigate sympathetic nerve activity in women with PCOS and possible associations with size at birth and hormonal, metabolic, hemodynamic, and anthropometrical parameters.

MATERIALS AND METHODS

Subjects. Twenty women with PCOS and 18 weight- and age-matched controls without PCOS were recruited from the Department of Obstetrics and Gynecology, Sahlgrenska University Hospital (Göteborg, Sweden), or through advertisement in the local community. PCOS was defined as typical ultrasonographic presentation of polycystic ovaries (at least 10 cysts 2–9 mm in size) and one of the

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following criteria: menstrual disturbance (oligo- or amenorrhea) and/or clinical evidence of hyperandrogenism (hirsutism or acne) according to the Rotterdam consensus report (45). All controls had normal ovarian morphology on ultrasound, regular menstrual cycles, and no signs of hyperandrogenism.

None of the women had taken any medication for at least 3 mo before the screening. Other potential endocrine or neoplastic causes of hyperandrogenemia including androgen-secreting tumors, Cushing’s syndrome, and congenital adrenal hyperplasia were excluded (45). Other exclusion criteria were pregnancy or breast-feeding within the last 6 mo.

The study was approved by the Ethics Committee at Göteborg University, and women gave their oral and written consent before entering the study. All investigations were conducted in accordance with guidelines in the Declaration of Helsinki.

**Study procedure.** Height, weight, waist-to-hip circumference ratio (WHR), and Ferriman-Gallwey assessment of hirsutism and/or acne (Coat-A-Count free testosterone and Coat-A-Count DHEA-SO4; Diagnostic Products, Los Angeles, CA). Serum total testosterone and insulin levels were measured by competitive immunochemistry with chemiluminescence technology (ADVIA Centaur TSTO ReadyPack primary reagents and ADVIA Centaur Insulin ReadyPack; Bayer Health Care, Tarrytown, NY). Serum sex hormone-binding globulin (SHBG), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were measured by chemiluminescence microparticle immunoassay (Architect SHBG reagent kit; Biokit, Barcelona, Spain for Abbott Laboratories Diagnostic Division, and Architect LH reagent and FSH reagent pack; Abbott Laboratories Diagnostic Division, Chicago, IL). Free thyroxine (T4) and IGF-I were measured with immunochemiluminescence technology (FT4 free thyroxine; Roche Diagnostics, Mannheim, Germany; and Immulite 2500 IG1, Euro/DPC, Gwynedd, UK). Thyroid-stimulating hormone (TSH) was measured with electrochemiluminescence immunoassay at 37°C (TSH thyrotropin; Roche Diagnostics). Serum triglycerides (TG; Roche/Hitachi), cholesterol (CHOL; Roche/Hitachi), and high-density lipoprotein (HDL)-cholesterol (HDL-C 2nd generation; Roche/Hitachi) and plasma glucose were measured with an enzymatic photometric method at 37°C (Roche Diagnostics, Mannheim, Germany). Low-density lipoprotein (LDL)-cholesterol is a calculation according to the Freiwalds formula when serum TG < 4.0: serum LDL-cholesterol = serum cholesterol − serum HDL-cholesterol − (0.45 × serum TG). Insulin sensitivity was estimated with a homeostasis model assessment for estimating insulin resistance (HOMA-IR) (25). HOMA-IR index was calculated according to the formula [fasting plasma glucose (mmol/l) × fasting plasma insulin concentration (mU/ml)]/22.5.

**Birth weight and gestational age.** Birth weight, height, and head circumference were obtained from birth registers and hospital files. Gestational age was calculated to the nearest week from the first day of the last menstrual period. Preterm births were defined as <37 gestational weeks. Small for gestational age (SGA) and large for gestational age (LGA) were defined as birth weights relative to gestational age below and above the 10th percentile (33).

**Sympathetic nerve recordings.** Direct recordings of multunit different postganglionic muscle sympathetic nerve activity (MSNA) were obtained with a tungsten microelectrode with a tip diameter of a few micrometers inserted into a muscle fascicle of the peroneal nerve, posterior to the fibular head. A low-impedance reference electrode was inserted subcutaneously a few centimeters from the fibular head. When a muscle nerve fascicle had been identified, small electrode adjustments were made until a site was found in which spontaneous, pulse-synchronous bursts of neural activity could be recorded. Details of the nerve recording technique and criteria for MSNA have been reported previously (24, 47). Bursts identified by inspection of the mean voltage neurogram were expressed as burst frequency [bursts/ min (BF)] and burst incidence [bursts/100 heartbeats (BI)]. The nerve recordings were assigned a code and analyzed blinded.

During the microneurographic recording, finger arterial blood pressure was measured noninvasively using the volume-clamp method (Finapres 2300; Ohmeda, Louisville, KY) (31), and heart rate was monitored via ECG chest electrodes.

MSNA consists of baroreceptor reflex-controlled vasoconstrictor impulses to the muscle vascular bed, involved in dynamic blood pressure regulation. Although MSNA only represents one subdivision of the sympathetic nervous system, at rest it correlates well with a global measure of sympathetic nerve activity, such as total body norepinephrine spillover, and with regional (heart, kidney, and subcortical) norepinephrine spillover (48 –50).

Because there are fluctuations of autonomic nervous outflow during the menstrual cycle (37), all recordings were made during the follicular phase of the menstrual cycle (days 1–7) in controls, whereas this was not possible in most of the women diagnosed with PCOS who had oligo- or amenorrhea.

Biochemical assessment. All analyses were carried out at an accredited laboratory in the Department of Clinical Chemistry, Sahlgrenska University Hospital. Serum free testosterone and dehydroepiandrosterone sulfate levels were measured by radioimmunooassay (Coat-A-Count free testosterone and Coat-A-Count DHEA-SO4; Diagnostic Products, Los Angeles, CA). Serum total testosterone and insulin levels were measured by competitive immunochemistry with chemiluminescence technology (ADVIA Centaur TSTO ReadyPack primary reagents and ADVIA Centaur Insulin ReadyPack; Bayer Health Care, Tarrytown, NY). Serum sex hormone-binding globulin (SHBG), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were measured by chemiluminescence microparticle immunoassay (Architect SHBG reagent kit; Biokit, Barcelona, Spain for Abbott Laboratories Diagnostic Division, and Architect LH reagent and FSH reagent pack; Abbott Laboratories Diagnostic Division, Chicago, IL). Free thyroxine (T4) and IGF-I were measured with immunochemiluminescence technology (FT4 free thyroxine; Roche Diagnostics, Mannheim, Germany; and Immulite 2500 IG1, Euro/DPC, Gwynedd, UK). Thyroid-stimulating hormone (TSH) was measured with electrochemiluminescence immunoassay at 37°C (TSH thyrotropin; Roche Diagnostics). Serum triglycerides (TG; Roche/Hitachi), cholesterol (CHOL; Roche/Hitachi), and high-density lipoprotein (HDL)-cholesterol (HDL-C 2nd generation; Roche/Hitachi) and plasma glucose were measured with an enzymatic photometric method at 37°C (Roche Diagnostics, Mannheim, Germany). Low-density lipoprotein (LDL)-cholesterol is a calculation according to the Freiwalds formula when serum TG < 4.0: serum LDL-cholesterol = serum cholesterol − serum HDL-cholesterol − (0.45 × serum TG). Insulin sensitivity was estimated with a homeostasis model assessment for estimating insulin resistance (HOMA-IR) (25). HOMA-IR index was calculated according to the formula [fasting plasma glucose (mmol/l) × fasting plasma insulin concentration (mU/ml)]/22.5.

**RESULTS**

Besides being matched for age and body mass index (BMI), the study groups did not deviate in terms of waist circumference, heart rate, and blood pressure (Table 1).

**Hormonal, metabolic, and anthropometric variables.** All hormonal and metabolic results are given in Table 1. FSH was lower and the LH/FSH ratio was significantly higher in the PCOS group compared with controls. Serum concentrations of total testosterone, free testosterone, and free androgen index [FAI; total testosterone (nmol/l)/SHBG (nmol/l) × 100] were increased and SHBG was decreased in women with PCOS compared with controls. Insulin, HOMA-IR index, cholesterol, and IGF-I concentrations were significantly increased in women with PCOS compared with controls.

Women with PCOS had significantly higher WHR, Ferriman-Gallwey, and acne scores compared with controls. The study groups did not deviate in terms of gestational age, weight, length, or head circumference at birth. One patient in the PCOS group and one in the control group were born LGA, whereas none were born SGA.

**Muscle sympathetic nerve activity.** Sympathetic nerve activity, expressed as BF and BI, was markedly increased in women with PCOS (30 ± 8 BF and 48 ± 12 BI) compared with the controls (20 ± 7 BF and 33 ± 11 BI) (Table 1 and Fig. 1). When assessed for the whole study group, MSNA was positively related to total and free testosterone levels (Table 2 and Fig. 2A), FAI, and serum cholesterol levels (Table 2 and Fig. 2B). Within the PCOS group, a positive correlation with similar r values was evident between MSNA and total testosterone, free testosterone, and serum cholesterol levels, whereas no such associations were found in the control group (Table 2).
MSNA was not related to other hormonal, metabolic, or anthropometrical features measured, whether assessed for the combined study group or for each group separately.

In a multiple regression analysis in which MSNA was used as a dependent variable and total testosterone \((r = 0.6, P < 0.0001)\), free testosterone \((r = 0.6, P < 0.0001)\), and cholesterol \((r = 0.4, P = 0.007)\) were used as independent variables, the regression weights (beta) for total testosterone, free testosterone, and cholesterol were 0.5 \((P < 0.001)\), 0.5 \((P < 0.002)\), and 0.3 \((P = 0.04)\), respectively. Serum cholesterol was not related to total testosterone or free testosterone levels, whether assessed for the combined study group or for each group separately.

### Table 1. Biometric, neuronal, hormonal, metabolic, and birth size variables in women with PCOS and in weight- and age-matched controls

<table>
<thead>
<tr>
<th>Biometric</th>
<th>PCOS</th>
<th>Controls</th>
<th>Independent t-Test, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>29.9 (3.9)</td>
<td>27.4 (3.4)</td>
<td>0.15</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.7 (2.9)</td>
<td>21.9 (1.8)</td>
<td>0.31</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>80.8 (7.7)</td>
<td>76.6 (5.3)</td>
<td>0.12</td>
</tr>
<tr>
<td>WHR</td>
<td>0.80 (0.05)</td>
<td>0.76 (0.04)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ferriman-Gallwey score</td>
<td>10.1 (7.8)</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Acne (yes/no)</td>
<td>0.77 (0.43)</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>105.1 (7.0)</td>
<td>107.1 (10.2)</td>
<td>0.47</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>105.8 (7.3)</td>
<td>107.1 (10.2)</td>
<td>0.23</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>66.7 (5.8)</td>
<td>67.1 (8.9)</td>
<td>0.84</td>
</tr>
<tr>
<td>Microneurography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSNA burst frequency</td>
<td>29.75 (8.07)</td>
<td>19.99 (6.94)</td>
<td>0.0003</td>
</tr>
<tr>
<td>MSNA burst incidence</td>
<td>48.10 (11.96)</td>
<td>32.71 (11.69)</td>
<td>0.0003</td>
</tr>
<tr>
<td>HR</td>
<td>62.75 (10.26)</td>
<td>61.91 (7.69)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

**Hormones**

- LH, IU/l: 9.6 (15.1) vs. 4.3 (1.8) 0.15
- FSH, IU/l: 4.3 (1.7) vs. 5.2 (1.2) 0.05
- LH/FSH: 2.2 (1.7) vs. 0.8 (0.3) 0.002
- Free T₃, pmol/l: 14.6 (3.8) vs. 15.3 (1.7) 0.50
- TSH, mIU/l: 3.0 (2.7) vs. 2.3 (1.0) 0.31
- Total testosterone, nmol/l: 2.1 (0.7) vs. 1.4 (0.3) 0.001
- Free testosterone, pmol/l: 4.1 (3.0) vs. 1.8 (0.3) 0.002
- SHBG, nmol/l: 49.6 (24.7) vs. 81.5 (22.7) 0.0001
- FAL: 5.1 (3.1) vs. 1.9 (0.6) 0.0001
- DHEAS, μmol/l: 4.9 (2.8) vs. 3.7 (1.3) 0.12
- IGF-1, μg/l: 207.6 (70.5) vs. 155.9 (28.4) 0.0006

**Blood lipids**

- Cholesterol, mmol/l: 4.1 (0.6) vs. 3.7 (0.7) 0.03
- Triglycerides, mmol/l: 0.7 (0.2) vs. 0.6 (0.2) 0.16
- HDL-cholesterol, mmol/l: 1.6 (0.3) vs. 1.6 (0.3) 0.91
- LDL-cholesterol, mmol/l: 2.2 (0.5) vs. 1.9 (0.5) 0.07

**Birth**

- Gestational age: 39.4 (1.9) vs. 40.7 (1.5) 0.06
- Weight, g: 351 (501) vs. 353 (534) 0.74
- Body length, cm: 50.2 (2.1) vs. 50.9 (2.9) 0.49
- Head circumference, cm: 34.8 (1.3) vs. 35.4 (1.5) 0.27

**Values**

Values are means (SD) for 20 women with polycystic ovary syndrome (PCOS) and 18 age- and BMI-matched controls. BP, blood pressure; DHEAS, dehydroepiandrosterone sulfate; FAL, free androgen index (total testosterone (nmol/l)/SHBG (nmol/l) × 100; FSH, follicle-stimulating hormone; HOMA-IR, homeostasis model assessment of insulin resistance; HDL, high-density lipoprotein; HR, heart rate; IGF-1, insulin growth factor-1; LDL, low-density lipoprotein; LH, luteinizing hormone; MSNA, muscle sympathetic nerve activity; SHBG, sex hormone-binding globulin; TSH, thyroid-stimulating hormone; WHR, waist-to-hip ratio.

**DISCUSSION**

Although the involvement of the sympathetic nervous system has been suggested in PCOS, this is the first time direct intraneural recordings of sympathetic nerve activity have been obtained in women with PCOS. The novel finding in this study is that PCOS is associated with increased sympathetic nerve activity, which, in turn, is positively related to elevated testosterone levels characterizing this condition. The augmented sympathetic outflow may contribute to the increased prevalence of vascular disease reported in these individuals (4, 30, 40), as well as being involved in the etiology of the condition (15).

**Androgens and MSNA.** In this study testosterone was identified as a predictor of sympathetic nerve activity in women with PCOS. The relationship between testosterone and the sympathetic nervous system is not clear, and studies have

### Table 2. Simple correlation between MSNA and hormonal and metabolic variables in women with PCOS and in weight- and BMI-matched controls

<table>
<thead>
<tr>
<th></th>
<th>PCOS</th>
<th>Controls</th>
<th></th>
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<tbody>
<tr>
<td>WHR</td>
<td>-0.40 (0.14)</td>
<td>-0.03 (0.92)</td>
<td></td>
</tr>
<tr>
<td>FSH</td>
<td>-0.13 (0.45)</td>
<td>-0.10 (0.66)</td>
<td>-0.27 (0.28)</td>
</tr>
<tr>
<td>LH/FSH</td>
<td>0.30 (0.07)</td>
<td>0.14 (0.54)</td>
<td>-0.07 (0.76)</td>
</tr>
<tr>
<td>Total testosterone</td>
<td>0.59 (0.001)</td>
<td>0.63 (0.004)</td>
<td>0.043 (0.87)</td>
</tr>
<tr>
<td>Free testosterone</td>
<td>0.58 (0.001)</td>
<td>0.57 (0.01)</td>
<td>0.28 (0.27)</td>
</tr>
<tr>
<td>FAI</td>
<td>0.47 (0.003)</td>
<td>0.27 (0.23)</td>
<td>0.16 (0.54)</td>
</tr>
<tr>
<td>SHBG</td>
<td>-0.28 (0.10)</td>
<td>0.07 (0.78)</td>
<td>0.01 (0.98)</td>
</tr>
<tr>
<td>IGF-1</td>
<td>0.20 (0.23)</td>
<td>-0.06 (0.81)</td>
<td>0.08 (0.77)</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.18 (0.29)</td>
<td>-0.09 (0.70)</td>
<td>0.002 (1.0)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.18 (0.26)</td>
<td>-0.08 (0.74)</td>
<td>0.15 (0.57)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.44 (0.007)</td>
<td>0.55 (0.01)</td>
<td>0.07 (0.79)</td>
</tr>
</tbody>
</table>

Values are Pearson linear correlation coefficients \((r)\) indicating correlation of MSNA with hormonal and metabolic variables for all 38 women as a group as well as grouped data for the 20 women with PCOS and the 18 age- and BMI-matched controls. Multiple regression analysis was used to determine differences in main end points between groups \((P\) values, in parentheses).
yielded conflicting results on the effect of the catecholamine epinephrine on testosterone secretion (7, 10, 23, 36). Whether testosterone, in turn, can influence the sympathetic nervous system still remains unknown, but a recent study by Weise et al. (51) showed that increased plasma norepinephrine concentration is related to puberty and increasing testosterone levels in young boys. Adolescent PCOS patients demonstrate a peripheral catecholaminergic alteration, which suggests a modification in norepinephrine deamination and/or reuptake in adolescent patients (11, 39). However, whether this modification is also present in sympathetic neurons innervating the ovaries is not known, but if so, it may be speculated that it would increase androgen secretion and thereby may play a potential role in the pathogenesis and/or maintenance of PCOS. There are strong indications that women with PCOS have increased ovarian nerve fiber density (16), and it has been demonstrated that women with PCOS have an increase in ovarian catecholaminergic nerve fibers compared with normal ovaries (38). Therefore, intrar ovarian nerve fibers may be considered as modulators of steroid production in the ovary (5, 29).

Sex-related differences in MSNA. In the normal population, men tend to have higher MSNA than women, but the underlying mechanisms remain largely unknown (27). The finding of a positive relationship between serum testosterone levels and MSNA in the present study raised our curiosity as to whether sympathetic outflow in women with PCOS resembled the level of sympathetic outflow in men. Comparing our results with those for a previously investigated age- and BMI-matched group of men, we found that sympathetic outflow expressed as BF and BI did not deviate between women with PCOS and the matched male cohort (29 and 27 BF vs. 48 and 47 BI, respectively). Despite the similarities in sympathetic outflow, women with PCOS, while having significantly higher testosterone concentrations than their female controls, have much lower testosterone concentrations than male controls. This indicates that in addition to modulating MSNA in women with PCOS, testosterone level is an important factor explaining the sex difference in sympathetic outflow seen in the normal population.

Thyrotropic and somatotropic hormonal axes and MSNA. Thyrotropin-releasing hormone (TRH) has been shown to increase MSNA in humans (46), and in conditions associated with thyroid dysfunction, TSH levels are positively related to MSNA levels (26). In the present study, TSH and free T4 concentration did not differ between the study groups, indicating that the thyrotropic hormonal axis cannot account for the difference in MSNA found in this study.

We have recently demonstrated that low serum IGF-I concentration is associated with high MSNA, showing that the GH-IGF-I axis is involved in the regulation of central sympathetic outflow (42–44). In this study, serum IGF-I concentration was increased in women with PCOS compared with controls but was not related to sympathetic nerve traffic. The elevated serum IGF-I levels in the present study are in line with a previous observation in lean PCOS women, whereas obese PCOS women exhibited normal levels (32, 53), indicating that it is the androgen excess that contributes to the elevated IGF-I levels.

Features of the metabolic syndrome and MSNA. Peripheral cardiovascular risk factors such as abdominal obesity, dyslipidemia, glucose intolerance, and insulin resistance (34), known to be associated with PCOS, may per se provoke changes in sympathetic nerve activity (8, 20, 21, 35, 41). Limited data are available related to the effects of androgens on cardiac autonomic function. However, in a recent study, autonomic innervation of the heart was shown to be affected in young women with PCOS with increased sympathetic and decreased parasympathetic components of HRV, and it was suggested that an increase in androgen levels plays a potential role for the alternation in HRV (54).

In three recent studies addressing sympathetic nerve activity in the metabolic syndrome itself, MSNA was shown to be directly related to waist circumference and HOMA-IR and not to hypertension (13, 14, 18), demonstrating that sympathetic activation is not limited to individuals whose metabolic syndrome is accompanied by hypertension, indicating that sympathetic hyperactivity is a central feature of the metabolic syndrome (13, 14). This is in line with our results showing that women with PCOS, a condition regarded as the female metabolic syndrome, are normotensive despite displaying intense sympathetic activation. The role of MSNA in blood pressure control is controversial given that previous studies on sympathetic activity in hypertension have yielded inconsistent results (44). A previously demonstrated independent action of MSNA...
and BMI on diastolic blood pressure in healthy males is in line with the findings of Grassi and coworkers (13, 14) and may help explain the highly variable results in former studies of MSNA and hypertension (44).

In the present study, WHR, cholesterol, and insulin concentrations as well as HOMA-IR index were significantly increased in women with PCOS compared with controls. WHR, insulin concentration, and HOMA-IR index, however, were not related to MSNA, showing that these metabolic abnormalities cannot explain the sympathoexcitation seen in this group. In this study, cholesterol concentration was related to MSNA (Fig. 2B). Previous studies have shown either no relation or a weak relation between cholesterol concentration and MSNA. Although the regression analysis of our present data identifies cholesterol levels as a predictor of MSNA in PCOS, its effect is weaker than that of testosterone, and the factors appear to act independently. Cholesterol levels were not related to testosterone levels.

Birth weight and MSNA. Girls born SGA are thought to run a higher risk of developing PCOS in adulthood than those born at weights appropriate for gestational age (19). Besides being associated with risk factors of the metabolic syndrome, SGA has previously been shown to be associated with increased sympathetic nerve traffic (3). In our cohort of women with PCOS, none were born SGA and one was born LGA, demonstrating that size at birth was not the underlying cause for the sympathoexcitation associated with PCOS in this study.

Conclusion. This is the first study to directly address sympathetic nerve activity in women with PCOS, and the novel finding is that women with PCOS have significantly higher sympathetic nerve activity than their matched controls. The increased sympathetic outflow is related to hormonal and metabolic features, and the study identifies testosterone and cholesterol as independent predictors of sympathetic nerve activity in PCOS. Although both are important factors for sympathetic activity, testosterone has a stronger impact than cholesterol. Because the degree of androgen concentration can reflect the severity of PCOS, the relationship between MSNA and testosterone concentration found in this cohort of women with PCOS indicates that the degree of sympathoexcitation is related to the degree of PCOS severity. The augmented sympathetic activity in PCOS contributes to the vascular risk factors associated with the condition, and therapies aimed at reducing sympathetic activity in this condition need to be studied.

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