Polycystic Ovary Syndrome
Androgens and Hypertension

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Polycystic ovary syndrome (PCOS) is a condition of ovarian dysfunction that affects 6% to 10% of women of reproductive age. The hallmarks of PCOS are menstrual cycle irregularities, androgen excess, and polycystic ovaries, as defined by the Rotterdam Consensus on Diagnostic Criteria for PCOS. Most women also exhibit elevated luteinizing hormone/follicular-stimulating hormone ratios but normal levels of estradiol. In addition, many women with PCOS are obese, and Ehrmann et al\textsuperscript{1} reported recently that 33.4% of US women with PCOS exhibit symptoms of the metabolic syndrome, such as increased hyperglycemia, insulin resistance, and dyslipidemia, although this percentage varies depending on the cohort studied. Frequently these young women exhibit hypertension as well.

Despite the list of characteristics that typically accompany PCOS, the exact mechanism(s) responsible for hypertension in women with PCOS is controversial. Many of the symptoms associated with PCOS have been shown to also be associated with increases in blood pressure, such as increases in body mass index and the presence of metabolic syndrome, with its accompanying insulin resistance and type 2 diabetes.

Whether androgens contribute to the hypertension in women with PCOS has not been shown previously. In the current issue of \textit{Hypertension}, Chen et al\textsuperscript{2} attempt to dissect the role that androgens may play in mediating the hypertension in young women with PCOS. Their studies were performed in a cohort of Taiwanese women, with an average age of 24 years. In multiple linear regression models, they found that the serum free androgen index or total testosterone levels were strongly independent of age, body mass index, insulin resistance, or dyslipidemia. In fact, they found that the odds ratio for free androgen index to predict an increased risk of hypertension was 3.817. These data strongly support a role for androgens in mediating the hypertension in young women with PCOS.

Whether androgens increase blood pressure is controversial. Men have been shown to have higher blood pressures than women when blood pressure is measured by the 24-hour ambulatory monitoring techniques.\textsuperscript{3} However, in men, hypertension and other chronic diseases are associated with lower levels of serum testosterone.\textsuperscript{4} These data have lead scientists and physicians to propose that androgens play no role in mediating hypertension in men. However, it is possible that androgens do contribute to the etiology of hypertension, but androgen levels then decrease once the hypertension is established and reflect a compensatory protective mechanism to lower serum androgens to further attenuate androgen-mediated cardiovascular disease.

In women, the role that androgens may play in modulating their blood pressure is even less well understood. In normal young women, any androgen-mediated effect on blood pressure would be offset by the much higher levels of estrogens. After menopause, the prevalence of hypertension becomes higher in women than in men,\textsuperscript{5} but whether androgens are elevated in women after menopause is also controversial. In serial studies of women in the Rancho Bernardo cohort, serum testosterone levels decreased significantly in early menopause, but with time serum testosterone levels increased, eventually reaching premenopausal levels by 70 to 80 years of age.\textsuperscript{6} The ovary in the postmenopausal woman can produce androgens, and it is likely that unopposed androgens contribute to the higher blood pressure in postmenopausal women. Although few studies have been done to determine whether women who suffered from PCOS when young showed a higher incidence of cardiovascular disease when elderly, Wild et al\textsuperscript{7} found that women who had had a history of PCOS 30 years previously did in fact have a higher prevalence of hypertension and other cardiovascular diseases later in life than did control subjects without PCOS.

The mechanism(s) by which androgens could increase blood pressure in women with PCOS, or in men, for that matter, is not clear. In the spontaneously hypertensive rat, males have higher blood pressures than females. However, androgen supplements in ovariecotomized female spontaneously hypertensive rats increase blood pressure in a dose-dependent manner. When the renin–angiotensin system (RAS) is blocked, androgen supplements in ovariecotomized females can no longer increase blood pressure.\textsuperscript{8} Furthermore, androgens in male rats are associated with increased expression of angiotensinogen in the kidney. These data support a role for the RAS in mediating androgen-stimulated increases in blood pressure.

The ovary has a functional RAS that is important in steroidogenesis and follicular function.\textsuperscript{9} In women with PCOS, plasma renin activity was found to be elevated compared with a nonoligomenorrheic group of age-matched women.\textsuperscript{10} Plasma prorenin has also been shown to be higher in women with PCOS and correlates positively with serum androgen levels.\textsuperscript{11} It is possible that androgens could increase blood
pressure in women with PCOS by increasing the expression of components of the RAS. Expression of renin and angiotensin has been shown to be present immunohistochemically in the thecal cell layer of normal women, but is strongly expressed in both granulosa and thecal cells. Thecal cells are responsible for production of androgens in the follicle. When women with PCOS were treated with an angiotensin-converting enzyme inhibitor, there was a significant reduction in hypertension and serum testosterone independent of serum hormone-binding globulin, suggesting that RAS blockade protects against androgen synthesis. Alternatively, alterations in the ovarian RAS may increase androgen synthesis and, thus, the increase in serum-free testosterone may be an indicator of RAS stimulation rather than being the stimulator itself.

Another possible mechanism responsible for hypertension in women with PCOS could be endothelin. Endothelin-1 has been found in human follicular fluid, and endothelin-1 mRNA expression has been found in ovarian tissues. In addition, the endothelin A receptor subtype has been found in granulosa cells. Diamanti-Kandarakis et al reported that serum endothelin levels were higher in women with PCOS independent of body mass index, and a positive correlation was found between free androgen index and plasma endothelin levels. When the women with PCOS were treated with metformin, serum endothelin levels decreased with no effect on body mass index, and hyperandrogenemia was normalized. Androgens have been shown to increase plasma endothelin in female-to-male transsexuals receiving testosterone therapy who themselves exhibit PCOS. Because angiotensin II has been shown to stimulate endothelin production, it is possible that androgens may directly stimulate endothelin or may stimulate the RAS to increase endothelin, thus leading to the expression of two powerful vasoconstrictors that could impact blood pressure in women with PCOS.

In summary, the article of Chen et al in this issue of Hypertension confirms a relationship between the higher level of androgens and blood pressure in women with PCOS who are not obese. However, the mechanisms by which hyperandrogenemia mediates the higher blood pressure in women with PCOS remain to be determined.

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References
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