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# Vascular compliance in women with polycystic ovary syndrome treated with spironolactone

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age in the United States and has been associated with several diseases including cardiovascular disease, obesity, and glucose intolerance. In this study, systolic blood pressure, diastolic blood pressure, pulse pressure (vascular compliance), large artery elasticity, systemic vascular resistance (SVR), total vascular impedance (TVI), and body mass index (BMI) were measured before and after treatment with spironolactone in 10 women with PCOS. Systolic BP, diastolic BP, and BMI were similar prior to treatment and after treatment. Pulse pressure decreased slightly post-treatment compared to pretreatment but not to significance ($P = 0.07$). The results show that after treatment with spironolactone, there was a statistically significant increase in large artery elasticity ($P = 0.047$), while there was a statistically significant decrease in SVR and TVI ($P = 0.0005$ and $P = 0.03$). This study indicates that treatment with spironolactone improves large artery elasticity and reduces systemic vascular resistance without any change in small artery elasticity.

## 1 | INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age in the United States, with research showing that about 5% to 18% of females between 18 and 44 affected with the disorder.[1,2] PCOS involves defects in the hypothalamic-pituitary axis, insulin secretion and action, and ovarian function, which can lead to elevated androgen levels, menstrual irregularities, and/or increased follicular number and volume in one or both ovaries.[1,3,4] Increased insulin levels cause ovarian overproduction of androgens, leading to anovulation.[1,5]

Women with PCOS are predisposed to higher rates of cardiovascular disease, obesity, dyslipidemia, hypertension, impaired glucose tolerance, type 2 diabetes mellitus, and endometrial cancer.[1,6] Cardiovascular disease is of concern for both women and men as it is the leading cause of mortality in the United States.[7] In addition, women with PCOS are reported to have surrogate markers of vascular diseases, such as impaired endothelial function and increased carotid artery intima-media thickness.[8,9]

The stiffness (or compliance) of the vascular wall is an important factor in cardiovascular disease, because it affects the contraction and expansion of the vessel in response to changes in transmural pressure.[10] Compliance is affected by components such as collagen, elastin, and smooth muscle.[11] The measurement of vascular compliance provides a way to detect the disease early before clinical signs and symptoms of vascular disease appear.[11]

There is a greater likelihood of subclinical cardiovascular disease in premenopausal women with PCOS which risks progression to more advanced cardiovascular disease with aging, compared to women without PCOS.[9] Central arterial stiffness is characterized by excess collagen versus elastin in the vessel wall, which is induced by inflammation and increased intraluminal pressure.[12-14] Greater arterial stiffness in postmenopausal women with PCOS, independent of age and systolic blood pressure, suggests a direct effect of PCOS risk factors on the vascular wall.[15] Furthermore, hypertension in PCOS, most likely due to insulin resistance and hyperinsulinemia, alters vascular smooth muscle cells causing vascular muscle wall hypertrophy with reduced compliance and interference with endothelium-dependent vasodilatation mechanisms.[16] The increased arterial stiffness in postmenopausal women with PCOS, which was independent of age and systolic blood pressure, implies a possible direct effect of PCOS components on the vascular wall.[15]

  

Aldosterone has also been implicated in inflammation, vascular smooth muscle hypertrophy, and collagen accumulation leading to aortic stiffness[17,18] and promotes structural and functional altering of the vasculature, resulting in loss of arterial compliance and increased peripheral resistance.[19] In patients with essential hypertension, a significant negative correlation was observed between plasma aldosterone and systemic arterial compliance, which was not influenced by age or blood pressure.[20] Aldosterone has also been shown to promote baroreceptor dysfunction and vascular damage and impairs arterial compliance.[21-24]

Spironolactone is a potassium-sparing diuretic, widely used in the treatment of hypertension, hyperaldosteronism, and congestive heart failure; it also blocks androgen receptors, decreasing acne, and hirsutism.[1,25] Spironolactone in patients with PCOS is typically given in combination with oral contraceptives because of the risk of teratogenic effects in male fetuses, affecting androgen-dependent developmental processes.[25] Spironolactone antagonizes aldosterone action, which has been found to improve endothelial function and arterial stiffness.[17,18,26-28]

Based on these findings, we expected that the use of spironolactone would increase vascular compliance, providing beneficial effects to patients with PCOS that use the medication. The aim of this study was to explore the effects of spironolactone on vascular compliance after 12 weeks of taking the medication.

## 2 | METHODS

### 2.1 | Patients

Our study was designed to be exploratory to see whether an effect on vascular compliance could be seen after treatment with spironolactone; therefore, no sample size calculation was performed. Ten women with PCOS with signs and symptoms of hyperandrogenism (anovulation, androgen excess, and/or polycystic ovaries), and normal serum levels of prolactin, FSH, TSH, and 17-OH progesterone signed an Institutional Review Board (IRB) approved consent form. Exclusion criteria were 35 years of age or older, pregnant, or had hypothyroidism, Cushing syndrome, diabetes mellitus, hyperprolactinemia, nonclassical adrenal hyperplasia, current and previous use of oral contraceptives, and the use of any medications.

### 2.2 | Design

Patients were treated with spironolactone 50 mg twice daily for 12 weeks. Systolic blood pressure, diastolic blood pressure, and pulse pressure, which is associated with vascular compliance, large artery elasticity, systemic vascular resistance (SVR), total vascular impedance (TVI), and body mass index (BMI) were measured prior to treatment and at the end of 12 weeks.

Arterial pulse contour analysis (Cardiovascular Profiling Instrument; HDI, Eagan, MN) estimates vascular compliance/stiffness of large and small arteries. The radial artery pulse is recorded noninvasively by applanation tonometry through this technique. A tonometer is positioned over the point of maximal pulsation of the artery, minimally compressing the vessel against the bony surface of the radius. The tonometer senses the electrical resistance, which varies with the intra-arterial pressure directly, allowing the accurate recording of the arterial waveform. A computerized algorithm analyzes the waveforms; the slope of the diastolic decay provides an estimate of large vessel compliance ($C_1$) while oscillations in the diastolic contour resulting from reflected pressure generated from blood striking resistance vessels and branch points represent small vessel compliance ($C_2$). Additional parameters including stroke volume, cardiac output, and systemic vascular resistance can be derived from the algorithm. Systolic and diastolic blood pressure as well as mean arterial pressure and pulse rate is determined oscillometrically from a cuff placed over the contralateral brachial artery.

### 2.3 | Statistical analysis

Data are presented as mean ± standard deviation. Comparisons between the data before and after treatment with spironolactone were made using t test. $P < 0.05$ was considered statistically significant.

## 3 | RESULTS

Table 1 shows the demographic data of the 10 study patients. All study patients were African American women who had a mean age of 28.7 8 years and a body mass index (BMI) of 27.4 1.2 kg/m$^2$.

Table 2 shows the analysis of vascular measurements for vascular compliance prior to treatment and after treatment with spironolactone in women with PCOS after 12 weeks. Spironolactone treatment had no significant effect on systolic and diastolic blood pressure: 118/69 mm Hg pretreatment versus 117/72 mm Hg post-treatment; pulse pressure 49 mm Hg pretreatment versus 45 mm Hg post-treatment; or BMI: 27.4 kg/m$^2$ pretreatment and 27.3 kg/m$^2$ post-treatment. Large artery elasticity was found to be 16.5 mL/mm Hg × 10 pretreatment versus 17.2 mL/mm Hg × 10 post-treatment ($P = 0.047$). SVR was found to be 1245 dynes/s/cm$^5$ pretreatment

**TABLE 1** Demographics

| Variables | Mean ± Standard deviation |
|---|---|
| Age (years) | 28.7 ± 8 |
| BMI (kg/m$^2$) | 27.4 ± 1.2 |
| Glucose (mg/dL) | 86.4 ± 14 |
| Insulin | 29.1 ± 10 |
| Total cholesterol (mg/dL) | 186.6 ± 8.6 |
| Triglycerides (mg/dL) | 86 ± 12 |
| HDL (mg/dL) | 56 ± 3 |

BMI, body mass index; HDL, high-density cholesterol.
Data are presented as mean ±SD or median.

**TABLE 2** Vascular Compliance in Women with PCOS

| | Pretreatment | Post-treatment | *P*-value |
|---|---|---|---|
| Systolic BP (mm Hg) | 118 ± 4 | 117 ± 4 | NS |
| Diastolic BP (mm Hg) | 69 ± 4 | 72 ± 3 | NS |
| Pulse Pressure (mm Hg) | 49 ± 2 | 45 ± 2 | 0.07 |
| Large Artery Elasticity/$C_1$ (mL/mm Hg × 10) | 16.5 ± 0.9 | 17.2 ± 1.2 | 0.047 |
| SVR (dynes/s/cm$^5$) | 1245 ± 66 | 1211 ± 66 | 0.0005 |
| TVI (dynes/s/cm$^5$) | 116 ± 8 | 109 ± 9 | 0.03 |
| BMI (kg/m$^2$) | 27.4 ± 1.2 | 27.3 ± 1.2 | NS |

BMI, body mass index; BP, blood pressure; NS, not significant; SVR, systemic vascular resistance; TVI, total vascular impedance.
Data are presented as mean ± SD or median.

versus 1211 dynes/s/cm$^5$ post-treatment ($P = 0.0005$). TVI was 116 dynes/s/cm$^5$ pretreatment versus 109 dynes/s/cm$^5$ post-treatment ($P = 0.03$; Refer to Table 2).

## 4 | DISCUSSION

This study showed that large artery elasticity increased while systemic vascular resistance and total vascular impedance decreased after 12 weeks of treatment with spironolactone.

SVR was reduced, which is consistent with an increase in large vessel elasticity. Peripheral blood pressure was unchanged; however, central blood pressure, which may be more closely related to cardiovascular events[29,30] and potentially a better indicator of antihypertensive response,[31] may have been lowered as was seen in clinical trials, such as the CAFÉ study.[32] Unfortunately, our device lacks the capability of calculating central blood pressure.

The finding of increased large vessel elasticity may be due to spironolactone's targeting of androgens, which have been found to contribute to endothelial dysfunction. It has been found that treatment with spironolactone in nonobese PCOS patients reversed endothelial dysfunction.[33] Endothelial dysfunction in patients with PCOS has been found to be associated with androgens, whose receptors are present in the vessel wall, suggesting a possible target for spironolactone therapy.[33] The RALES trial showed that there was a significant reduction in both pro-collagen I and III in patients who were randomized to spironolactone versus placebo.[34,35] It was also found in patients with nonischemic dilated cardiomyopathy that spironolactone reduces aortic stiffness after 6 months of treatment compared with placebo.[17]

Spironolactone may have also increased large vessel elasticity through its effect on aldosterone. Data suggest that mineralocorticoid receptor antagonism may be useful for the treatment of hypertension and that it improves endothelial function and arterial stiffness.[26,27,36] Druppel et al also found that spironolactone prevents the time-dependent appearance of stiff endothelial cell syndrome by downregulating mineralocorticoid receptors that increased in the presence of aldosterone alone, improving endothelial function long term.[37] Furthermore, independent of systemic blood pressure changes, spironolactone reduces arterial collagen and increases carotid distensibility in young or old spontaneously hypertensive rats.[38-40] Eplerenone, a more selective mineralocorticoid receptor antagonist, which does not block androgen receptors, has been shown to improve intima-media thickness in people with primary aldosteronism.[28] Also, in patients with heart failure, the use of spironolactone or eplerenone to block aldosterone has been associated with reductions in morbidity and mortality rates.[28,41,42]

There are no prospective studies showing increased cardiovascular issues or increased mortality due to cardiovascular disease in patients with PCOS. Other studies about increased cardiovascular morbidity and mortality in women with PCOS conducted remain inconclusive.[16,43-45]

The purpose of this study was to understand the effect of spironolactone on vascular compliance. This study has shown that spironolactone may have a beneficial effect on vascular components, such as large artery elasticity, SVR, and TVI. This information could have implications for the treatment of conditions associated with PCOS and women who already have cardiovascular conditions and hypertension, which increase the risk of cardiovascular disease. However, there are no studies that show the effect of spironolactone on cardiovascular health in women with PCOS. Further study is required to understand the impact of spironolactone on the cardiovascular health in women with PCOS.

This study may be limited by several factors. Since our study was meant to be an exploratory investigation into the effects of spironolactone on vascular compliance, our sample size was very small. Further research should be done by expanding the sample size and possibly using a crossover study or control group to better assess the effects of spironolactone on large artery elasticity, SVR, and TVI. We also had our results reported only at the end of 12 weeks, as that is the usual follow-up time for our patients with PCOS. It would be nice to have taken measurements at smaller intervals in order to identify the time during which the spironolactone began to take effect as well as time after 12 weeks to see how beneficial the effect is.

## 5 | CONCLUSIONS

The treatment with spironolactone shows that large artery elasticity improved. There was also a highly significant reduction in systemic vascular resistance without any change in small artery elasticity. There was no significant change in blood pressure resulting from the functional and structural changes in large blood vessels.

## CONFLICT OF INTEREST

The authors report no conflict of interests to disclose.

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## REFERENCES

1. Ndefo UA, Eaton A, Green MR. Polycystic ovary syndrome: a review of treatment options with a focus on pharmacological approaches. *P T*. 2013;38(6):336-355.
2. NIH Department of Health and Human Services. *Beyond infertility: polycystic ovary syndrome (PCOS)*. Bethesda, MD: NIH; 2008.
3. Umland EM, Klootwyk J. Menstruation-related disorders. In: DiPiro JT, Talbert RL, Yee GC, et al. *Pharmacotherapy: a pathophysiologic approach*, 10th edn. New York: McGraw-Hill; 2011:1393.
4. Kim HJ, Adams JM, Gudmundsson JA, Arason G, Pau CT, Welt CK. Polycystic ovary morphology: age-based ultrasound criteria. *Fertil Steril*. 2017;108(3):548-553.
5. Diamanti-Kandarakis E, Kandarakis H, Legro RS. The role of genes and environment in the etiology of PCOS. *Endocrine*. 2006;30(1):19-26.
6. McFarland C. Treating polycystic ovary syndrome and infertility. *MCN Am J Matern Child Nurs*. 2012;37(2):116-121.
7. National Center for Health Statistics. *Health, United States, 2016: with chartbook on long-term trends in health*. Hyattsville, MD: National Center for Health Statistics; 2017.
8. Wild RA, Carmina E, Diamanti-Kandarakis E et al. Dumesic assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS). *J Clin Endocrinol Metab*. 2010;95(5):2038-2049.
9. Meyer ML, Malek AM, Wild RA, Korytkowski MT, Talbott EO. Carotid artery intima-media thickness in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update*. 2012;18(2):112-126.
10. Winer N, Sowers JR. Vascular compliance in diabetes. *Curr Diab Rep*. 2003;3(3):230-234.
11. Muneyyirci-Delale O, Winer N, Oklander V et al. Vascular compliance in women with polycystic ovary syndrome and healthy women. *J Cardiometab Syndr*. 2007;2(1):40-44.
12. Scicchitano P, Dentamaro I, Carbonara R et al. Cardiovascular risk in women with PCOS. *Int. J Endocrinol Metab*. 2012;10(4):611-618.
13. Federici A, Ciccone M, Cicinelli E et al. Effects of estrogen therapy on arterial resistance and pulsatility in postmenopausal women. *Angiology*. 2001;52(1):15-23.
14. Zieman S, Meleovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler, Thromb Vasc Biol*. 2005;25(5):932-943.
15. Armeni E, Stamatelopoulos K, Rizos D et al. Arterial stiffness is increased in asymptomatic nondiabetic postmenopausal women with a polycystic ovary syndrome phenotype. *J Hypertens*. 2013;31(10):1998-2004.
16. Palomba S, Santagni S, Falbo A, La Sala GB. Complications and challenges associated with polycystic ovary syndrome: current perspectives. *Int J of Womens Heath*. 2015;7:745-763.
17. Vizzardi E, Pina PD, Caretta G et al. The effect of aldosterone-antagonist therapy on aortic elastic properties in patients with non-ischemic dilated cardiomyopathy. *J Cardiovasc Med (Hagerstown)*. 2015;16(9):597-602.
18. Cachofeiro V, Miana M, de Las HN et al. Aldosterone and the vascular system. *J Steroid Biochem Mol Biol*. 2008;109(3–5):331-335.
19. Ovaert P, Bernay F, Guillot E, Bardon T. Aldosterone receptor antagonists – how cardiovascular actions may explain their beneficial effects in heart failure. *J Vet Pharmacol Ther*. 2009;33:109-117.
20. Blacher J, Amah G, Girerd X et al. Association between increased plasma levels of aldosterone and decreased systemic arterial compliance in subjects with essential hypertension. *Am J Hypertens*. 1997;10:1326-1334.
21. Dieterich HA, Wendt C, Saborowski F. Cardioprotection by aldosterone receptor antagonism in heart failure: the role of aldosterone in heart failure. *Human Physiol*. 2005;31(6):97-105.
22. Sun Y, Ramires FJ, Weber KT. Fibrosis of atria and great vessels in response to angiotensin II or aldosterone infusion. *Cardiovasc Res*. 1997;35(1):138.
23. Wang W. Chronic administration of aldosterone depresses baroreceptor reflex function in the dog. *Hypertension*. 1994;24:571.
24. Rocha R, Khanna K, Zuckerman A, Stier CT Jr. Mineralocorticoid blockade reduces vascular injury in stroke-prone hypertensive rates. *Hypertension*. 1998;31:451-458.
25. McCartney CR, Marshal JC. Polycystic ovary syndrome. *N Engl J Med*. 2016;375(1):54-64.
26. Dudenbostel T, Glasser SP. Effects of antihypertensive drugs on arterial stiffness. *Cardiol Rev*. 2012;20(5):259-263.
27. Schiffrin EL. Remodeling of resistance arteries in essential hypertension and effects of antihypertensive treatment. *Am J Hypertens*. 2004;17(12):1192-1200.
28. Matsuda Y, Kawate H, Matsuzaki C et al. Eplerenone improves carotid intima media thickness (IMT) in patients with primary aldosteronism. *Endoc J*. 2016;63(3):249-255.
29. Carmel M, McEniery J, Roman MJ, Franklin SS, Wilkinson IB. Central blood pressure: current evidence and clinical importance. *Eur Heart J*. 2014;35(26):1719-1725.
30. Valachopoulos C, Aznouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *Eur Heart J*. 2010;31(15):1865-1871.
31. Trudeau L. Central blood pressure as an index of antihypertensive control: determinants and potential value. *Can J Cardiol*. 2014;30(5):S23-S28.
32. Williams B, Lacy PS, Thom SM et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation*. 2006;113:1213-1225.
33. Studen KB, Sebestjen M, Pfeifer M, Prezelj J. Influence of spironolactone treatment on endothelial function in non-obese women with polycystic ovary syndrome. *Eur J Endocrinol*. 2011;164(3):389-395.
34. Milliez P, DeAngelis N, Rucker-Martin C et al. Spironolactone reduces fibrosis of dilated atria during heart failure in rats with myocardial infarction. *Eur Heart J*. 2005;26:2193-2199.
35. Zannad F, Alla F, Dousset B, Perez A, Pitt B. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure:

insights from the randomized aldactone evaluation study (RALES). *Circulation*. 2000;102(22):2700-2706.
36. Krum H, Hector N, Workman D, He W, Roniker B, Krause S. Fakouhi K. Efficacy of eplerenone added to renin-angiotensin blockade in hypertensive patients. *Hypertension*. 2002;40:117-123.
37. Drüppel V, Kusche-Vihrog K, Grossmann C et al. *Long-term application of the aldosterone antagonist spironolactone prevents stiff endothelial cell syndrome*. 2013;27(9):3652-3659.
38. Nehme JA, Lacolley P, Labat C et al. Spironolactone improves carotid artery fibrosis and distensibility in rat post-ischemic heart failure. *J Mol Cell Cardiol*. 2005;39:511-519.
39. Benetos A, Lacolley P, Safar ME. Prevention of aortic fibrosis by spironolactone in spontaneously hypertensive rats. *Arteriosc Thromb Vascular Biol*. 1997;17(6):1152-1156.
40. Lacolley P, Safar ME, Lucet B, Ledudal K, Labat C, Benetos A. Prevention of aortic and cardiac fibrosis by spironolactone in old normotensive rats. *J Am Coll Cardiol*. 2001;37(2):662-667.
41. Pitt B, Zannad F, Remme WJ et al. Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709-717.
42. Pitt B, Neaton J, Martinez F et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309-1321.
43. Cibula D, Cifkova R, Fanta M, Poledne R, Zivny J, Skibova J. Increased risk of non-insulin dependent diabetes mellitus, arterial hypertension and coronary artery disease in perimenopausal women with a history of the polycystic ovary syndrome. *Hum Reprod*. 2000;15(4):785-789.
44. Elting MW, Korsen T, Schoemaker J. Obesity, rather than menstrual cycle pattern or follicle cohort size, determines hyperinsulinaemia, dyslipidaemia and hypertension in ageing women with polycystic ovary syndrome. *Clin Endocrinol*. 2001;55(6):767-776.
45. Wild S, Pierpoint T, Jacobs H, McKeigue P. Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study. *Hum Fertil(Camb)*. 2000;3(2):101-105.

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