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Abstract—Salt sensitivity of blood pressure is associated with an elevated risk of developing hypertension (HTN) and is an independent risk factor for cardiovascular disease. The prevalence of HTN increases after menopause. The aim of this study was to investigate prospectively whether the loss of ovarian hormones increases the occurrence of salt sensitivity among healthy premenopausal women. We enrolled 40 normotensive, nondiabetic women (age 47.2±3.5), undergoing hysterectomy–oophorectomy for nonneoplastic processes and not on hormone replacement, to determine the effect of changes in sodium intake on blood pressure the day before and subsequently 4 months after surgical menopause. Salt loading was achieved using a 2-L normal saline infusion and salt depletion produced by 40 mg of intravenous furosemide. A decrease >10 mm Hg in systolic blood pressure between salt loading and salt depletion was used to define salt sensitivity. Before and after menopause, salt-sensitive women exhibited higher waist/hip and waist/thigh ratios ($P<0.01$). Although all of the women remained normotensive, the prevalence of salt sensitivity was significantly higher after surgical menopause (21 women; 52.5%) than before (9 women; 22.5%; $P=0.01$), because 12 (38.7%) salt-resistant women developed salt sensitivity after menopause. In summary, we demonstrated that the prevalence of salt sensitivity doubled as early as 4 months after surgical menopause, without an associated increase in blood pressure. Epidemiological studies indicate that development of HTN may not occur until 5 to 10 years after menopause. The loss of ovarian hormones may unmask a population of women prone to salt sensitivity who, with aging, would be at higher risk for the subsequent development of HTN and cardiovascular disease. **(*Hypertension*. 2006; 47:1168-1174.)**

Key Words: risk factors ■ hormones ■ gender ■ cardiovascular diseases

Hypertension (HTN) is a major risk factor for cardiovascular disease (CVD), which is the leading cause of morbidity and mortality in postmenopausal women.[1,2] After menopause, the sharp increase in the prevalence of HTN to levels that equal or surpass that of men suggests that ovarian hormones participate in the protection afforded to premenopausal women.[1,3–7] However, not all postmenopausal women develop HTN and CVD; therefore, identifying those women at risk is of critical importance.

Acute blood pressure elevation with increasing salt intake (salt sensitivity [SS]) has been reported in certain segments of the population, particularly among those with renal disease, diabetes, obesity, HTN, and older age.[8,9] Studies by Weinberger et al[10] conducted in mixed groups of subjects revealed that 26% of normotensive subjects and 51% of hypertensive subjects could be reproducibly classified as SS and that SS normotensive subjects are at an increased risk for subsequent age-related HTN.[11] Importantly, SS is an independent risk factor for increased cardiovascular morbidity and mortality in normotensive and hypertensive individuals.[12,13]

Postmenopausal women have been shown to be more SS than premenopausal women.[14,15] A study conducted in postmenopausal women showed that SS correlated inversely with levels of circulating ovarian hormones,[16] suggesting that decreases in ovarian hormone levels and increased sensitivity to dietary sodium may be important factors in the genesis of postmenopausal HTN. It has been reported that, compared with premenopausal women, the pressure–natriuresis curve of postmenopausal women is significantly shifted to the right.[15] This indicates that blood pressure becomes SS after the menopause, as first suggested by Weinberger et al.[10] However, whether this increase in SS that develops after the menopause is because of aging only or because of the loss of ovarian hormones remains to be determined. The World Health Organization Cardiovascular Diseases and Alimentary Comparison Study found that there was a strong sodium–blood pressure association, independent of age, in postmenopausal women.[17] They suggested 2 possible explanations. One is that women who have increased SS after menopause

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may have had SS before menopause. The other is that hormonal changes that occur immediately after menopause may lead directly or indirectly, to some extent, to an increase in SS. The purpose of the present study was to investigate prospectively the prevalence rate of SS among a group of healthy, normotensive, premenopausal women scheduled to undergo hysterectomy and oophorectomy for nonneoplastic processes to determine whether the loss of ovarian hormones after surgical menopause increases SS.

Methods

Selection of Patients

Fifty women with preserved ovarian function scheduled to undergo hysterectomy and ovariectomy for nonneoplastic gynecological problems were initially considered eligible for the study. The patients were selected from a group of 265 women who underwent a preoperative examination at the Surgical Department of the Hospital Materno Infantil of Malaga. To select the patients, the women were asked to answer a self-administered questionnaire concerning their gynecological history; personal history of CVDs, diabetes mellitus, or other endocrine diseases; and previous use of hormone therapy or nonsteroidal antiinflammatory drugs. After completion of the questionnaire and a personal interview, women <45 years of age (except if they required ovariectomy) and >52 years of age; women with arterial HTN, diabetes mellitus, and other cardiovascular and endocrine diseases; and women with a body mass index (BMI) >32 were excluded from the study. Patients with gynecological cancers were also excluded from the study. None of the women were tobacco smokers. From the initial group of 50 women considered eligible for the study, 7 were subsequently excluded because they underwent hysterectomy without ovariectomy, and 3 refused to participate in the study after the surgery. Therefore, the final study population consisted of 40 normotensive, nondiabetic women with a mean age of 47 years (range, 43 to 52 years).

Study Design

The Ethics Committee of the Hospital Materno Infantil of Malaga approved the research. All of the patients gave informed consent. The procedures followed were in accordance with institutional guidelines. To determine the effect of loss of ovarian hormones on the development of SS, the patients underwent an acute salt-loading and an acute salt-depletion protocol the day before and subsequently 4 months after surgical menopause (hysterectomy and oophorectomy). The patients were placed on a diet containing 120 mmol/day of sodium chloride for 1 week before being admitted for the acute study protocol. The patients were admitted the day before the acute study protocol, and body weight, height, BMI (weight in kg/height in m^2), waist, hip, and thigh circumferences; blood pressure; and heart rate were recorded. Blood samples for hemoglobin, hematocrit, glucose, insulin, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, apolipoprotein B, uric acid, and creatinine were obtained after 12 hours of fasting. We obtained 24-hour urine collections for sodium at baseline and after the administration of furosemide. Urinary albumin excretion (mg/24 hours) was also measured from the 24-hour collection obtained at baseline. Salt loading was achieved with 2 L of normal saline infused over 3 hours. After the salt loading, body weight and blood pressure measurements were recorded, and salt depletion was produced by 40 mg of IV furosemide. Body weight was determined using the same scale (Atlantida, Sayol) at baseline and after the acute volume expansion and depletion phases. Blood pressure monitoring was performed with an ambulatory, automated, noninvasive oscillometric device (SpaceLabs 90207, SpaceLabs, Inc). The average of 3 consecutive readings obtained at baseline, after the completion of the saline infusion, and 3 hours after the administration of intravenous furosemide were used to classify the patients into the SS and salt-resistant groups. The cutoff used to define SS was a decrease >10 mm Hg in systolic blood pressure between salt loading and salt depletion. Our acute protocol has not been compared with the established technique of Weinberger et al.[10] Although the study time was shorter, we expect that this would, if anything, underestimate the number of patients defined as SS. We hypothesized that, in those patients with SS of blood pressure, an acute volume expansion followed by acute depletion would result in the same altered hemodynamic response regardless of the time period during which it is achieved.

Statistical Analysis

Values are expressed as mean±SD. Unpaired or paired Student *t* test or 1-way ANOVA with Bonferroni posttest for multiple comparisons, when appropriate, was used to compare the different parameters obtained between SS and salt-resistant women before and after surgical menopause. Differences in proportions were tested by χ^2 statistics. $P<0.05$ was used to reject the null hypothesis.

Results

Patient Characteristics Before Surgical Menopause

Table 1 shows the clinical characteristics and biochemical data of the 40 premenopausal women scheduled for hysterectomy and oophorectomy who were included in the study. No differences were observed in terms of age, BMI, baseline systolic and diastolic blood pressures, serum creatinine, hemoglobin, and hematocrit between premenopausal women classified as SS versus salt resistant. Regarding the

TABLE 1. Clinical and Biochemical Data of Study Participants Before Surgical Menopause

Variables	SS (n=9)	Salt Resistant (n=31)	P*
Characteristics			
Age, y	48.5±3.5	47±3.8	NS
Weight, kg	68.9±6.5	68.2±11.3	NS
BMI, kg/m^2	28.4±1.8	27.9±4.1	NS
WC, cm	88.0±9.1	85.6±7.7	NS
Waist/hip ratio	0.85±0.05	0.82±0.04	0.001
Waist/thigh ratio	1.58±0.14	1.50±0.13	0.005
SBP, mm Hg	129±14	127±14	NS
DBP, mm Hg	76±9	79±8	NS
Serum biochemistry			
Hemoglobin, g/L	12.3±1.2	12.7±1.0	NS
Hematocrit, %	37.0±2.6	37.5±2.3	NS
Glucose, mmol/L	5.82±0.47	5.41±0.95	NS
Insulin, mIU/mL	12.1±6.0	9.9±8.7	NS
Triglycerides, mmol/L	1.70±1.15	0.99±0.36	NS
Total cholesterol	5.44±0.67	5.38±0.93	NS
HDL, mmol/L	1.22±0.39	1.32±0.37	NS
LDL, mmol/L	3.67±0.85	3.51±0.88	NS
Uric acid, μmol/L	266±38	218±52	NS
Creatinine, mmol/L	80.4±13.3	82.2±11.5	NS
Urine albumin, mg/day	20.2±21.9	4.5±8	0.08

Values are presented as mean±SD. WC indicates waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant.

*P for SS vs salt resistant is from unpaired *t* tests between the 2 groups.

TABLE 2. Clinical and Biochemical Data of Study Participants After Surgical Menopause

Variables	SS (n=21)	Salt Resistant (n=19)	P*
Characteristics			
Age, y	47.9±3.7	46.7±3.7	NS
Weight, kg	71.0±10.7	66.9±11	NS
BMI, kg/m^2	29.2±3.9	27.2±4.1	NS
WC, cm	88.2±8.2	83.5±7.9	NS
Waist/hip ratio	0.87±0.06	0.79±0.03	<0.001
Waist/thigh ratio	1.60±0.12	1.45±0.13	<0.001
SBP, mm Hg	128±18	127±17	NS
DBP, mm Hg	79±9	75±12	NS
Serum biochemistry			
Hemoglobin, g/L	12.7±1.2	13.2±1.2	NS
Hematocrit, %	38.7±3.5	40.0±3.6	NS
Glucose, mmol/L	5.48±0.75	5.28±0.66	NS
Insulin, mIU/mL	15.3±6.6	10.0±3.2	0.002
Triglycerides, mmol/L	1.34±0.94	1.03±0.35	NS
Total cholesterol	5.49±0.88	5.28±0.88	NS
HDL, mmol/L	1.25±0.31	1.41±0.44	NS
LDL, mmol/L	3.61±0.86	3.33±0.86	NS
Uric acid, μmol/L	256±59	217±50	0.02
Creatinine, mmol/L	74.3±16.8	69.0±14.1	NS
Urine albumin, mg/day	14.4±20.3	5.75±4.7	0.06

Values are presented as mean±SD. WC indicates waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant.

*P for SS vs salt resistant is from unpaired t tests between the 2 groups.

metabolic variables measured, no significant differences were noted in waist circumference; fasting insulin; glucose; uric acid; triglycerides; and total, HDL, and LDL cholesterols. In contrast, waist/hip and waist/thigh ratios were significantly higher in those classified as SS as compared with salt resistant. Women classified as SS exhibited a higher 24-hour urinary albumin excretion rate that approached but did not reach statistical significance (P=0.08).

Patient Characteristics 4 Months After Surgical Menopause

The clinical characteristics and biochemical data of the patients 4 months after surgical menopause are shown on Table 2. As noted before menopause, waist/hip and waist/thigh ratios were significantly greater, and 24-hour urinary albumin excretion rate was higher, although of borderline significance (P=0.06), in postmenopausal women classified as SS versus salt resistant, whereas BMI; waist circumference; systolic and diastolic blood pressures; fasting glucose; triglycerides; and total, HDL, and LDL cholesterol were not different between the groups. Of note, all of the women remained normotensive 4 months after hysterectomy and oophorectomy.

There were no statistically significant differences in BMI, waist/hip and waist/thigh ratios, or insulin and uric acid levels before as compared with 4 months after surgical menopause among the SS women who remained SS, the salt resistant who became SS, or the salt resistant who remained salt resistant, according to our classification (Table 3). There was a nonsignificant increase in insulin levels after surgical menopause among the SS women who remained SS and among the salt-resistant women who became SS, whereas there was no change in insulin levels among those who remained salt resistant after menopause. Similarly, we found a nonsignificant increase in uric acid levels after menopause among the women who became SS. The difference in insulin and uric acid levels became statistically significant when the postmenopausal SS group was compared with the postmenopausal salt-resistant group (Table 2). Of note, the premenopausal salt-resistant women who developed SS within 4 months after surgical menopause manifested waist/hip and waist/thigh ratios that were similar to those of the SS women who remained SS but significantly higher than those of the salt-resistant women who remained salt resistant after surgical menopause (Table 3).

Prevalence of SS Before and 4 Months After Surgical Menopause

The baseline blood pressures and body weights and the blood pressure and body weight responses to salt loading and salt depletion before and 4 months after hysterectomy and oopho-

TABLE 3. Clinical and Biochemical Data of SS and Salt-Resistant Women Before and 4 Months After Surgical Menopause

	SS (n=9)		Salt Resistant to SS (n=12)		Salt Resistant (n=19)	
Variable	Premenopausal	Postmenopausal	Premenopausal	Postmenopausal	Premenopausal	Postmenopausal
Characteristics						
BMI, kg/m^2	28.4±1.8	29.0±4.0	28.5±4.0	29.4±3.9	27.7±4.9	27.2±4.1
Waist/hip	0.85±0.05*	0.86±0.07†	0.88±0.07*	0.87±0.05†	0.79±0.03	0.79±0.03
Waist/thigh	1.58±0.14*	1.59±0.11†	1.60±0.12*	1.60±0.13†	1.43±0.14	1.45±0.13
Biochemistry						
Insulin, mIU/mL	12.1±6.0	15.6±6.5	9.8±7.8	15.0±7.5	9.9±6.3	10±3.2
Uric acid, μmol/L	266±38	260±58	220±50	253±59	216±54	217±50

Values are expressed as mean±SD. Biochemical data obtained from serum.

*P<0.05 vs premenopausal salt resistant; †P<0.05 vs postmenopausal salt resistant.

TABLE 4. Blood Pressure and Body Weight Responses to Salt Loading and Depletion Before Surgical Menopause

Variable	Baseline	Salt-Loaded Period	Salt-Depleted Period	Δ Between Periods
Systolic blood pressure				
SS	129±14	138±15	125±16	12.2±1.8
Salt resistant	127±14	127±16	119±17	7.8±1.7
P for sensitive vs resistant*	NS	NS	NS	<0.001
Diastolic blood pressure				
SS	76±9	90±10	80±9	10.8±0.2
Salt resistant	79±8	80±8	74±9	5.9±0.9
P for sensitive vs resistant*	NS	NS	NS	<0.001
Body weight				
SS	68.9±6.5	70±6	69±7	1.4±0.2
Salt resistant	68.2±11.3	69±11	68±11	0.9±0.1
P for sensitive vs resistant*	NS	NS	NS	<0.001

Values are presented as mean±SD. NS indicates not significant.
**P* for SS (n=9) vs salt-resistant (n=31) is from unpaired *t* tests between the 2 groups.

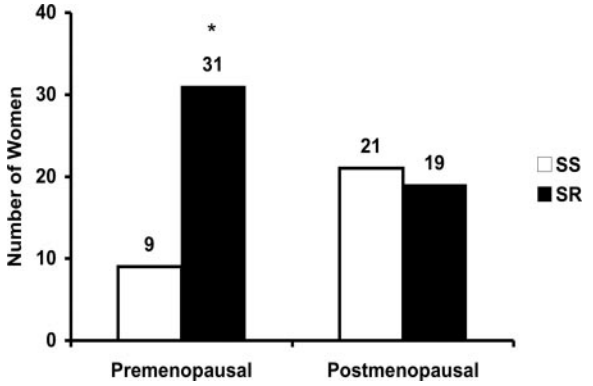
rectomy are shown in Tables 4 and 5. Before menopause, systolic and diastolic blood pressures after salt loading were higher (albeit not significantly) in women classified as SS versus salt resistant, whereas systolic and diastolic blood pressures after salt depletion were similar (Table 4). The fall in systolic (and diastolic) blood pressure after salt depletion was significantly greater in the SS than in the salt-resistant premenopausal women. The SS group manifested a greater weight gain and, thus, a greater weight loss in response to salt loading and salt depletion, respectively, as compared with the salt-resistant group. However, both groups returned to their baseline weight after salt depletion. Sodium excretion (mmol/24 hours) at baseline was not significantly different between the 2 groups (148.2±4.6 versus 168.3±16.8, Na^+ mmol/24 hours, SS versus salt resistant; $P=0.07$). However, after diuretic administration, sodium excretion was significantly higher in the salt-resistant group (182.2±7.5 versus 240.1±19.4, Na^+ mmol/24 hours, SS versus salt resistant; $P<0.001$).

After surgical menopause, systolic and diastolic blood pressures after salt loading were significantly higher in women classified as SS versus salt resistant, whereas systolic and diastolic blood pressures after salt depletion were similar (Table 5).[10,18] As expected, the fall in systolic (and diastolic) blood pressure after salt depletion was significantly greater in the SS than in the salt-resistant postmenopausal women. As noted during the premenopausal period, the change in body weight from salt loaded to salt depleted was slightly, but significantly, greater in the SS postmenopausal women but returned to baseline in both groups, as did the blood pressures. Sodium excretion at baseline was slightly but significantly greater in the SS group (183.5±41.2 versus 160.9±15.3, Na^+ mmol/24 hours, SS versus salt resistant; $P=0.02$), whereas sodium excretion after diuretic administration was greater in the salt-resistant group (233.4±13.9 versus 279.0±19.8, Na^+ mmol/24 hours, SS versus salt resistant; $P<0.001$). The greater urinary sodium excretion in response to the diuretic exhibited by the salt-resistant groups

TABLE 5. Blood Pressure and Body Weight Responses to Salt Loading and Depletion After Surgical Menopause

Variable	Baseline	Salt-Loaded Period	Salt-Depleted Period	Δ Between Periods
Systolic blood pressure				
SS	128±18	146±20	129±14	16.2±5.8
Salt resistant	127±17	132±14	123±18	9.0±4.1
P for sensitive vs resistant	NS	0.01	NS	<0.001
Diastolic blood pressure				
SS	79±9	92±8	79±9	12.8±1.3
Salt resistant	75±12	80±11	75±10	4.9±0.3
P for sensitive vs resistant	NS	<0.001	NS	<0.001
Body weight				
SS	71±10.7	73±11	71±11	1.7±0.1
Salt resistant	66.9±11	68±11	67±11	1.1±0.2
P for sensitive vs resistant	NS	NS	NS	<0.001

Values are presented as mean±SD. NS indicates not significant.
**P* for SS (n=21) vs salt resistant (n=19) is from unpaired *t* tests between the 2 groups.



Number of study participants with SS (□) and salt resistance (SR, ■) just before (premenopausal) and 4 months after hysterectomy and ovariectomy (postmenopausal). *Significant increase in number of women with SS after surgical menopause (P=0.01).

was reflected in the relatively greater change in blood pressure after the diuretic than after sodium loading (Tables 4 and 5). The lesser sodium excretion produced by the diuretic in the SS groups, both in the premenopausal and postmenopausal states, may reflect an enhanced sodium conservation by SS women.[18]

Based on our definition used to classify patients as SS (a decrease >10 mm Hg in systolic blood pressure from the salt-loaded to the salt-depleted phase, as described in the Methods section), the prevalence of SS was significantly higher after surgical menopause (21 women; 52.5%) than before (9 women; 22.5%; P=0.01; Figure), because 12 (38.7%) salt-resistant women developed SS after menopause.

Discussion

The major finding of this study is that the loss of ovarian hormones after surgical menopause, independent of aging, was associated with the development of SS in a substantive number of previously salt-resistant women, as determined by our acute protocol of salt loading and salt depletion. Indeed, the number of women classified as SS was significantly greater 4 months after surgical menopause. Our findings are novel given that, to our knowledge, no previous study examined in a longitudinal fashion the link between ovarian hormones and the blood pressure response to salt loading in humans. The World Health Organization Cardiovascular Diseases and Alimentary Comparison Study suggested that one of the mechanisms by which the menopause exerts its effects on risk of CVD is a tendency for a strong sodium-blood pressure association to develop, and our findings support that notion. Thus, after menopause, the loss of the ovarian hormones may unmask a population of women predisposed to SS and HTN that would be at higher risk for cardiovascular morbidity and mortality. The fact that this occurs in young women not affected by other established cardiovascular risk factors, which could confound our interpretation, provides support for the role of estrogen in modulating a potential important component in the pathogenesis of postmenopausal HTN.

The present observations may have important implications for CVD. SS hypertensive patients have a higher incidence of left ventricular hypertrophy,[19,20] endothelial dysfunction,[21] hyperlipidemia,[22,23] and microalbuminuria[22–24] compared with salt-resistant hypertensive patients. In addition, an association between insulin resistance and SS in nondiabetic, nonobese, essential hypertensive subjects has been reported.[22,25] Associations between high normal urinary albumin excretion and SS and between insulin resistance and SS have also been found in young, healthy, normotensive subjects.[24,26,27] Together, these findings indicate that SS patients display a cluster of cardiovascular risk factors and, thus, highlight the important link between SS and CVD.[28]

In the present study, we found that the women classified as SS, both before and after surgical menopause, exhibited greater urinary albumin excretion than their salt-resistant counterparts, although the differences did not reach statistical significance. Low levels of urinary albumin excretion, well below the current microalbuminuria threshold, have been shown in recent studies to be associated with increased risk of coronary heart disease and death independent of age, sex, renal function, diabetes mellitus, HTN, and plasma lipids.[29–31]

Interestingly, we also found that, as compared with the respective salt-resistant women, premenopausal and postmenopausal SS women had significantly higher waist/hip and waist/thigh ratios, which are estimations of the proportion of abdominal or upper-body fat. In addition, postmenopausal SS women exhibited significantly higher fasting insulin and uric acid levels. To the extent that abdominal body fat and insulin and uric acid levels have been proposed to constitute markers of cardiovascular risk, the present study provides further support for the linkage between SS and CVD.[32–34]

In our study population of women, blood pressure did not rise after surgical menopause. An increment in visceral adipose tissue deposition and worsening insulin-stimulated glucose disposal has been observed during the menopause transition.[35,36] We did not observe differences in any of the measured parameters before as compared with 4 months after surgical menopause among the SS women who remained SS, the salt resistant who became SS, or the salt resistant who remained salt resistant (Table 3). These findings suggest that, although salt-resistant women developed SS within 4 months after surgical menopause, elevation of blood pressure and changes in metabolic profile do not occur within this time frame. In fact, the premenopausal women with SS and those with salt resistance who developed SS after menopause exhibited higher waist/hip and waist/thigh ratios as compared with those who remained salt resistant after menopause. These data indicate that, among those with increased abdominal adiposity, loss of ovarian hormones may promote the development of SS.

There is evidence that metabolic syndrome/insulin resistance increases with aging and is associated with increased risk of developing CVD.[32,33] Epidemiological studies indicate that development of HTN and CVD may not occur until 5 to 10 years after menopause.[37,38] Therefore, we surmise that the loss of ovarian hormones may unmask a population of women predisposed to SS that, with aging and its associated loss of vascular compliance, would subsequently be at higher risk for the development of HTN and CVD.

The present findings suggest a mechanism whereby loss of estrogen may foster postmenopausal HTN.[4,5] We and others have demonstrated previously that ovariectomized SS rats develop HTN while receiving a "normal" salt (0.5% NaCl) diet, suggesting that the loss of ovarian hormones lowers the threshold for the hypertensinogenic effect of salt.[39,40] The development of SS postovariectomy HTN was linked to an upregulation of renal angiotensin type 1 receptor expression[39,40] and a reduction in renal medullary endothelial nitric oxide synthase activity[41] and was prevented by estrogen replacement,[39,40] angiotensin type 1 receptor antagonism,[39,40] or very low salt diet (0.1% NaCl).[39] These findings support an important role of angiotensin II and NO on sodium homeostasis and point to the loss of estrogen modulation of the renin–angiotensin and NO systems as pathogenic mechanisms in postmenopausal HTN and as additional targets for reducing the risks of CVD in postmenopausal women.

The main limitation of our study is the technique used to classify the patients. The protocol time was shorter than the acute protocol established by Weinberger et al.[10] We surmise that, in those patients with an altered hemodynamic response to salt loading (ie, SS), an acute volume expansion with saline followed by acute depletion with furosemide would result in the same pathophysiological response regardless of the time period during which it is achieved. Our acute protocol may, if anything, underestimate the number of patients defined as SS.

Perspectives

The report from the National Health and Nutrition Examination Survey revealed that women are among those with the highest rates of HTN and the lowest rates of control, especially after age 60, highlighting the need for interventions that would target prevention in this group.[7] Our present results may provide new insights to explain why the incidence of HTN and CVD increases in postmenopausal women[3] and provide the basis for the design of larger, observational as well as interventional studies in this population.

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