

Aldosterone Stimulation by Angiotensin II

Influence of Gender, Plasma Renin, and Familial Resemblance

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Abstract—The aldosterone response to infused angiotensin II (Ang II) in patients receiving a low-salt diet has been described as an important phenotype for genetic studies on human hypertension. The objectives of the present study were to determine the parameters that influence this intermediate phenotype as a quantitative trait and to assess the importance of its familial resemblance in hypertensive sibling pairs. Two hundred one white hypertensive subjects (95 families: 84 pairs and 11 trios) were selected in 3 centers. The patients followed the same protocol, which included a 4-week withdrawal period of antihypertensive therapy, a 1-week period on a low-salt diet, and a 30-minute infusion of Ang II. The increase in the aldosterone level was greater in women than in men (29.1 ± 16.2 versus 18.2 ± 9.6 ng/dL, $P < 0.0001$). A strong relationship was found with age ($r = -0.54$, $P < 10^{-4}$) and plasma renin activity ($r = 0.32$, $P < 10^{-4}$) in women but not in men. Weak correlations of the aldosterone response to Ang II were observed for the whole set of sibling pairs ($r = 0.11$, NS). Conversely, strong sibling correlations were found among brother-brother pairs ($r = 0.40$, $n = 36$) and among sister-sister pairs as soon as age or menopausal status was considered. Similar results were obtained when the Ang I–aldosterone response was analyzed as a qualitative trait ($\kappa = 0.35$, $P < 0.008$ in brother-brother pairs). We conclude that age, gender, and plasma renin are strong determinants of the aldosterone response to Ang II, with strong sibling correlations in men and postmenopausal women. These relationships will have to be considered in future linkage and association studies. (*Hypertension*. 2000;35:710-716.)

Key Words: hypertension, arterial ■ genetics ■ renin-angiotensin system ■ aldosterone ■ age ■ gender

The identification of genes that are involved in the pathogenesis of human essential hypertension is hampered by the complexity of the blood pressure regulation, its multifactorial nature, and the presence of multiple susceptibility genes that act alone or in combination with other genes or the environment.¹ This complexity limits the power of classic linkage analysis studies and justifies the study of large numbers of patients and families to detect small genetic effects.² However, studies on most of the genes involved in human essential hypertension have so far provided negative or conflicting results.³ One of the main reasons for such disappointing results is the variability of blood pressure according to physiological (eg, age, menopause) and environmental (especially nutrition and weight) factors and the panoply of physiological systems that regulate this parameter, thus making the detection of alleles of genes that confer susceptibility to hypertension very difficult.

An alternative strategy is to subdivide the hypertensive population into more homogeneous subgroups that share a distinct and heritable clinical phenotype. Such a trait, or “intermediate phenotype,” should reflect a more homoge-

neous genetic subset of the hypertensive population and facilitate genetic analysis.⁴ Nonmodulation of adrenal and renal vascular responses to stimulation with angiotensin (Ang) II is one such intermediate phenotype. It is characterized by an attenuated adrenal response of aldosterone secretion to the infusion of Ang II when the subject has been placed on a low-salt diet.⁵ This response is closely correlated with the fall in renal plasma flow in response to a similar Ang II infusion when the subject is on a high-salt diet.⁶ Thus, salt intake fails to modulate target tissue responsiveness to Ang II in individuals defined as nonmodulators, resulting in salt balance occurring at a higher total body salt concentration and an increased prevalence of salt-sensitive hypertension.

Arguments for a genetic heritability of nonmodulation are the bimodality of the trait and significant familial aggregation of nonmodulation.⁷ However, little is known about the physiological parameters responsible for the trait. The objectives of the present study were to determine the parameters that influence the plasma aldosterone response to Ang II infusion and to assess the importance of the familial resemblance of this intermediate phenotype in hypertensive sibling

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TABLE 1. Clinical Characteristics of Hypertensive Sibling Pairs

	All Patients	Men	Women
n	201	113	88
No. of families (pairs/trios)	95 (84/11)	30 (28/2)*	17 (16/1)*
Age, y	48.7±7.7	48.3±7.8	49.2±7.7
Age of onset, y	38.7±10.5	38.0±10.9	39.7±9.2
Casual blood pressure at entry, mm Hg			
Systolic	146.3±22.0	144.1±20.5	148.6±23.4
Diastolic	91.4±12.4	92.1±11.6	90.6±13.2
Treated patients, %	89	91	86
BMI, kg/m ²	27.1±3.9	27.7±3.6	26.4±4.0

BMI indicates body mass index.

*Gender-concordant pairs.

pairs. Age, gender, and plasma renin were the strong determinants of the aldosterone response to Ang II, particularly in women, in whom age and menopause seem to play a crucial role. Strong sibling correlations were found as soon as subjects were classified according to gender and menopause, which suggests genetic influences of the trait.

Methods

Patients

A total of 201 hypertensive patients were studied at the Clinical Research Centers of the Hospital Broussais (Paris, France; n=95), Brigham and Women's Hospital (Boston, Mass; n=47), and University of Utah Medical Center (Salt Lake City, Utah; n=59). Only white sibships with ≥2 hypertensive siblings who satisfied the following criteria were considered for entry into the study: (1) age of 18 to 65 years; (2) hypertension defined as a diastolic blood pressure of >100 mm Hg off all medications, >90 mm Hg on 1 antihypertensive agent, or the need for ≥2 antihypertensive medications at the time of the screening; and (3) no secondary or malignant form of hypertension. Other exclusion criteria included diabetes mellitus, substantial obesity (body mass index of >31 kg/m²), cardiac failure, acute myocardial infarction within the past 6 months, impaired renal function, or any other significant medical problem. Menopause was defined as a positive history of amenorrhea of >1 year or the presence of hormonal replacement therapy. Women with menstrual irregularities were defined as nonmenopausal. Individuals were classified as having a low renin level if plasma renin activity (PRA)

for the subject on a low-salt diet and in the upright position was ≤2.4 ng · mL⁻¹ · h⁻¹. The remaining subjects were classified as nonmodulators if the Ang II–induced aldosterone increase was ≤15 ng/dL (<416 pmol/L) and as modulators if the increase was more than 15 ng/dL.⁵ The study was approved by the human subjects committee at each center, and all patients provided informed written consent before enrollment. To avoid sibship size discrepancies, no more than 3 sibs from each sibship participated in the study.

Study Protocol

All patients discontinued antihypertensive therapy for ≥4 weeks before the study began. A calcium channel blocker was administered if the diastolic blood pressure rose to >115 mm Hg, but it was stopped at least 1 week before the first evaluation. Patients with a diastolic blood pressure of >120 mm Hg were excluded. The first evaluation was performed after 1 week on a high-salt diet (200 mmol NaCl/d) and will be reported elsewhere. Patients were then placed on an isocaloric low-salt diet for 7 days (10 mEq sodium, 100 mEq potassium, and 800 mg calcium daily).⁵ The patients entered the clinical research unit the day before undergoing Ang II infusion, and their low-salt balance was checked with a 24-hour urine collection (natriuresis <30 mmol/d).

All subjects remained in the lying position for ≥6 hours before the test. A venous catheter was inserted in the arm opposite that arm receiving the Ang II infusion at 7:00 AM, and blood pressure was measured every 3 minutes with a Dinamap blood pressure monitor (Critikon, Inc). Three blood samples were taken at 8:00 AM (baseline levels), and an Ang II (Hypertensin; Ciba) infusion was started. A dosage of 1 ng · kg⁻¹ · min⁻¹ was administered for 10 minutes to

TABLE 2. Clinical and Biological Changes After Ang II Infusion in Hypertensive Subjects on a Low-Salt Diet

Characteristic	Basal	After Infusion	P
Automated blood pressure, mm Hg			
Systolic	136.4±18.3	160.0±22.7	<0.0001
Diastolic	81.8±10.8	94.6±11.7	<0.0001
Plasma renin level			
Prorenin, pg/mL	205.1±104.3	202.8±101.5	0.15
Active renin, pg/mL	41.5±37.5	31.8±28.2	<0.0001
PRA, ng · mL ⁻¹ · h ⁻¹	2.42±2.09	1.42±1.23	<0.0001
Plasma aldosterone, ng/dL	19.1±13.5	42.0±18.8	<0.0001
Plasma cortisol, μg/dL	11.8±4.4	10.3±5.1	<0.0001

PRA indicates plasma renin activity.

For plasma prorenin, active renin, and PRA, the paired Student's *t* test was performed on log-transformed values.

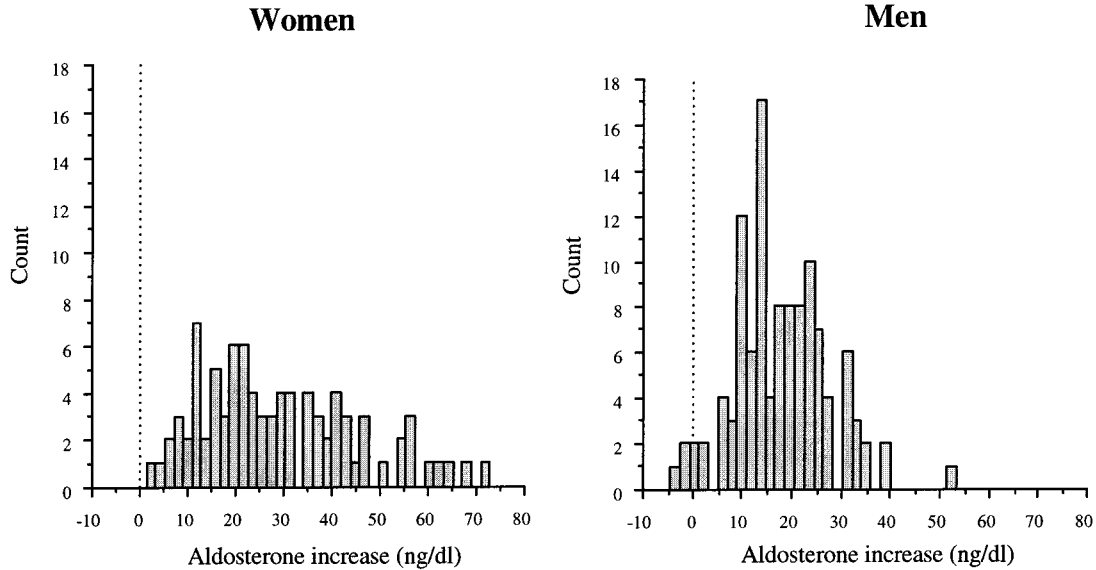


Figure 1. Increases in plasma aldosterone after Ang II infusion according to gender. Histograms show distribution of unadjusted values.

recognize any marked blood pressure rise. This infusion was maintained at this level for 30 minutes in 2 patients because their diastolic blood pressure rose to ≥ 115 mm Hg. The rate of infusion was increased to $3 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 30 minutes in the other patients. Blood samples were taken 3 times (5 minutes apart) at the end of the infusion, and the average of these measurements was used as the stimulated level.

Biological Measurements

Blood samples were taken with a venous catheter located in the arm opposite the arm receiving the infusion. Urine was stored at -20°C without preservatives or additives, until assay. Serum or plasma was separated from venous blood and stored at -20°C . Frozen samples were sent to a research laboratory in Boston. Sodium and potassium were measured through direct potentiometry with an ion-selective electrode (NOVA Analyzer 1; Nova Biochemical). Aldosterone was

measured with a commercial radioimmunoassay kit (Instar Corp). Total and active renin levels were measured with a commercial radioimmunoassay kit (Nichols Institute Diagnostics). For active renin, the intra-assay coefficient variation (CV) ranged from 4% to 8%, with an interassay CV of 7% to 12%. Similar CVs were observed for total renin. Plasma prorenin was calculated as the difference between total and active renin levels. PRA was measured as previously reported.⁸

Statistical Analysis

All information (demographic, clinical, biological, and genetic) was entered into a database for statistical analysis. For descriptions of patient characteristics, we used mean and SD values for continuous variables and counts and percentages for discrete variables. Normality was checked for each variable, and log-transformation was used when appropriate (ie, plasma renin levels). Ang II-induced changes

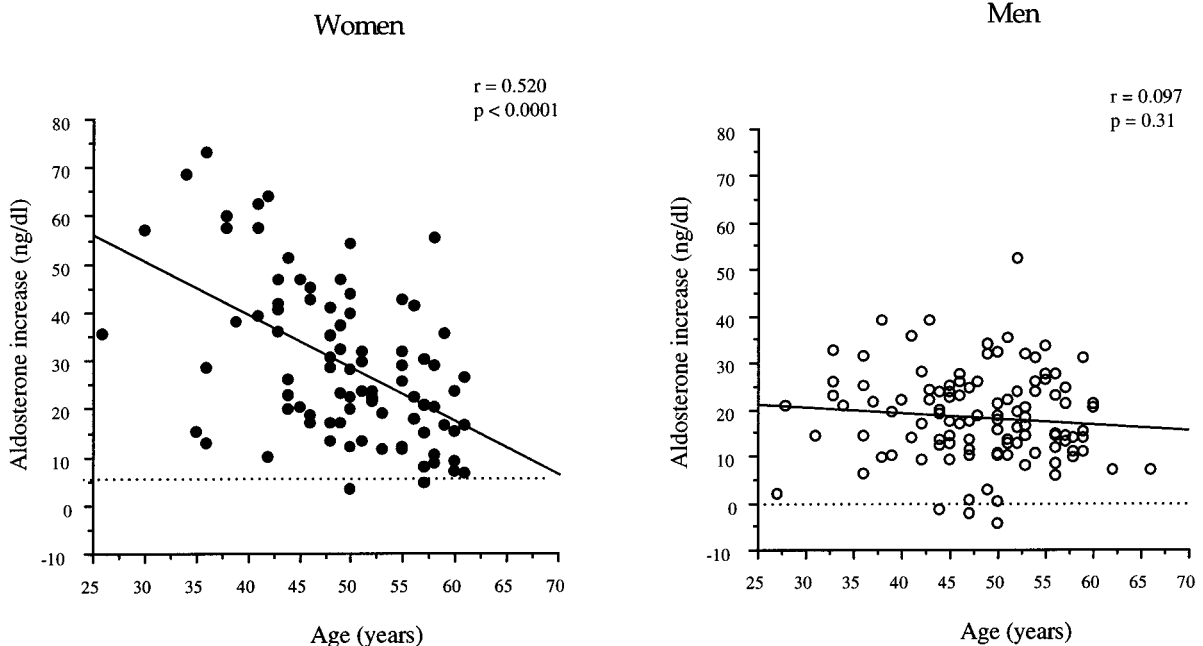


Figure 2. Correlations between increase in aldosterone after Ang II infusion and age according to gender.

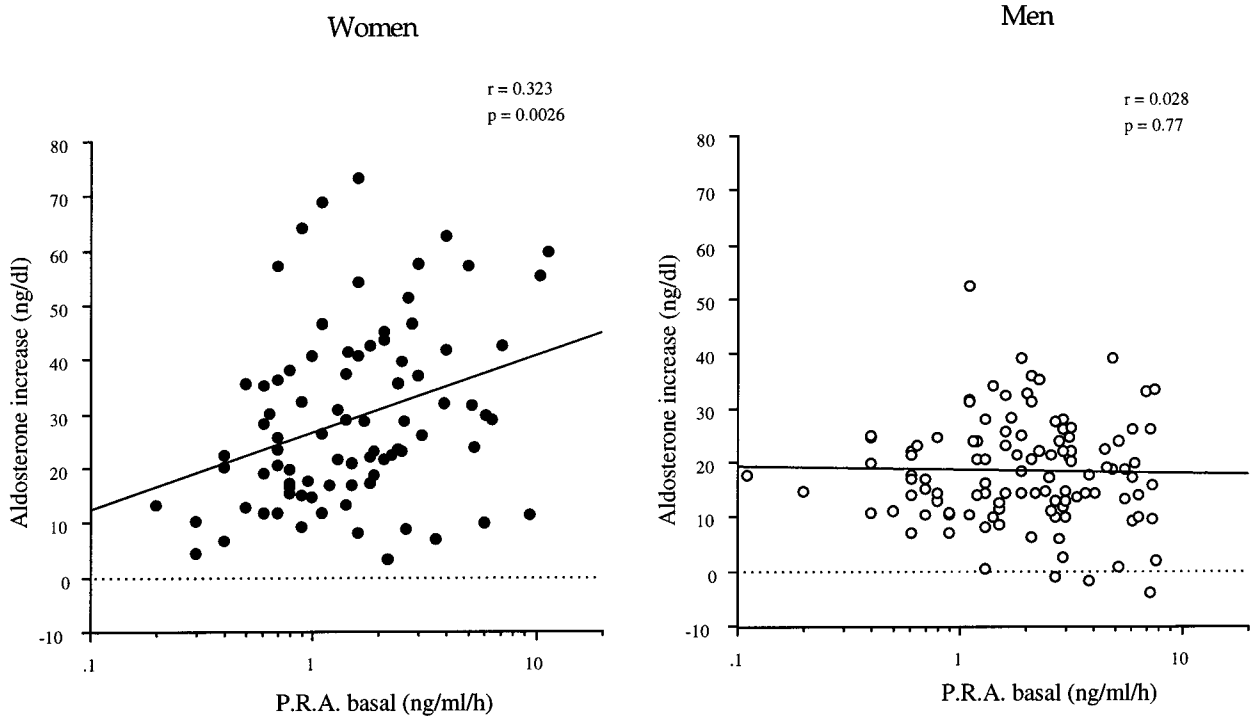


Figure 3. Correlations between increase in aldosterone after Ang II infusion and PRA according to gender. A logarithm scale has been used for PRA.

in blood pressure and plasma hormone changes from baseline were tested for significance with Student's *t* test for paired values. These calculations were performed with Statview 5.0 software (Abacus Concepts Inc).

Univariate analyses were used to search for parameters that influence plasma aldosterone at baseline or during Ang II stimulation, with generalized linear model regression techniques, and the results are expressed as correlation coefficients through the use of SAS 6.12 statistical package (SAS Institute). Significant factors were then considered to be covariates when the sibling correlations were analyzed. Intraclass sibling correlations were used to estimate familial association.⁹ Estimates were calculated with the double pairwise method with equal weighting on sibship size through the use of the S.A.G.E. statistical package.¹⁰ This method does not rely on any distributional assumption or on the sib order in the sibships. It yields the same results as maximum likelihood estimates for a constant sibship size. To indicate a statistical significance, we assumed that the *z*-transform of the correlation coefficient had a normal distribution (Dr R. Elston, personal communication). Kappa coefficients were used to estimate the concordance of the modulation nonmodulation phenotype between hypertensive siblings. An inferior 95% confidence limit of >0 indicates a significant concordance.

Results

Clinical and Biological Characteristics

The main clinical characteristics of the selected hypertensive subjects are shown in Table 1. There were 84 sibling pairs and 11 trios belonging to 95 white sibships, with a small predominance of men (56%). In addition to the presence of ≥ 2 hypertensive subjects in the sibship, hypertension had been discovered in patients before the age of 50 years (mean 38.7 ± 10.7 years). Their average blood pressure at entry into the protocol was $146.3 \pm 22.0/91.4 \pm 12.4$ mm Hg.

All patients completed a 1-week low-salt diet (urinary sodium 15 ± 7 mmol/24 h). The Ang II infusion ($3 \text{ ng} \cdot \text{kg}^{-1} \cdot$

min^{-1}) increased the systolic blood pressure by 17.1% (23.6 mm Hg) and the diastolic blood pressure by 15.6% (12.8 mm Hg) similarly in men and women. Plasma aldosterone was increased 2.2-fold, and active renin decreased by 23% (Table 2), but there was no significant change in prorenin during this short period of time. The slight fall in the cortisol level was about what was expected due to circadian rhythm; the blood samples for basal values were taken at 8:00 AM, and after the infusion, samples were taken 45 minutes later.

The mean value of the Ang II–induced aldosterone increase was higher in women than in men (29.1 ± 16.2 versus 18.2 ± 9.6 ng/dL, $P < 0.0001$). An obvious difference was observed in the distribution of the trait, which was much wider in women than in men (Figure 1).

Influence of Gender and Renin on the Aldosterone Response to Ang II

We first tested whether the Ang II–induced increase in plasma aldosterone was related to any of the classic clinical or biological parameters. Low-salt baseline and Ang II–stimulated plasma aldosterone levels were significantly correlated ($r = 0.66$, $P < 10^{-4}$). Systematic univariate regression analysis showed significant relationships with age, basal PRA, and plasma potassium ($r = -0.20$, $P < 0.01$) but no relation with body mass index ($r = 0.03$, NS) or creatinine clearance ($r = 0.12$, $P = 0.25$). No relation was observed with urinary sodium excretion, probably due to the very strict low-salt diet and, consequently, the very short range of this parameter (3 to 35 mmol/24 h). The relationship with plasma potassium was not gender dependent and was no longer significant in a multivariate regression analysis. The relationships with age

TABLE 3. Plasma Renin and Aldosterone Levels According to Gender and Menopausal Status

Hormonal Parameter	Women			Significance		
	Nonmenopausal (n=46)	Menopausal (n=42)	Men (n=113)	P1	P2	P3
PRA basal, ng · mL ⁻¹ · h ⁻¹	2.2±2.1	2.1±2.3	2.6±2.0	0.56*	0.18*	<0.05*
Aldosterone basal, ng/dL	20.2±19.4	14.5±11.1	20.4±10.2	<0.05	0.14	<0.01
Aldosterone post-Ang II, ng/dL	55.5±26.2	36.5±16.2	38.6±12.9	<0.0001	<0.0001	0.49
Aldosterone increase, ng/dL	35.8±16.9	22.0±12.1	18.2±9.6	<0.0001	<0.0001	0.08

P1 indicates nonmenopausal vs menopausal women; P2, nonmenopausal women vs men; and P3, menopausal women vs men.
*Significance calculated on log-transformed values.

and renin were markedly different in men and women. There was a highly significant negative correlation between plasma aldosterone increase and age in women ($r=0.52$, $P<0.0001$) but not in men ($r=0.09$, NS) (Figure 2). The hypertensive women <50 years old had a much higher response (30.3 ± 16.2 ng/dL; $n=57$) than did those >50 years old (21.0 ± 14.4 ng/dL, $P=0.006$; $n=36$) or the men (18.4 ± 9.5 ng/dL, $P<0.0001$; $n=105$). The aldosterone response to Ang II in the 11 women receiving oral contraceptive treatment (42.3 ± 15.4 ng/dL) was not significantly different from that observed in the nonmenopausal women (35.1 ± 17.8 ng/dL, $P=0.27$; $n=33$).

A significant and positive correlation was observed between basal PRA and the increase in plasma aldosterone only in women, not in men (Figure 3), whereas basal PRA was significantly related to basal plasma aldosterone levels in both men ($r=0.446$, $P<0.0001$) and women ($r=0.397$, $P<0.0001$). Similar results were observed with plasma active renin (not shown). After adjustment for age, PRA was still related to the aldosterone response in women ($r=0.27$, $P<0.03$) and not in men ($r=0.07$, NS).

We suspected that menopausal status could play a role in this particular age, renin, and gender interaction. As shown in Table 3, and despite almost identical plasma renin levels, postmenopausal women had the same adrenal response as men, which was about half of that observed in nonmenopausal women. Interestingly, this effect was not reversed in women receiving estrogen-based replacement therapy (22.1 ± 11.3 ng/dL, $n=20$) compared with those without such

therapy (22.0 ± 13.2 ng/dL, NS; $n=22$). However, in a multiple stepwise regression analysis, only age ($P<10^{-4}$), gender ($P<10^{-4}$), PRA ($P=0.07$), and the interactions between gender and age ($P<10^{-3}$) and between gender and PRA ($P<0.01$) were independent and significant contributors that accounted for 34% of the variance of the Ang II-induced aldosterone response.

Sibling Correlations

By evaluating sibling correlations for the age- and gender-adjusted increase in aldosterone, giving equal weight to sibships, we estimated the familial component of the adrenal response to Ang II and the transmission of the trait. Table 4 shows the sibling correlations for aldosterone response, which were assessed with both the SIBPAL and generalized linear model (GLM) programs. Similar results were obtained when the analyses were carried out separately for each center (data not shown). Weak correlations of the aldosterone response to Ang II were observed for the whole set of sibling pairs ($r=0.11$, NS); however, a strong influence of gender was observed with either the crude or the age-adjusted variable. Significant correlations were observed among brother-brother pairs, suggesting a familial component only in men. When the sister-sister pairs were separated according to menopause status, strong correlations were observed among the few postmenopausal pairs ($r=0.70$, $n=7$). Almost similar levels of concordance were observed if low-renin hypertension was defined as PRA of <2.0 ng · mL⁻¹ · h⁻¹ or <1.5 mg · mL⁻¹ · h⁻¹ (data not shown). However, it became

TABLE 4. Intrafamilial Correlations of Plasma Ang II-Induced Aldosterone Increase

Pairs	n	S.A.G.E.-FCOR		General Linear Model		
		Unadjusted	Adjusted*	n'	Unadjusted	Adjusted*
All	115	0.15	0.11	95	0.11	0.12
Sister-sister	24	0.22	0.17	17	0.05	0.04
nm-nm	9	-0.21	-0.10	7	-0.22	-0.19
nm-pm	8	0.75†	0.25	5	0.26	0.26
pm-pm	7	0.69†	0.71†	5	0.50	0.74†
Sister-brother	55	0.08	-0.02	48	0.04	0.03
Brother-brother	36	0.40†	0.39†	30	0.35†	0.35†

n indicates number of all pairs comparisons, with equal weight given to each family; n', number of families in whom comparisons were performed between siblings; nm, nonmenopausal; pm, postmenopausal; and FCOR, the Familial Correlations program of S.A.G.E. software.

*Adjusted for age and gender († $P<0.05$).

TABLE 5. Familial Concordance of Modulation Phenotype Among Hypertensive Siblings

	SIB 1*			SIB 1†			SIB 1‡		
	LR	M	NM	LR	M	NM	LR	M	NM
SIB 2									
LR	16	9	2	4	1	1	11	3	2
M	13	35	15	2	14	5	4	20	10
NM	5	12	8	1	4	4	3	11	7
	$\kappa=0.251$ (0.107–0.396)			$\kappa=0.351$ (0.074–0.629)			$\kappa=0.305$ (0.116–0.493)		
	$P=0.0004$			$P=0.008$			$P=0.001$		

Hypertensive siblings were classified into 1 of 3 categories (see the text): LR indicates low renin; M, modulator; and NM, nonmodulator.

The table shows the numbers of pairs concordant for each class, the weighted κ coefficient indicating the concordance of each hypertensive sibling group, its 95% confidence limits, and its exact P value.

*All siblings pairs ($n=115$).

†Brother-brother pairs ($n=36$).

‡All siblings except nonmenopausal women ($n=71$).

nonsignificant if patients were grouped into only 2 groups (modulators compared with nonmodulators and low-renin hypertensives as the second group).

The gender-dependent resemblance of the trait was confirmed when patients were classified as low renin ($n=50$), modulators ($n=105$), or nonmodulators ($n=46$). There was a significant concordance for this classification on the overall set of siblings (weighted $\kappa=0.25\pm 0.07$, $P<0.001$, Table 5). It was increased in the group of brother-brother pairs ($\kappa=0.35\pm 0.14$, $P=0.008$) but not in that of sister-sister (0.33 ± 0.17 , $P=0.10$) or brother-sister (0.12 ± 0.10 , $P=0.24$) pairs. A significant concordance was also observed on the overall set of siblings when only men and postmenopausal women were considered (0.31 ± 0.10 , $P=0.001$).

Discussion

There is ample evidence that the pathogenesis of essential hypertension does not result from a single process but rather from the interaction of multiple environmental and genetic factors. It is therefore important to identify more homogeneous subgroups to facilitate the recognition and description of the mechanisms responsible for increases in blood pressure and hence to design a specific therapeutic strategy. This study, which was performed with a large number of white hypertensive sibling pairs, confirms the heritability of the adrenal response to Ang II in persons receiving a low-salt diet, which behaves markedly differently in hypertensive men and women.

Our first objective was to better define several characteristics of the aldosterone response to Ang II infusion as an intermediate phenotype. A strong and negative relationship was observed between age and this phenotype in women, but no such relation was observed in men. This interaction between age and gender was not initially reported, because most of the first studies describing the nonmodulation phenotype have dealt with normotensive and hypertensive men.⁴ However, it was found in a recent study of 225 hypertensive patients (age 18 to 66 years) by Fisher et al¹¹ that nonmodulation was strikingly less frequent among the 70 women (26%) than among the 155 men (49%, $P=0.001$). In this study, the women >55 years old reached a 47% nonmodu-

lation frequency, equal to that observed in men. Our results are in complete agreement with these findings. Both studies show that age is a very significant contributing factor to the aldosterone response to Ang II in women but not in men.

Plasma renin level was the third main predictor of the aldosterone response to Ang II, in interaction with gender and age. A strong difference was observed when hypertensive women were separated according to their age or menopause status. Similar results were obtained when we considered the information on familial clusters with the use of estimating equations (data not shown). The impact of gender was also found in a series of 48 healthy men and women who were tested for renal response to Ang II.¹² The decrease in female gender hormones with age is the main physiological change that parallels the changes in this phenotype. Lack of estrogens could act via increased peripheral resistance¹³ or changes in the renin-angiotensin system, or both. Plasma renin levels tend to decrease with age in normal subjects and have been found repeatedly to be lower in women than in men.¹⁴ A recent population survey showed that the average prorenin and renin levels in men were 50% and 30% higher than those in women, and younger women had lower prorenin levels than older women.¹⁵ Like the present study, that study found that plasma renin levels correlated with plasma aldosterone, reflecting the stimulation of aldosterone release by Ang II. Interestingly, an altered adrenal sensitivity to Ang II was recently demonstrated in patients with low-renin essential hypertension.¹⁶ Thus, despite different responses in renin secretion in patients in the upright position, striking similarities are observed between hypertensive patients classified as low renin or nonmodulators.¹⁷ This blunted aldosterone response to Ang II infusion in both syndromes may reflect the decrease of aldosterone synthesis, possibly through angiotensin receptor downregulation.^{18,19} Estrogens have also been found to modify the Ang II receptor density in the adrenal cortex.²⁰

Our second objective was to test the familial resemblance of the adrenal response to Ang II in a large set of white hypertensive sibling pairs. Several studies that show an association between nonmodulation and a positive family

history of hypertension have suggested that this trait could be genetically determined.^{21–23} However, this association was recently disputed in a population-based sample of adults aged 20 to 50 years who participated in the Rochester Family Heart Study.²⁴ Conversely, the study of 31 hypertensive siblings from 14 Utah sibships demonstrated a high degree of concordance for the nonmodulation phenotype based on the renal blood flow response to Ang II.⁷ We used the aldosterone response to Ang II as a quantitative trait and a large series of white hypertensive siblings who followed the same protocol in 3 centers. Compared with the qualitative trait, this strategy gives more power, allows the familial correlations to be weighted according to sibship size, and prevents the possible bias due to the selection of arbitrary thresholds used to stratify patients into low renin, modulators, and nonmodulators. Two statistical tests showed significant sibling correlations between the unadjusted and the age-adjusted values for aldosterone increase but only in hypertensive brothers. The absence of an overall relationship between sister-sister and sister-brother pairs is likely a reflection of the effect of age and hormonal status on the trait, as confirmed by the concordance of the modulation phenotype, which is significant only in men and older women. We could not further test the inheritance pattern of the aldosterone response to Ang II because it requires a large representative population of siblings for accurate conclusions to be reached on the respective contribution of genes and environment to the transmission of the trait.²⁵

In conclusion, the results of the present study confirm the familial resemblance of the aldosterone response to Ang II analyzed as both a quantitative and a qualitative trait in hypertensive sibling pairs. It also highlights the importance of age, gender, and plasma renin levels in determination of this intermediate phenotype. These relationships will have to be considered in future linkage and association studies.

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Aldosterone Stimulation by Angiotensin II: Influence of Gender, Plasma Renin, and Familial Resemblance

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