

# Impaired Sodium Excretion During Mental Stress in Mild Essential Hypertension

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**Abstract**—In hypertensive rats, environmental stress causes sodium retention by an exaggerated increase in renal sympathetic nerve activity, which is modulated by angiotensin II. We tested whether similar effects can be observed in humans. In 66 normotensive subjects (half of them with a family history of hypertension) and 36 subjects with mild essential hypertension, urinary sodium excretion and renal hemodynamics were examined at rest and during mental stress treated either with placebo or ACE inhibition in a double-blind, randomized, cross-over design. Despite a marked increase in glomerular filtration rate in response to mental stress ( $\Delta$ glomerular filtration rate,  $4.3 \pm 7.7$  mL/min in normotensives without versus  $5.6 \pm 8.4$  mL/min in normotensives with a family history versus  $10.1 \pm 5.7$  mL/min in patients with mild essential hypertension;  $P < 0.002$ ), the increase in urinary sodium excretion was blunted in patients with mild essential hypertension ( $\Delta$ urinary sodium excretion,  $0.12 \pm 0.17$  mmol/min versus  $0.10 \pm 0.14$  mmol/min versus  $0.05 \pm 0.14$  mmol/min;  $P < 0.05$ ). ACE inhibition corrected the natriuretic response to mental stress in subjects with mild essential hypertension ( $\Delta$ urinary sodium excretion,  $0.05 \pm 0.14$  mmol/min with placebo versus  $0.13 \pm 0.19$  mmol/min with ACE inhibition;  $P < 0.01$ ); thus, after ACE inhibition, urinary sodium excretion increased similarly in all 3 groups. In conclusion, impaired sodium excretion occurs during mental stress in human essential hypertension but not in subjects with positive family history of hypertension. This abnormality in sodium handling during activation of the sympathetic nervous system appears to be mediated by angiotensin II. (*Hypertension*. 2001;37:923-927.)

**Key Words:** sodium ■ hypertension, essential ■ stress ■ renin-angiotensin system

The kidney acts as a major long-term regulator of blood pressure by controlling extracellular sodium and water balance.<sup>1</sup> According to Guyton's<sup>2</sup> hypothesis, failure of the kidneys to excrete the sodium load at a normal blood pressure level is the primary cause of essential hypertension. Sodium and water retention leads to elevated blood pressure, which in turn restores sodium excretion ("pressure natriuresis concept").

In spontaneously hypertensive rats, environmental stress provokes sodium retention mediated by an exaggerated increase in renal sympathetic nerve activity, thereby contributing to the development of hypertension.<sup>3,4</sup> Similarly, Light et al<sup>5</sup> have shown in a pilot study in humans that natriuresis during mental stress is impaired in subjects at high risk for essential hypertension, for example, subjects with a parental history of hypertension or with borderline systolic hypertension. These data suggest that very early in the course of human essential hypertension, an impaired sodium excretion during activation of the sympathetic nervous system occurs.

Interestingly, nerve-mediated antinatriuresis during environmental stress can be abolished by the administration of an angiotensin (Ang) II antagonist in normotensive rats.<sup>6</sup> Thus, Ang II appears to modulate nerve-mediated antinatriuresis in

rats. In this study, we investigated the effects of ACE inhibition on renal sodium handling and renal hemodynamics during mental stress in patients with mild essential hypertension and in normotensive healthy volunteers with and without a positive family history of hypertension.

## Methods

### Study Population

Young white male students, 18 to 40 years old, were screened for participation in the study at the campus of the University of Erlangen-Nuremberg. Thirty-three normotensive control subjects without (nFH) and 33 with a positive family history of hypertension (pFH) and 36 subjects with mild essential hypertension (EH, World Health Organization stage I) were enrolled in the study.

Normotension was defined by systolic blood pressure (SBP)  $< 140$  mm Hg and diastolic blood pressure (DBP)  $< 90$  mm Hg on 4 blood pressure readings. If the average SBP was  $\geq 140$  mm Hg or the DBP was  $\geq 90$  mm Hg, the subjects were classified as having mild EH. A positive family history of hypertension was defined as SBP  $\geq 160$  mm Hg or DBP  $\geq 95$  mm Hg of the father, the mother, or one of the siblings before the age of 60 years. Blood pressure readings were taken in the sitting position after 5 minutes of rest with a standard mercury sphygmomanometer on 2 different occasions at least 2 weeks apart (according to World Health Organization recommendations).

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TABLE 1. Clinical Characteristics of Examined Subjects

Characteristics	Normotensives (nFH) n=33	Normotensives (pFH) n=33	Hypertensives (EH) n=36	P ANOVA
Age, y	25±3	25±3	26±2	NS
Height, cm	182±7	180±7	183±7	NS
Weight, kg	76±8	75±9	82±9*†	<0.001
Body surface area, m <sup>2</sup>	1.97±0.13	1.94±0.13	2.04±0.13*†	<0.01
Body mass index, kg/m <sup>2</sup>	22.8±1.8	23.0±2.5	24.7±2.8*†	<0.01
SBP, mm Hg	123±8	121±8	153±9*†	<0.0001
DBP, mm Hg	77±6	79±5	94±5*†	<0.0001
GFR, mL/min per 1.73 m <sup>2</sup>	115.3±14.1	108.6±12.3	113.8±12.2	NS
RPF, mL/min per 1.73 m <sup>2</sup>	592±118	554±90	599±96	NS
FF, %	20.1±4.0	20.0±3.1	19.3±2.8	NS
24-h UNa, mmol/24 h	145±53	166±58	184±77	NS
Plasma renin activity, ng A1/mL per h	1.8±0.8	1.9±0.8	1.8±1.2	NS
Ang II, pg/mL	9.6±7.4	10.4±5.4	10.2±5.0	NS
Aldosterone, pg/mL	171±25	178±11	169±22	NS

\* $P<0.05$ , EH vs pFH; † $P<0.05$ , EH vs nFH (Bonferroni).

None of the subjects had ever received cardiovascular medication, none followed any specific dietary guidelines, and none had a secondary form of hypertension or target organ damage caused by hypertension. All participants underwent a clinical examination including 12-lead ECG, fundoscopy, sonography of the kidneys and adrenal glands, Doppler sonography of the renal arteries, and routine laboratory tests. Written informed consent was obtained from each individual, and the study protocol was approved by the local ethics committee.

### Study Design

The study protocol followed a randomized, double-blind cross-over design. Participants were randomly allocated either to receive placebo for 1 week (baseline examination) followed by a washout period of 7 days, and then ACE inhibition with 2.5 mg cilazapril once daily for another week (ACE inhibitor phase) or the same regimen with the sequence reversed. Pill counts were performed to ensure compliance, and patients were informed that serum drug levels would be measured (but eventually not done). Evaluation of urinary sodium excretion (UNa), renal hemodynamics, and the humoral status of the renin-angiotensin system was performed at the end of the placebo and the ACE inhibitor phase, respectively. Participants were asked to refrain from smoking and drinking coffee or alcoholic beverages on the day before the studies.

### Experimental Methods

To activate the sympathetic nervous system with mental stress, we used a modified time reaction task device (Wiener Determination-sgerät) with a computerized feedback system to hold stimulus intensity constant over 30 minutes of stress testing.<sup>7</sup> In this test, the speed of the task is adjusted to the performance of each participant to keep stress intensity constant over a prolonged period of time. The rationale of using a stress test with low stimulus intensity was to measure renal hemodynamics in parallel to sodium excretion. Only low stress stimulus intensity provides a hemodynamic response sustained up to 30 minutes,<sup>7,8</sup> and the constant infusion technique requires at least 20 minutes to achieve a new steady-state condition.<sup>8</sup>

To determine glomerular filtration rate (GFR) and renal plasma flow (RPF), we applied the constant infusion technique without urine sampling as previously described.<sup>8</sup> Filtration fraction (FF) was calculated by dividing GFR by RPF. Blood pressure was measured every minute (Dinamap). Parameters of the renin-angiotensin-aldosterone system were all determined by radioimmunoassay.

### Statistics

All data were analyzed with the PC version of the Statistical Package for Social Sciences.<sup>9</sup> One-way ANOVA was used to detect any significant difference among the 3 groups, and the Bonferroni method was applied for subsequent tests. Paired *t* tests were done for comparisons within groups between rest and stress values and between treatment phases. Pearson's correlation coefficients were calculated when indicated. Results are given as mean±SD in the text and as mean±SEM in the figures.

## Results

### Baseline Characteristics

The baseline characteristics are given in Table 1. By study design, blood pressure was higher in hypertensive patients than in normotensive control subjects. Baseline renal hemodynamics, 24-hour UNa, and plasma concentrations of the renin-angiotensin-aldosterone system components were similar at baseline. With respect to these parameters, no difference was noted between normotensives with and those without a family history of hypertension.

### Central and Renal Hemodynamics During Mental Stress

In response to mental stress, SBP, DBP, and heart rate increased, whereas RPF decreased slightly, with no difference among the groups (Table 2). GFR and FF increased in all 3 groups. However, in hypertensive subjects, the increase was significantly greater. With regard to both parameters, no difference was found between normotensive subjects with and those without a family history of hypertension.

Ang II concentrations increased only in hypertensive subjects. The increase in GFR was greater, the more plasma Ang II concentration increased ( $r=0.31$ ;  $P<0.001$ ). Aldosterone values decreased similarly in all 3 groups.

ACE inhibition blocked the increase of Ang II concentration in hypertensive subjects ( $\Delta$ Ang II,  $+4.6\pm5.3$  pg/mL with placebo versus  $+1.1\pm5.5$  pg/mL with ACE inhibition,  $P<0.05$ ) and blocked the increase in GFR ( $\Delta$ GFR,

TABLE 2. Response to Mental Stress

Characteristic	Normotensives (nFH) n=33	Normotensives (pFH) n=33	Hypertensives (EH) n=36	P ANOVA
Change during stress				
SBP, mm Hg	+8±7‡	+10±7‡	+11±7‡	NS
DBP, mm Hg	+3±4‡	+5±3‡	+4±4‡	NS
MAP, mm Hg	+5±5‡	+8±6‡	+7±5‡	NS
Heart rate, bpm	+8±8	+9±8	+8±7	NS
GFR, mL/min per 1.73 m <sup>2</sup>	+4.3±7.7‡	+5.6±8.4‡	+10.1±5.7‡§	<0.005
RPF, mL/min per 1.73 m <sup>2</sup>	−18±22‡	−9±40*	−22±25‡	NS
FF, %	+1.4±2.4‡	+1.4±1.5‡	+2.5±1.4‡§	<0.05
Plasma renin activity, ng A1/mL	−0.2±0.7*	+0.2±0.3*	+0.1±0.9	NS
Ang II, pg/mL	−0.8±2.6	+0.2±1.6	+4.6±5.3*§	<0.0001
Aldosterone, pg/mL	−31±12‡	−23±19‡	−17±34‡	NS

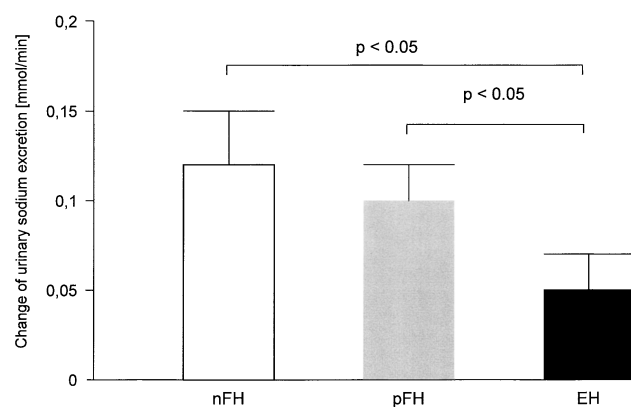
\* $P<0.05$ , † $P<0.01$ , ‡ $P<0.001$  for difference between baseline and during mental stress (paired  $t$  test).

§ $P<0.05$ , EH vs pFH; || $P<0.05$ , EH vs nFH (Bonferroni).

+10.1±5.7 mL/min with placebo versus +8.7±6.1 mL/min with ACE inhibition,  $P<0.02$ ). As a consequence, under ACE inhibition, no differences were found between the groups with respect to the aforementioned parameters.

### UNa During Mental Stress

UNa at rest was similar among the 3 groups. Mental stress produced a significant and similar rise of UNa in both normotensive groups, whereas in hypertensive subjects, no significant rise was observed ( $\Delta$ UNa, 0.12±0.17 mmol/min in nFH versus 0.10±0.14 mmol/min in pFH versus 0.05±0.14 mmol/min in EH;  $P<0.05$ , or as median and 25% and 75% quartile, 0.07 [0.02, 0.23] mmol/min in nFH versus 0.10 [0.02, 0.15] mmol/min in pFH versus −0.005 [−0.04, 0.11] mmol/min in EH,  $P<0.05$ ). In parallel, fractional excretion of sodium increased in the normotensive subjects, whereas it decreased in the hypertensive subjects ( $\Delta$ fractional excretion of sodium, 0.32±0.52 in nFH versus 0.28±0.37 in pFH versus −0.20±0.49 in EH,  $P<0.05$ ). Thus, a blunted response of sodium excretion was noted in hypertensives only (Figure 1 and Table 3).



**Figure 1.** Change of UNa (in mmol/min) in response to mental stress in normotensive subjects with (pFH) and those without (nFH) family history of hypertension and in subjects with mild EH.

With ACE inhibition, UNa in response to mental stress rose significantly in hypertensives ( $\Delta$ UNa, +0.05±0.14 mmol/min with placebo versus +0.13±0.19 mmol/min with ACE inhibition;  $P<0.05$ ) and reached the level of normotensive control subjects (Figure 2). Thus, ACE inhibition normalized UNa during mental stress in patients with EH.

### Discussion

Our principal finding is that stress-induced natriuresis is impaired in patients with mild EH but was restored by ACE inhibition.

Which mechanism may account for the observed blunted natriuresis? Because the increase in glomerular filtration in response to mental stress was higher in hypertensive subjects, thereby confirming earlier results of our study group,<sup>10</sup> an impaired increase in filtered sodium does not account for the blunted natriuretic response.

Differences in stimulation of the adrenal gland and consequently in aldosterone concentration are unlikely to explain the observed antinatriuresis in EH because the decrease in aldosterone concentrations during mental stress, which has been reported previously,<sup>11</sup> was similar in all 3 groups. Furthermore, aldosterone-mediated changes in distal tubular sodium transport need >45 minutes to take place,<sup>12</sup> but our stress phase lasted only 30 minutes.

The effect of the renal nerves on stress-induced sodium retention has been shown to be mediated by  $\alpha_1$  receptors at the proximal tubular site.<sup>13</sup> In spontaneously hypertensive and in DOCA-NaCl hypertensive rats, increased efferent renal sympathetic nerve activity appears to be critical in the initiation and development of EH by provoking sodium retention.<sup>3,4</sup> In these animal models, the air jet as a model of environmental stress leads to exaggerated activation of the renal sympathetic nerves.

In Sprague-Dawley rats, it has been shown that renal nerve-mediated sodium retention during environmental stress can be inhibited by renal nerve ablation or Ang II type 1 receptor blockade, pointing to the crucial role of Ang II in modulating the antinatriuretic response.<sup>6</sup> Ang II facilitates

TABLE 3. Urinary Sodium (mmol/min) Excretion During Mental Stress

Phase	Normotensives (nFH) n=33	Normotensives (pFH) n=33	Hypertensives (EH) n=36	P ANOVA
Placebo				
At baseline	0.18±0.07	0.18±0.09	0.23±0.07	NS
During mental stress	0.29±0.18‡	0.28±0.14‡	0.26±0.15	NS
Change in response to mental stress	+0.12±0.17	+0.10±0.14	+0.05±0.14  ¶	<0.05
ACE inhibition				
At baseline	0.21±0.12	0.25±0.11	0.26±0.15	NS
During mental stress	0.30±0.17†	0.35±0.17†	0.39±0.23†§	NS
Change in response to mental stress	+0.09±0.19	+0.09±0.15	+0.13±0.19§	NS

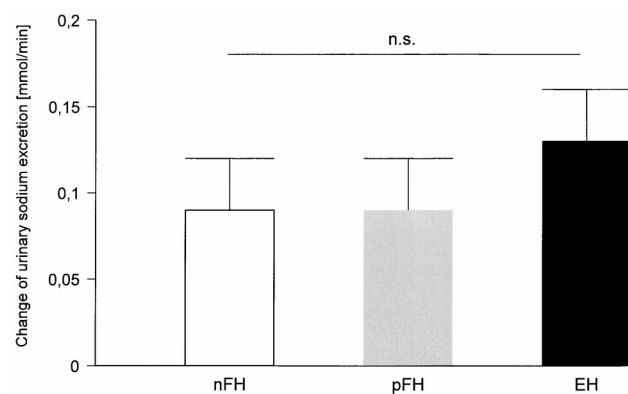
† $P<0.01$ , ‡ $P<0.001$  for difference between baseline and during mental stress (paired  $t$  test).

§ $P<0.05$  for difference between ACE inhibition and placebo.

|| $P<0.05$ , EH vs pFH; ¶ $P<0.05$ , EH vs nFH (Bonferroni).

release of noradrenergic transmitters at the presynaptic site and acts postsynaptically with released norepinephrine in a synergistic manner.<sup>14–17</sup> In addition, Ang II is known to influence renal sodium retention indirectly by a decrease in medullary blood flow and renal interstitial pressure and by an enhanced sodium reabsorption through an enhanced filtration fraction leading to augmented peritubular capillary colloid-osmotic pressure.<sup>18</sup>

In human hypertension, much less is known about the activity of the renal sympathetic nerves. Although direct renal nerve activity recording is not feasible in humans, Esler et al<sup>19</sup> found under resting conditions an increased renal venous norepinephrine outflow in patients with EH pointing to an increased activation of the sympathetic nervous system. Interestingly, norepinephrine outflow from the kidney was greater than that from the heart or liver, thereby suggesting a disproportionally increased activation of the renal sympathetic nerves. Apart from the sympathetic nervous system, our finding of a correction of stress-induced natriuresis in hypertensives by ACE inhibition further points to the renin-angiotensin-system as an important underlying pathogenic mechanism in humans.



**Figure 2.** Change of UNa (in mmol/min) in response to mental stress under ACE inhibition in normotensive subjects with (pFH) and those without (nFH) family history of hypertension and in subjects with mild EH.

Recently, we have demonstrated that hypertensive subjects display an enhanced antinatriuresis in response to exogenously administered Ang II,<sup>20</sup> confirming the hyperresponsiveness to Ang II, which has been described for the renal vasculature<sup>10,21,22</sup> and for cardiac structure.<sup>23</sup>

In contrast to Light et al,<sup>5</sup> we did not find a difference in stress-induced natriuresis between normotensive subjects with and those without a family history of hypertension. This might be explained by different stress stimulus intensity. The stress test used in the current study elicited a rather mild increase in blood pressure ( $\Delta$ BP) and heart rate ( $\Delta$ HR) in offspring of hypertensive parents ( $\Delta$ BP systolic, 10 mm Hg;  $\Delta$ BP diastolic, 5 mm Hg;  $\Delta$ HR,  $9\pm 8$  bpm) as opposed to the stress test used by Light et al ( $\Delta$ BP systolic, 19 mm Hg;  $\Delta$ BP diastolic, 8 mm Hg;  $\Delta$ HR, 22 bpm). Moreover, Light et al not only included normotensive subjects but subjects with borderline systolic hypertension as well. Additionally, an impaired sodium excretion was only shown in the subgroup responding with a higher increase in heart rate in response to mental stress but not in those with a lower increase in heart rate.<sup>5</sup>

A blunted stress-induced natriuresis in subjects with mild EH compared with normotensives despite similar central hemodynamic changes suggests that the renal response to mental stress is a better marker for early alterations in the course of EH than the central cardiovascular response.

## Conclusions

Our data indicate that patients with EH show blunted natriuresis during activation of the sympathetic nervous system that appears to be mediated by an overproportional increase of Ang II.

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