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Effects of angiotensin II receptor antagonism on the renal hemodynamic response to cardiovascular stress

Helga Frank, Hans-Paul Schobel, Jan Vitkowsky, Roland E. Schmieder, and Karsten Heusser

Medical Clinic IV, Department of Internal Medicine, University of Erlangen-Nuremberg, Erlangen, Germany

Effects of angiotensin II receptor antagonism on the renal hemodynamic response to cardiovascular stress.

Background. To elucidate the effect of the angiotensin type 1 (AT1) receptor antagonist (AT1RA) eprosartan (E) on renal hemodynamics in normotensive and borderline hypertensive subjects, we investigated the hormonal and renal hemodynamic responses during cardiopulmonary stress testing.

Methods. In a prospective, double-blind, randomized, placebo-controlled crossover study, the effects of E on renal plasma flow (RPF), renal blood flow (RBF), glomerular filtration rate (GFR), and the concentration of angiotensin II (Ang II) levels were measured with the subjects at rest and during perturbation of cardiopulmonary baroreceptors using lower body negative pressure (LBNP). Ten normotensive male subjects (NT) versus 14 males with mild hypertension (HT), matched for age and body mass index, who were all free of any medication, were randomly assigned to receive placebo or E 600 mg/day PO for seven days (intake phase 1). After a washout period of four weeks the subjects started the intake of the other substance for seven days in a crossover manner (intake phase 2). The measurements were taken on day 7 of both intake phases.

Results. During the LBNP test, RPF and RBF were reduced significantly in all subjects; GFR, however, decreased significantly during cardiopulmonary stress testing in the subjects taking the placebo ($P < 0.05$) and remained unchanged in those under treatment with AT1RA. Ang II levels increased significantly during cardiopulmonary stress test only in the subjects with hypertension who were on placebo, whereas the Ang II levels did not change in normotensive subjects or those treated with the AT1RA.

Conclusions. The data confirm that with cardiovascular stress simulating orthostasis or volume depletion, subjects with AT1RA can maintain their GFR level, suggesting that AT1RA potentially is renoprotective. Additionally, the neurohumoral system is activated after cardiovascular stress in subjects even at an early stage of hypertension.

Blood pressure regulation is strongly affected by a complex interaction between the renin-angiotensin system (RAS) and the sympathetic nervous system, with the common target of renal hemodynamics to control water and sodium homeostasis. In this context, the cardiopulmonary baroreflex is an important contributor to the hemodynamic response for systemic and renal circulatory control, especially when the subject is in a state of volume depletion or orthostatic stress [1]. Unloading of cardiopulmonary baroreceptors by intravascular volume depletion leads to an increased sympathetic efferent outflow to the effector organs such as heart, kidneys and resistance vessels [2]. Furthermore, sustained deactivation of cardiopulmonary baroreceptors by lower body negative pressure (LBNP) causes a significant reduction of glomerular filtration rate (GFR) and filtration fraction (FF), with maintenance of effective renal plasma flow (RPF) in healthy men [3].

The early state of arterial hypertension is characterized by an augmented sensitivity of the cardiopulmonary baroreflex together with an increase in central blood volume [4]. This suggests that the disturbance in renal hemodynamics and sodium and water regulation is conditioned by an altered interaction of the RAS and the sympathetic nerve system.

Inhibition of the RAS by angiotensin II type 1 receptor antagonists (AT1RA) has been shown to be effective in the treatment of arterial hypertension [5]. Concerning the effect on renal hemodynamics, experimental data showed a decrease of renal vascular resistance under AT1RA in the isolated perfused kidney [6, 7]. Animal studies demonstrated losartan to enhance renal blood flow (RBF). Glomerular filtration rate (GFR), however, either did not change or increased [8–10]. The systemic and renal hemodynamic effects of eprosartan in healthy normotensive subjects showed a dose dependent fall in arterial blood pressure and a slight renal vasodilator effect, whereas renal clearance tests were unchanged and filtration fraction decreased [11].

The impact of AT1RA on renal hemodynamics and the neurohumoral response during orthostatic stress simulated by LBNP, a frequent cardiovascular stress factor, is not clear. Furthermore, the effects of antagonizing the augmented neurohumoral response to orthostatic stress

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by AT1RA in hypertension are unknown. In this setting, the role of a disturbed neurohumoral and sympathetic interaction for the pathomechanism even in an early stage of hypertension is yet to be elucidated.

Therefore, the aims of the present study were (*1*) to study the effects of AT1RA on renal hemodynamics; (*2*) to examine the effects of cardiopulmonary baroreflex unloading on renal hemodynamics and neurohumoral activity; (*3*) to investigate the effects of AT1RA on renal hemodynamics and activity of RAS during orthostatic stress testing; and (*4*) to prove differences of renal hemodynamic and neurohumoral responses to cardiovascular stress in normotensive and mildly hypertensive patients.

METHODS

Study cohorts

Twenty-four white males without any clinical or laboratory evidence of heart, liver, kidney or endocrine diseases were included in this prospective, double-blind, placebo-controlled study. In a screening phase the subjects were classified as normotensive (NT; $N = 10$) and mildly hypertensive (HT, $N = 14$) based on four casual blood pressure readings with a standard sphygmomanometer at different times, with the subject sitting after five minutes of rest. Normotension was defined by average casual blood pressure readings $\leq$140/90 mm Hg, mild hypertension was assumed with an average blood pressure value of $>$140/90 mm Hg and $\leq$160/95 mm Hg. Exclusion criteria were secondary hypertensive organ damage according to World Health Organization (WHO) stage II or more as well as secondary forms of hypertension, any alcohol or nicotine consumption, or any current medication. Salt restriction was not practiced. All study participants were students and received the customary catering at the Friedrich Alexander University campus. The mean age of the subjects was 27.9 $\pm$ 4.3 years (NT) and 26.4 $\pm$ 4.0 years (HT; P = NS). Their mean weight and body mass index was 74.5 $\pm$ 7.5 kg and 23.0 $\pm$ 1.8 kg/m^2 (NT) and 80.4 $\pm$ 12.4 kg and 24.3 $\pm$ 2.6 kg/m^2 (HT), respectively (NS). A complete physical examination, laboratory tests [comprised of electrolytes, creatinine, blood urea nitrogen (BUN), liver enzymes, red and white blood cell count], including urine tests and an electrocardiogram, were performed before inclusion. Serum creatinine was normal in all subjects. The study protocol was approved by the Ethical Committee of the University of Erlangen-Nuremberg, and written informed consent was obtained from each subject.

Study design

Normotensive and hypertensive subjects received either placebo for seven days, followed by a washout period of four weeks and thereafter eprosartan (E) 600 mg once a day orally for another seven days, or the sequence of placebo and E was reversed in a crossover manner. The sequence of the placebo and drug periods was randomized for the normotensive and hypertensive study cohort separately. Pill counts were performed to ensure compliance which was $>$95%. Measurements of renal and systemic hemodynamics and endocrine parameters were performed at day 7 of both intake phases; tests started two hours after the last intake of drug or placebo, respectively.

Measurement of systemic and renal hemodynamics

Systolic and diastolic blood pressure was measured noninvasively beat to beat by a photoplethysmographic finger device (Finapres; Ohmeda, Englewood, CO, USA) as described in detail [12]. Central venous pressure (CVP) was measured by a 16-gauge indwelling catheter inserted through an antecubital vein and advanced to the superior vena cava. Careful determination of the gain as well as adjustment of the pressure transducer to heart level ensured precise absolute values. Measurements of renal and systemic hemodynamics and endocrine parameters were made at rest and under cardiovascular stress testing.

Glomerular filtration rate (GFR) was assessed by the determination of inulin (IN) clearance and renal plasma flow (RPF) by the para-aminohippuric acid (PAH) clearance. The filtration fraction (FF) was calculated as the quotient of clearance of IN/clearance of PAH.

Clearances of IN and PAH were determined by the constant infusion technique without urine sampling [13]. Under steady state conditions the excreted amounts of IN (Inutest; Linz, Austria) and PAH (Nephrotest; Merck, Sharp and Dohme, Hoddesdon, UK) were equal to the infused doses of each indicator. By this assumption, the following equation can be set:

$$\text{GFR (mL/min)} = \text{rate of infusion (mg/min)/P (mg/mL)}$$

where P is the plasma concentration of each indicator.

This technique has proven to be a valid and reliable method to determine renal hemodynamics [13] without the necessity of spontaneous urine voiding or bladder catheterization, which alter the hemodynamic measurements. Since PAH is not excreted completely, this method overestimates the true PAH clearance by approximately 10 to 20% [14]. However, this bias is constant, since the extraction of PAH is approximately 90% and similar in the case of a renal plasma flow greater than 300 mL/min.

A central venous catheter was inserted via the left versus basilica for the infusion of both indicators, and an intravenous line at the opposite arm was applied for withdrawing blood samples. A bolus injection of both indicators (18 mg PAH/kg, 45 mg IN/kg) was given over 15 minutes at which the bolus dose has been calculated according to the distribution volumes of both indicators [15]. Subsequently, a constant infusion dose of both substances was calculated (0.75 g/h PAH, 1.5 g/h IN) assuming a normal creatinine clearance and a continuous infusion was started. PAH concentrations were measured by

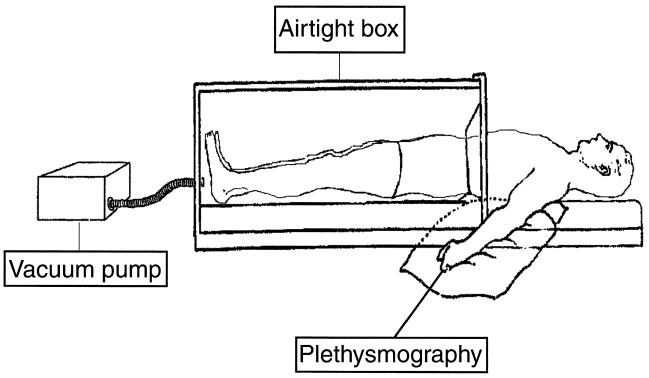

Fig. 1. Experimental device for the lower body negative pressure (LBNP) test.

the method of Pratton and Marshall as modified by Smith et al [16]. IN was measured indirectly by converting IN into fructose and subsequently measuring fructose by an enzymatic method (716260; Boehringer Mannheim, Mannheim, Germany). The filtration fraction (FF) was calculated by dividing the GFR by the RPF.

Lower body negative pressure test

Each subject was submitted to a negative pressure device consisting of an airtight box in which the lower half of the body down from the iliac crests was inside. The subjects remained in a supine position during the entire study period. The vacuum in the box was achieved by the use of a standard vacuum cleaner motor and the level of the vacuum was continuously measured by a standard mercury manometer connected to the inside of the box. Each subject was submitted to a level of −15 mm Hg for 30 minutes. The target level was achieved within 5 seconds. Measurements of systemic and renal hemodynamics and endocrine parameters were performed under steady state conditions after at least 20 minutes of LBNP. Symptoms such as syncope or vertigo did not occur. The experimental LBNP device is shown in Figure 1.

Endocrine parameters

Blood samples to measure angiotensin II (Ang II) levels were placed into prechilled tubes, immediately centrifuged at 0°C and stored for final evaluation at −18°C. All samples were analyzed within three months of storage. Plasma concentrations of Ang II were determined by radioimmunoassay [17].

Statistical analysis

All results are presented as means ± standard deviation. All data were analyzed by using the SPSS/PC version of the statistics package for social sciences [18]. Two-way analysis of variance (ANOVA) for repeated measurement design and the Student paired and unpaired *t* tests (normotensive vs. hypertensive subjects) were used when indicated. Values with a $P < 0.05$ were considered as statistically significant.

Table 1. Baseline characteristics of subjects with normotension and mild hypertension

	NT ($N = 10$)	HT ($N = 14$)	P
Age *years*	27.9 ± 4	26.4 ± 4	NS
Body mass index kg/m^2	23 ± 1.8	24.3 ± 2.6	NS
RR casual			
Systolic *mm Hg*	125 ± 10	142 ± 10	<0.05
Diastolic *mm Hg*	74 ± 4	82 ± 8	<0.01
RR 24 hours			
Systolic *mm Hg*	125 ± 9	132 ± 10	<0.05
Diastolic *mm Hg*	73 ± 4	88 ± 8	<0.05
Heart rate min^{-1}	60 ± 7	62 ± 7	NS
Central venous pressure *mm Hg*	7 ± 1.8	7.2 ± 1.6	NS
RPF *mL/min*	604 ± 67	548 ± 68	<0.05
GFR *mL/min*	110 ± 10	112 ± 12	NS
Filtration fraction *%*	18	20	NS
Angiotensin II concentration *ng/mL*	6.6 ± 2.5	7.2 ± 2.9	NS

Abbreviations are: NT, normotensive subjects; HT, mild hypertensive subjects; RR, >140/90 mm Hg and <160/95 mm Hg; RPF, renal plasma flow; GFR, glomerular filtration rate; FF, filtration rate; NS, not significant.

RESULTS

Subject characteristics as well as baseline renal and systemic hemodynamics and angiotensin II levels are presented in Table 1. Effects of AT1RA on renal and systemic hemodynamics are shown in Table 2 and responses of systemic and renal hemodynamics to LBNP are presented in Table 3. The effects of AT1RA on the renal hemodynamic response to orthostatic stress is shown in Figure 2 and on endocrine parameters in Figure 3.

AT1RA effect on blood pressure

Systolic and diastolic blood pressure was significantly higher in the group of HT (142 ± 10/82 ± 8 mm Hg) compared to the group of NT (125 ± 10/74 ± 4 mm Hg, $P < 0.05$) at the beginning of the study. Under AT1RA, blood pressure decreased significantly in HT by 7 ± 2 mm Hg (systolic) and by 4 ± 2 mm Hg (diastolic, $P < 0.05$), whereas in NT there was no change of systolic or diastolic blood pressure under AT1RA (105 ± 10/54 ± 5 vs. 109 ± 14/57 ± 9 mm Hg under placebo; NS).

AT1RA effect on systemic and renal hemodynamics

Renal plasma flow was significantly lower in subjects with mild hypertension (548 ± 68 mL/min) compared to normotensive subjects (604 ± 67 mL/min, $P = 0.05$) at rest, whereas GFR was not different in both groups. For those taking the AT1RA, RPF increased significantly in normotensive subjects (681 ± 117 vs. 604 ± 67 mL/min under placebo, $P < 0.05$) as well as in hypertensive subjects (632 ± 84 vs. 548 ± 68 mL/min with placebo, $P < 0.05$). This increase of RPF under AT1RA was greater in HT than in NT ($P < 0.01$, Table 2).

A slight, but not significant rise in GFR was observed only for the total study group (114 ± 13 vs. 111 ± 11 mL/min under placebo, $P = 0.07$). However, in each group separately, no change of GFR could be found.

Table 2. Effects of eprosartan on systemic and renal hemodynamics in NT ($N = 10$) vs. HT ($N = 14$)

Parameter	NT	HT	P
ΔHR *bpm*	1 ± 0.5	5 ± 7	<0.05
ΔSAP *mm Hg*	−4 ± 1.4	−7 ± 16	<0.05
ΔDAP *mm Hg*	−4 ± 0.8	−3 ± 1.5	NS
ΔCVP *mm Hg*	+0.5 ± 0.3	+0.8 ± 0.5	NS
ΔRPF *mL/min*	+77 ± 26	+84 ± 11	<0.01
ΔGFR *mL/min*	+3 ± 1.1	+4 ± 1.2	NS
ΔFF %	+2 ± 0.3	+2 ± 0.5	NS

Values are means ± SD and are expressed as changes from baseline. Abbreviations are: NT, normotensives; HT, mild hypertensives; HR, heart rate; SAP/DAP, systolic/diastolic arterial pressure; CVP, central venous pressure; RPF, renal plasma flow; GFR, glomerular filtration rate; FF, filtration fraction.

Table 3. Effects of LBNP (−15 mm Hg) on systemic and renal hemodynamics in the entire group (NT + HT, $N = 24$)

Parameter	Rest	LBNP	P
HR *bpm*	61 ± 7	63 ± 6	<0.05
SAP *mm Hg*	117 ± 15	120 ± 9	<0.05
DAP *mm Hg*	61 ± 9	65 ± 11	<0.01
CVP *mm Hg*	7.1 ± 1.3	2.8 ± 1.2	<0.0001
RPF *mL/min*	575 ± 73	540 ± 75	<0.01
GFR *mL/min*	110 ± 11	108 ± 10	<0.01
FF %	19 ± 1	19 ± 2	NS

Abbreviations are: NT, normortensives; HT, mild hypertensives; HR, heart rate; SAP/DAP, systolic/diastolic arterial pressure; CVP, central venous pressure; RPF, renal plasma flow; GFR, glomerular filtration rate; FF, filtration fraction.

Filtration fraction did not change under therapy with AT1RA either in normotensives (0.16 vs. 0.18 under placebo) or in subjects with mild hypertension (0.18 vs. 0.20 under placebo; NS).

Effect of LBNP on systemic and renal hemodynamics

At a LBNP level of −15 mm Hg, central venous pressure fell significantly ($P < 0.0001$). Heart rate rose in all subjects significantly ($P < 0.05$) and a slight increase of systolic as well as a significant increase of diastolic blood pressure occurred during LBNP. This systemic hemodynamic reaction was not different in NT and HT.

Lower body negative pressure led to a significant reduction of RPF in all subjects ($P < 0.01$, Table 3). The renal hemodynamic responses to LBNP of NT and HT were not different. As well, GFR decreased significantly under cardiopulmonary baroreflex discharge (108 ± 10 vs. 110 ± 11 mL/min at rest, $P < 0.05$) in normotensive and hypertensive subjects. FF remained stable (0.19) at rest as well as under LBNP in all subjects.

AT1RA effects on renal hemodynamic response to LBNP

The effects of E on renal hemodynamics during unloading of the cardiopulmonary baroreflex are presented in Figure 2. The LBNP-induced reduction of RPF was not influenced by the therapy with E [absolute change from baseline (ΔRPF) −19 ± 29 mL/min vs. −16 ± 21 mL/min under placebo; NS]; no significant difference was found between the group of NT and HT under AT1RA (ΔRPF −18 ± 33 mL/min in NT vs. −20 ± 26 mL/min in BHT; NS). The LBNP-induced decline of GFR, however, was prevented under treatment with AT1RA. Under E, GFR rose in all subjects during LBNP (ΔGFR +1 ± 3 mL/min under E vs. −2 ± 2 mL/min under placebo). This GFR-maintaining effect of E during cardiovascular stress was significant ($P < 0.01$) and similar in the group of NT and HT.

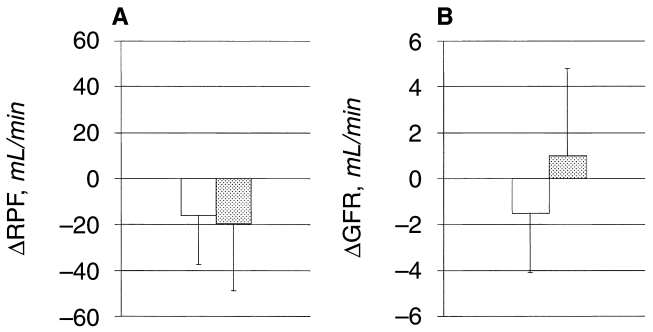

Fig. 2. Effects of angiotensin II type 1 receptor antagonist (AT1RA) with placebo (□) and eprosartan (▩) on the renal hemodynamic response to LBNP.

Effects of AT1RA and LBNP on endocrine parameters

Under treatment with E, plasma Ang II levels increased significantly in all subjects ($P < 0.001$). At a LBNP level of −15 mm Hg, a significant rise of plasma Ang II levels ($P < 0.001$) was noticed in all subjects. However, this increase during LBNP was significantly enhanced in the group of HT compared to the group of NT ($P < 0.05$; Fig. 3).

DISCUSSION

The present study shows that there is a significantly lower RPF in patients with mild hypertension and normal renal function compared to normotensive subjects. Interestingly, with the AT1RA administration, the RPF rose in both groups, and this increase was significantly higher in hypertensive than in normotensive subjects. Unloading of cardiopulmonary baroreceptors significantly reduced the RPF and GFR in all subjects. AT1RA prevented this renal hemodynamic response during cardiovascular stress testing, as during LBNP the GFR was maintained in both normotensive and hypertensive subjects.

Already in this early stage of hypertension, there was a significantly higher increase of Ang II release during cardiovascular stress with the LBNP compared to normotensive subjects.

Effects of AT1RA on systemic and renal hemodynamics

In accordance with earlier results [19, 20], there was a significant decrease of blood pressure in the mildly hypertensive subjects under AT1RA therapy. In addition,

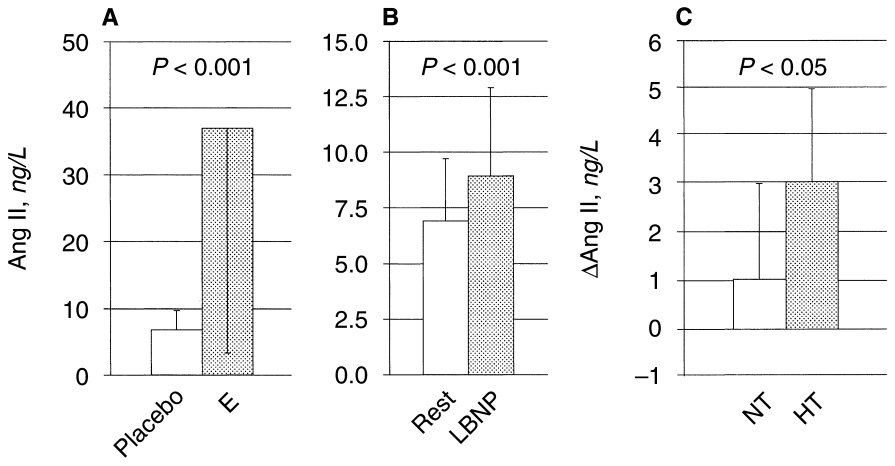

Fig. 3. Effects of AT1RA on angiotensin II release with eprosartan and LBNP. Abbreviations are: NT, normotension; HT, mild hypertensives; E, eprosartan; Ang II, angiotensin II levels (ng/L).

eprosartan, a representative of the class of AT1RA typified with a carboxy benzyl imidazole acrylic acid, has been shown to exert central sympathoinhibitory effects by blocking the presynaptic AT1 receptors promoting sympathetic nerve activity [19, 21]. However, in normotensive subjects the blood pressure levels decreased only slightly during the E administration in our study. This could be explained statistically by the small number of study subjects and also by the fact that E may have sympathoinhibitory effects, especially in a state of an activated sympathetic nervous system as hypertension.

Only few clinical data exist on renal hemodynamic effects of AT1RA. In normotensive subjects, AT1RA have been shown to have no effect on the GFR, and to induce either no change or a modest increase in RBF [22, 23]. Price et al's study of healthy men who were on a low salt diet and given E orally, demonstrated renal vasodilator effects of a significant rise of RPF. Glomerular filtration rate did not change and a significant decrease of filtration fraction was noted. The decrease of RPF as a renal hemodynamic response to exogenous Ang II was blunted by an oral administration of E at a dose of 200 mg, as there was a renewed increase of RPF; this indicates that a parallel shift of the dose-response curve occurred, thus supporting the concept that E acts as a competitive antagonist [11]. Our objective was to assess the renal hemodynamic response not only in normotensive subjects, but also in patients with mild hypertension. Our hypothesis that E antagonizes the augmented neurohumoral response in the kidneys in the state of early hypertension is confirmed.

We found a significantly reduced RPF in the patients with mild hypertension and normal renal function. The reason for this finding may be that the renin-angiotensin system is stimulated in this state of mild hypertension [24], with a vasoconstrictive action located at the afferent glomerular arteriole. Remarkably, in mildly hypertensive subjects the renal vasodilator effect after AT1RA administration was more marked, with a highly significant increase of RPF than found in normotensive subjects. This surplus effect could be due to the striking effect of the AT1 receptor blockade, with relatively more substantial vasodilating actions occurring in conditions of a stimulated renin-angiotensin system, like hypertension [24], compared to a state of balanced renin-angiotensin system, such as is found in normotension.

Systemic and renal hemodynamic response to LBNP with and without AT1RA

Our studies clearly demonstrate that deactivation of the cardiopulmonary baroreflex by LBNP, substantiated by a significant fall of central venous pressure and thus simulating orthostatic stress, leads to both a systemic and a regional hemodynamic response, as shown by the decrease of RPF. These effects, together with the LBNP-induced increase of Ang II, prove that the interaction between the sympathetic nervous system and the RAS exists in the regulation of blood pressure and volume homeostasis.

In agreement with previous studies [25, 26], a LBNP level of −15 mm Hg in our study caused no fall of blood pressure, but a significant increase of diastolic and a slight increase of systolic blood pressure were noted. This result may be explained by the acute activation of the renin-angiotensin system, which has been verified for normal subjects during unloading of the cardiopulmonary baroreflex [27–29]. The increase of heart rate in all subjects can be assumed to be a consequence of reflex sympatho-excitatory response to deactivated atrial baroreceptors, as demonstrated earlier by the microneurographic measurements by Sundlof and Wallin [30].

In our study, a continuous LBNP level of −15 mm Hg caused a significant decline of RPF and GFR in all subjects, suggesting that this cardiovascular stress-simulating orthostasis leads to an enhancement of renal vascular resistance caused by an increased sympathetic outflow

and/or an effect of an increased Ang II release. However, previous studies showed only little alterations of renal vascular resistance in healthy subjects at lower levels of LBNP (<20 mm Hg) [27, 28]. Würzner et al found no changes in renal hemodynamics in normal subjects up to a LBNP level at −22.5 mm Hg [31]. At higher levels, a trend toward a decrease in GFR and RPF was seen. As well, splanchnic vascular resistance has been shown to rise only at high levels of LBNP [32], whereas forearm muscle vascular resistance increases during selective unloading of cardiopulmonary baroreceptors by lower levels of LBNP [33]. Therefore, the threshold for each cardiopulmonary and arterial baroreceptor deactivation and the equivalent LBNP level are not clearly defined.

Experimental data demonstrated a close relationship between decreases in RPF and elevations of Ang II concentrations in the isolated perfused rat kidney [34]. Our data confirm this association of decreased RPF and stimulated circulating Ang II during cardiopulmonary baroreflex discharge.

It is remarkable that no difference of the hemodynamic pressure response to LBNP in normotensive and mild hypertensive subjects was seen, suggesting that the neural circulatory reflex response is similar in both groups.

Of note, in our study, therapy with AT1RA preserved the decrease of GFR as a renal circulatory response to LBNP in all subjects. AT1RA raised RPF at rest; however, under cardiovascular stress RPF decreased. The RPF response to LBNP did not change after AT1RA administration. These dissociations may illustrate that a subset of endocrine and neural mechanisms influence renal hemodynamic autoregulation differentially during cardiovascular stimuli. Thus, Tidgren et al showed a diverging release of dopamine and noradrenaline renal overflow during LBNP [27], suggesting that a portion of the dopaminergic nerve participates in the control of renal circulation. Furthermore, while angiotensin converting enzyme (ACE) inhibitors block the enzymatic dissimilation of kinins and thus lead to an intensified renal vasodilation, AT1RA does not influence the kinin metabolism [11]. Hence, the renal vascular tone under AT1RA is not affected by enhanced kinin concentrations [24]. These effects could explain that, in this experimental situation with reduced RPF as a response to LBNP, GFR does not decline further by additional effects due to kinins and prostaglandins.

Our previous study examined the effects of an ACE inhibitor on renal hemodynamics in 20 normotensive and 20 mildly hypertensive subjects at rest and during mental stress [35]. In this earlier study, sympathetic activation during mental stress led to an increase of GFR in both study groups, and this was more pronounced in the hypertensive patients. Interestingly, ACE inhibition tended to attenuate the more marked increase of GFR in hypertensive subjects, pointing to an excessive synthesis of Ang II in the unique situation of sympathetic stimulation by mental stress. Yet, in comparison with these former findings, cardiopulmonary stress testing by LBNP caused a decrease of GFR in all subjects, indicating a vasoconstriction in the renal vascular bed. The renal hemodynamic response in this setting is similar to reactions during physical stress and aerobic exercise that are known to lead to a decrease in GFR [35].

This finding of a sustained GFR during LBNP by AT1RA could be a useful clinical action in situations of intravascular volume depletion or heart failure with reduced renal perfusion, and implicate AT1RA as being renoprotective in clinical states that are affected with a high risk of acute renal failure.

Effect of LBNP and AT1RA on endocrine parameters

As expected and also documenting the validity of our data, we observed a rise of Ang II concentrations in all subjects under AT1RA. In several earlier studies, Burnier et al demonstrated that a competitive angiotensin receptor blocker induces a compensatory increased release of Ang II [36, 37]. In agreement with previous data, we found no difference in the enhanced Ang II release in normotensive and hypertensive subjects under AT1RA [38].

Our data confirm that the baroreflex discharge by LBNP leads to a significant increase of Ang II levels as well. Decreased venous return to the heart caused by LBNP acts as a stimulus for the juxtaglomerular cells via sympathetic nerve control to raise the circulating Ang II. Tidgren et al studied 10 healthy volunteers and likewise demonstrated that LBNP administered with stepwise increases up to −40 cm H_2O enhances circulating angiotensin II [27]. However, when the Ang II responses to LBNP for normotensive and mildly hypertensive subjects were analyzed separately, we found a significantly exalted reaction in the mildly hypertensive compared to normotensive subjects. This finding emphasizes that cardiovascular stress caused by LBNP which imitates orthostasis induces an enhanced neurohumoral stimulation yet in mild hypertension. Thus, even in an early stage of hypertension, there are hints for a disturbed neurohumoral reflex response of cardiopulmonary baroreceptor discharge.

Taken together, these results provide new insights into the disturbed neurohumoral blood pressure regulation in mild forms of hypertension after excessive stimulation of RAS induced by cardiovascular stress appropriate to orthostasis. Moreover, our results show that AT1RA may exert renoprotective effects in clinical situations of volume depletion by its ability to sustain GFR in a state of reduced cardiac preload.

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Reprint request to Helga Frank, M.D., Medical Klinik IV, Universität Erlangen-Nürnberg, Krankenhausstraße 12, 91054 Erlangen, Germany. E-mail: Helga.Frank@rzmail.uni-erlangen.de

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