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The exaggerated natriuresis of essential hypertension occurs independently of changes in renal medullary blood flow

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Abstract

Aims In patients with essential hypertension abnormal renal sodium handling includes exaggerated natriuresis in response to extracellular volume expansion. We tested the hypothesis that exaggerated natriuresis is associated with increases in medullary and/or cortical renal blood flow.

Methods Patients with mild essential hypertension, but no signs of end organ damage, and control subjects were studied after four days of dietary standardization (<60 mmol Na^+ day^{-1}) preceded in patients by a 14-days drug washout period. On the study day, subjects received a 4-hour intravenous volume expansion with saline (2.1% of body mass). Renal medullary and cortical blood flows were measured by PET scanning using $H_2{}^{15}O$ as tracer; anatomical regions of interest were defined by contrast-enhanced CT scanning.

Results In patients, arterial blood pressure increased during volume expansion (107±2 to 114±3 mmHg, $p<0.05$) in contrast to the control group (92±2 to 92±2 mmHg). Renal sodium excretion increased more in patients than in controls (+133±31 µmol min^{-1} vs. +61±14 µmol min^{-1}, respectively, $p<0.05$) confirming exaggerated natriuresis. During volume expansion, renal medullary blood flow did not change significantly in patients (2.8±0.4 to 2.5±0.5 ml (g tissue)$^{-1}$ min^{-1}) or in controls (3.2±0.3 to 3.1±0.2 ml (g tissue)$^{-1}$ min^{-1}). In control subjects, renal cortical blood flow fell during volume expansion (4.1±0.3 to 3.7±0.2 ml (g tissue)$^{-1}$ min^{-1}, $p<0.05$) in contrast to patients in which deviations remained insignificant.

Conclusion Exaggerated natriuresis, a hallmark of essential hypertension, is not mediated by increases in regional, renal blood flow.

Keywords hypertension, renal hemodynamics, renal blood flow, volume expansion, sodium sensitivity, low salt diet

Introduction

Sodium balance and blood pressure regulation are clearly related, but the relationship remains controversial.[1,2] In normotensive subjects, salt sensitivity of arterial blood pressure is a continuous, normally distributed physiological trait[3] which is defined arbitrarily[4,5] and is present in minor subgroups[6,7] to a variable extent dependent on subject characteristics and methodology. Generally, normal subjects are salt resistant[5]. However, the finding that salt sensitivity is more prevalent in hypertensive patients[3] is often taken to indicate that some deficiency in the renal excretion of sodium is a key element in hypertension.[8-10] However, distinct disagreement prevails with regard to the specific change in renal function involved in hypertension.[1,5,9,11]

It is well known, but not often in focus, that patients with essential hypertension show exaggerated natriuresis, i.e., they excrete a saline load faster than appropriate control subjects.[12-21] This phenomenon is not uniquely associated with hypertension, but exaggerated natriuresis does not seem to be immediately congruent with deficiencies in the mechanisms regulating renal sodium excretion.

In a previous study of a small group of patients with essential hypertension, we confirmed the phenomenon of exaggerated natriuresis, and found that baseline plasma concentrations of fluid balance hormones showed abnormal pro-natriuretic levels compatible with a response to sodium retention.[22] Natriuresis in response to saline loading may be elicited by neurohumoral and/or renal hemodynamic changes. Renal medullary blood flow has been considered an important element in the regulation of renal sodium excretion and thereby in blood pressure regulation. It was suggested that increased oxidative stress in the renal medulla decreases medullary perfusion and thereby increases sodium

reabsorption during hypertension.[23] We have adapted imaging technology to quantify regional renal blood flows in man[24,25] allowing imaging procedures to be added to measurements of hemodynamic, hormonal and renal responses to volume expansion. For the present study, we hypothesized that in patients with mild essential hypertension, but no measurable target organ damage, the response of local renal flow to saline loading differs from baseline and from the response of normotensive subjects.

Results

Subjects. The primary results consist of data from six hypertensive (HYP) and 12 normotensive control (CON) subjects. Results including all eight patients (see Materials and Methods for clarification) are described in the Supplementum. For all subjects, plasma sodium, potassium, and osmolality values were normal, as were ECG and data for kidney and liver function (Table 1). The 24-h sodium excretion rates on the day prior to investigation were indistinguishable between groups and compatible with compliance with the dietary regimen.

Baseline hemodynamics and renal function. In HYP, mean arterial BP was mildly elevated (107±2 vs. 92±2 mmHg, $p<0.01$; Fig. 2A). Heart rates and systemic vascular resistances were similar in HYP and CON (63±4 vs. 61±2 bpm and 16±1 vs. 17±1 mmHg min L^{-1}, respectively), but cardiac index was elevated in HYP (3.5±0.3 vs. 2.8±0.1 L min^{-1} m^{-2}, $p<0.05$) (Fig. 2 B, C, D). Baseline GFR values were similar in HYP and CON (87 ±10 ml min vs. 98 ±5 ml min) (Fig. 5C). With regard to regional renal blood flows, the values of renal medullary blood flow (RMBF) were indistinguishable (2.8±0.4 vs. 3.2±0.3 ml (g tissue)$^{-1}$ min^{-1}) for HYP and CON, respectively. Similarly, renal cortical blood flows (RCBF) were not different between HYP and CON; however, HYP values tended to be lower than

those of CON (3.3±0.4 vs. 4.1±0.3 ml (g tissue)$^{-1}$ min^{-1}) (Fig. 3 A, B). Sodium and potassium excretion rates did not differ between groups (Fig. 4 C, D). Free water clearances (2.5±0.4 vs. 3.2±0.7 ml min^{-1}) and osmolar clearances (2.5±0.2 vs. 2.7±0.1 ml min^{-1}) also were indistinguishable (Fig. 5 A, B) despite the finding that plasma vasopressin values were higher in HYP than in CON (see below).

Baseline plasma concentrations. Plasma sodium, potassium (Fig. 4 A, B), creatinine (87 ±6 vs. 85 ±3 µmol L^{-1}) and osmolality (283 ±2 vs. 283 ±2 mOsm L^{-1}) were not different between groups. No differences were found in plasma levels of renin or AngII between hypertensives and controls at baseline (renin: 54±12 vs. 39±4 mIU L^{-1}; AngII: 18 ±7 vs. 26 ±9 pg mL^{-1}) (Fig. 6 A, C). However, baseline aldosterone levels were significantly elevated in hypertensives (170 ±23 vs. 104 ±15 pg mL^{-1}, $p<0.05$) (Fig. 6B). Baseline levels of vasopressin (AVP) were 2.5-fold higher in hypertensives than in controls (6.1 ±1.3 vs. 2.4 ±0.3 pg mL^{-1}, $p<0.05$) (Fig. 6D).

Volume expansion. During volume expansion, the rate of sodium excretion increased almost 5-fold in HYP and almost 3-fold in CON (Fig. 4C, both: $p<0.01$). Peak sodium excretion rates reached higher levels in HYP than in CON (166±35 vs. 92±15 µmol min^{-1}, $p<0.05$, t-test) compatible with exaggerated natriuresis. Within the time of observation HYP excreted a significantly larger fraction of the infused sodium during volume expansion (8.4 ± 2.4 vs 3.9 ± 0.7 %, $p<0.05$, t-test). Potassium excretion increased transiently at t=120 and subsequently decreased to baseline level (Fig. 4D). Free water clearance remained unchanged in HYP as well as in CON. Likewise, free water clearances were statistically indistinguishable between the two groups (Fig. 5B). Osmolar clearance was unaffected by volume expansion (Fig. 5A).

Renal medullary blood flow (RMBF) did not change significantly in HYP or in CON, and differences in RMBF between groups were not observed (Fig. 3A). With volume expansion, RCBF tended to be lower in HYP than in CON ($p<0.1$) (Fig. 3B). Similar to RMBF, volume expansion did not change renal cortical blood flow (RCBF) in HYP ($p<0.1$); however, in CON, RCBF decreased significantly with volume expansion (Fig. 3B, $p<0.05$). Arterial blood pressure increased significantly in HYP (+7 mmHg, $p<0.05$), but not in CON (Fig. 2A).

During volume expansion, glomerular filtration rate increased initially in both groups, but transiently and similarly (Fig. 5C). Heart rate was unchanged and cardiac index decreased significantly in HYP ($p<0.05$), while heart rate decreased significantly, and cardiac index only decreased transiently in CON (HR $p<0.01$ and CI p=ns, Fig. 2 C, D). Systemic vascular resistance increased significantly in both HYP ($p<0.01$) and CON ($p<0.01$; Fig. 2B). During volume expansion, cardiac index was significantly increased in HYP compared to CON ($p<0.01$) while systemic vascular resistance and heart rate did not differ between HYP and CON (fig 2 B, C).

During volume expansion, plasma levels of renin and aldosterone were suppressed in HYP as in CON (Fig. 6 A, B). Plasma levels of vasopressin decreased significantly in HYP ($p<0.01$), but not in CON (Fig. 6D). Noradrenaline levels were similar in HYP and CON at baseline (1.4±0.1 vs. 1.2±0.1 pmol ml^{-1}) and did not change with volume expansion.

Despite our efforts to provide saline with a sodium concentration similar to that of plasma, plasma sodium concentrations showed significant and similar increases in the two groups (HYP: 133 ±1 to 138 ±1 mmol min^{-1}, $p<0.01$, CON: 135 ±1 to 139 ±1 mmol min^{-1}, $p<0.01$; Fig. 4A). Plasma potassium concentrations remained unchanged (Fig. 4B).

Discussion

The present results confirm that in hypertensive subjects, the natriuresis elicited by acute saline infusion is exaggerated compared to control subjects, but reject our working hypothesis because this response was not associated with increases in renal cortical or medullary blood flow. In addition, the results confirm that also in normal subjects, the saline-mediated natriuresis occurs without measurable increases in cortical or renal medullary blood flow.

Regional renal blood flows were measured by PET/CT as previously described.[24,25] The applied standard PET/CT procedure provides data which quantitatively should be considered with some reservation primarily because of the complexity of the renal circulation and the relative simplicity of the model by which renal flows are calculated.[25] However, the principles and techniques applied for flow calculation are verified and widely used in neuroimaging[26,27] and the manual volume identification technique very accurately discerns renal cortical from renal medullary tissue supporting the assumption that the method is valid.[28] Our previous results showed that the method is reliable with regard to qualitative changes in cortical and medullary renal blood flows in response to standard procedures,[25] but direct comparisons between regional renal blood flows measured by the present PET/CT approach and other methods, such as magnetic resonance imaging (MRI) in man[29] or laser-Doppler flowmetry[23] in animals, have apparently not been performed. Therefore, we can conclude that the saline-driven natriuresis in normal man and the exaggerated natriuresis in hypertensive man are not associated with increases in regional renal blood flows measurable by a method which detects renal blood flow changes generated by altered availability of nitric oxide.

In the normotensive control group, the marked saline-mediated increase in sodium excretion occurred without any change in arterial blood pressure in analogy with previous studies in our lab indicating that acute saline infusion at rates below 25 μmol kg^{-1} min^{-1} for several hours does not elevate arterial pressure (see review by Bie[2]). This means arterial pressure is not affected by administration during 2 h of some 200 mmol of NaCl equivalent to 24 h intake in many industrialized societies. This supports the notion that under most physiological conditions renal sodium excretion is regulated primarily by changes in neurohumoral pathways to the kidney[2].

The present study was focused on uncomplicated, essential hypertension in an attempt to assess more clearly the basic mechanisms of the disease and the exaggerated natriuresis associated with it. The protocol was highly standardized with regard to selection criteria, low-sodium baseline conditions, and slow rates of saline infusion (2.1% of body mass in 4 h). Somewhat unexpectedly, only a limited number of patients fulfilled the present inclusion criteria.

The conditions were designed to optimize measurements of renal excretory function, notably increases in renal sodium excretion, as well as decreases in the activity of the renin angiotensin aldosterone system. Volume expansion by saline infusion was performed by use of a slightly hypotonic saline solution. Nevertheless, plasma sodium concentration increased during the procedure, in patients as well as in control subjects. The increase may be related to the systematic postural changes, since identical volume expansion of very similar patients in the seated position was no associated with changes in plasma sodium (137 ±1 to 138 ±1 mmol/L).[30] However, the specific nature of this relationship remains elusive. This underscores the notion that volume expansion by isotonic or slightly hypotonic saline

solutions is not a simple dilution of the aqueous phase of the extracellular fluid, cf. recent reviews.[2,31] However, this issue was outside the focus of the present study, and seems less important for the differences between normotensives and hypertensives because the increases in plasma sodium concentration were similar in the two groups.

The exaggeration of the natriuresis in the hypertensive group could be due to aberration in several signal pathways such as the increase in arterial pressure, altered anti-natriuretic/natriuretic hormone levels, and changes in renal sympathetic nervous activity.

Our finding that in hypertensives the arterial pressure rose during a saline infusion regimen which in the control subjects did not affect blood pressure, is consistent with the notion that sodium sensitivity of arterial blood pressure is augmented in hypertensives.[32,33] The role of such blood pressure increase in the augmentation of the natriuresis is difficult to delineate, but several findings appear relevant. Firstly, changes in medullary blood flow may influence sodium excretion,[34] but the present results show that (our protocol of slow) sodium loading did not elevate medullary blood flow, thus eliminating blood pressure driven changes in medullary perfusion as a mediator of sodium excretion under the present conditions. There is a risk of a type 1 statistical error due to the small sample size in the HYP group. Yet, the non-significant trend for change in RMBF is towards a decrease, making such an error less likely. One could also speculate whether the values of RMBF did not increase due to measurement bias from renal tubular flow. However, GFR did not decrease and urine flow increased markedly indicating that renal tubular flow also increased. Therefore, it is difficult to see how measuring bias from renal tubular flow could cause overestimation of RMBF. Secondly, in similar - and similarly prepared - hypertensive patients we found that very similar, but spontaneous, blood pressure changes were not associated with changes in renal

sodium excretion.[22] Volume expansion did not elevate blood pressures beyond the spontaneous fluctuations in the same hypertensive patients.[22] There seem to be no reports of investigations in which the renal response to volume expansion has been studied in hypertensive patients under conditions where blood pressure increases during saline infusion have been prevented. In the absence of such direct evidence, only the mentioned observations of the spontaneous increases in arterial blood pressure seem to indicate that the small, slow change in arterial pressure measured under the present study probably had little effect on renal sodium excretion. This notion is supported by results from experimental animals as recently reviewed.[2]

Levels of fluid balance hormone levels in hypertensive patients may vary. It has been found that patients categorized as low-renin hypertensives show a larger natriuretic response to saline loading than other patients with hypertension.[19] In the present study, plasma values of renin and angiotensin II were not lower in patients compared to the normotensive controls; therefore, it is unlikely that the exaggerated natriuresis in our patients were related to subnormal activity of the renin system. Under similar conditions in a previous study we found that hormonal changes (renin system and atrial natriuretic peptide) at baseline were compatible with a pro-natriuretic setting (suppression and activation, respectively),[22] but the present data are not supporting this notion. Minor differences with regard to hemodynamic and hormonal patterns between the results of our previous study[22] performed in sitting subjects and the present data could be related to the shifts in body position imbedded in the present protocol. In man, even minor orthostatic changes cause measurable deviations in cardiovascular and renal function.[35] Nevertheless, it seems puzzling that the present hypertensive patients had increased cardiac index, but the patients of the previous study[22] were hypertensive due to increased peripheral resistance.

Reliable indices of 'sympathetic tone' to vasculature and kidney are difficult to obtain also because changes in the sympathetic drives to different organs do not necessarily change in parallel, see recent review.[36] Generally, less than half of the patients with essential hypertension show elevated indices of sympathetic activity also when advanced methods are applied.[36] Here we measured only the concentration of noradrenaline in venous plasma and found no differences between or within the two groups of subjects and, therefore, no evidence of involvement of the sympathetic nervous system on this basis. However, more detailed analysis including noradrenaline spillover is required to reject a role of sympathetic tone in the present context.

Somewhat unexpectedly, the plasma levels of vasopressin in the hypertensive patients were consistently elevated; in addition, the saline infusion was associated with a decrease in plasma vasopressin in hypertensives, while the trend for a decrease in the control subjects was not significant. Judged from the effects of infusion of vasopressin to normal man,[37] a doubling of plasma vasopressin reflects an increase in secretion rate of some 20-40 pmol min^{-1} $(kg\ body\ mass)^{-1}$. A doubling of plasma vasopressin in essential hypertension has been found before,[38] albeit not consistently.[39] As small, acute increases in plasma vasopressin have been shown to decrease sodium excretion[37] the present fall in vasopressin may contribute to the increase in sodium excretion in the hypertensive subjects, but it seems unlikely that this mechanism has a dominating role.

In summary, the exaggerated natriuretic response to acute saline infusion is interesting because the phenomenon seems at odds with the possibility that impairment of renal sodium excretion is a crucial element in the development of hypertension. The present results demonstrate that the exaggeration is not associated with measurable increases in either

cortical or medullary blood flows. Together with our previous results, the data indicate that the primary reason for the hypertension could be an aberration in the neurohumoral control of renal function or a primary increase in renal vascular resistance associated with inappropriate anti-natriuresis.

Materials and Methods

Subjects included were male Caucasians with mild (<160/<100 mmHg) essential hypertension and no sign of target organ damage, metabolic malfunctions or obesity, proteinuria, elevated liver enzymes, body mass index (BMI > 28 $kg \cdot m^{-2}$) cardiac hypertrophy, dyslipidaemia, hyperglycaemia, isolated systolic hypertension, documented stroke or heart attack. The study was approved by the local ethics committee (S-20120025) and complied with the Declaration of Helsinki. Informed, written consent was obtained from all participants. Subjects were identified among outpatients of the hypertension clinic at Odense University Hospital. Patients in treatment (n = 6) were subjected to a washout period for 18 d leading up to the acute investigation. Untreated, referred patients (n = 2) were included on the basis of office blood pressure (BP) ≥ 140/90 mmHg. Subjects for the control group were recruited via local advertisements. One subject, recruited as a control subject, was transferred to the patient group because of consistent measurements of BP ≥ 140/90 mmHg.

All subjects underwent a thorough clinical assessment to rule out target organ damage and concurrent disease by means of medical history, echocardiography or electrocardiogram, plasma concentrations of electrolytes, glucose, creatinine, alkaline phosphatase, alanine aminotransferase, HbA1c, and lactate dehydrogenase as well as urine albumin concentration. Criteria of exclusion included signs of cardiac disease by ultrasound, severe hypertension, BMI >28 kg m^2, plasma creatinine >110 µmol l^{-1}, and urine albumin >20 mg l^{-1} as well as

diabetes, a recent circulatory event (within 6 months) or any other sign of organ pathology. Control subjects underwent the same examination protocol as the patients. A total of 9 patients and 14 controls were accepted for the study; 6 patients and 12 controls completed the protocol. In addition, two patients with a BMI >28 kg m^2 were investigated.

Pre-treatment. For four days prior to the experimental day, patients were provided a low-sodium diet prepared by the kitchen division for special meals at Odense University Hospital. The diet was designed to include a sodium intake of 50-60 mmol d^{-1}; a control measurement of the sodium content in a standard daily portion provided a value of 58 mmol. Low-salt snacks were permitted in case of hunger. Dietary compliance was assessed by measurement of the sodium content of a 24-h urine sample obtained on the last day of pretreatment (0700-0700 h) and deemed acceptable if the 24-h sodium excretion was <70 mmol. All participants agreed to keep physical activity to a minimum during the 4 d of dietary standardization.

Acute intervention. On the experimental day, the patients were awakened for urine collection prior to 0700 h followed by a standardized, light breakfast including 500 mL of water. At the department (≈1 h later), the patients were weighed and before instrumentation they drank 200 ml of sodium-free lemonade containing glucose (20 g l^{-1}). Two intravenous catheters (Venflon, Becton Dickinson) were inserted, one in a cubital vein of the right arm for blood sampling, and another in a dorsal hand vein in the opposite arm for infusions and bolus injections. Glomerular filtration rate was assessed by ^{51}Cr-EDTA clearance; a bolus of ^{51}Cr-EDTA (2.5 MBq) was given i.v. immediately after catheterization followed by a constant i.v. infusion of 1.0 MBq h^{-1} (in glucose, 50 g l^{-1}¸ 25 ml h^{-1}) delivered by an infusion pump (Argus 707V, Codan Argus, Baar, Switzerland). Cardiac output and total peripheral resistance were calculated continuously from heart rate and stroke volume monitored by impedance

cardiography (PhysioFlow PF-03, Manatec Biomedical, Macheren, France) after autocalibration based on subject's characteristics according to the manufacturer's instructions and divided by body surface area (BSA) as calculated by the Du Bois formula ($BSA=0.007184 \times weight^{0.425} \times height^{0.725}$)[40] to yield cardiac index.

Regional blood flows in the kidney were quantified from analyses of PET/CT images obtained before and at the end of volume expansion. The physical properties of the PET/CT scanner allow measurements only in the supine position. Therefore, the protocol was designed to include systematic changes in body position from seated to supine to even out potential bias introduced by the body position during scans (Fig. 1). PET scans (GE-Discovery VCT PET/CT-scanner, GE Healthcare, Milwaukee, WI, USA) were carried out using $H_2{}^{15}O$ as tracer.[25] After the PET scans were completed, the renal anatomy was visualized by contrast enhanced CT scanning (Ultravist®, Bayer Schering Pharma, Berlin, Germany) and images were analyzed as previously described and illustrated. [24,25]

The protocol included 80 min of baseline observations followed by three consecutive 80 min periods with saline infusion (Fig. 1). The baseline measurements were initiated by a blood sample (25 ml) and emptying of the urine bladder by voluntary micturition. Each of the following 80 min intervals were concluded by blood and urine collection (Fig. 1). Volume expansion was performed by infusion of slightly hypotonic saline; standard saline (154 mmol L^{-1}) was diluted to 135 mmol L^{-1} by sterile water and administered i.v. at a rate of 12 µmol (kg body mass)$^{-1}$ min^{-1} for 240 min, i.e. ≈21 ml^{-1} (kg body mass)$^{-1}$. A reclining chair was used for the seated position and a standard hospital bed for the supine position. The subjects were motivated to stay awake throughout the day. Standing occurred briefly only during micturition. Throughout the day, participants ingested 100 ml of glucose solution every 30

min to maintain a standardized degree of hydration, to increase diuresis thereby facilitating accurate clearance measurements, and to suppress the feeling of hunger.

Plasma and urine analyses. Blood samples were centrifuged immediately at 4°C. Electrolyte concentrations and osmolality were determined on the day of the experiment by flame photometry and freezing-point osmometry, respectively. Plasma renin concentration (PRC) was determined by the rate of AngI generation measured by the antibody trapping principle[41] in the presence of excess substrate; concentrations of AngI, AngII, vasopressin and aldosterone were measured as previously described.[42] Plasma noradrenaline concentrations were measured by HPLC after extraction.[43]

Imaging data analysis. Regional renal blood flows were estimated using the anatomical method as described by Damkjær et al.[24] The contrast enhanced CT images were manually fitted to the corresponding PET scans using the imaging software "MNI register" (Open-source program register, Montreal Neurological Institute, McGill University, Montreal, Canada, http://bic.mni.mcgill.ca/~david/). Six renal surface tag points were used for overlaying of the PET and CT images.

Statistics. Comparisons within and between groups were performed by one-way and two-way ANOVA, respectively, adjusted for repeated measures. In case of significant differences, post-hoc Bonferroni tests were performed. Statistical calculations were performed with GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA). Results are presented as mean ± standard error of the mean (SEM).

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Conflict of interest

The authors have no conflicts of interest to declare.

Publication principles

The submitted material conforms with Good Publishing Practice in Physiology.[44]

Table 1

Baseline characteristics at inclusion.

Parameter	**Hypertensives**	**Controls**
No. of subjects	6	12
Age (years)	55±4	51±4
BMI (kg/m^2)	26±0.4	24±1
Office Systolic BP (mmHg)	137±6**	114±4
Office Diastolic BP (mmHg)	88±4*	78±2
P-Creatinine (µmol/L)	84±6	86±3
U-Albumin (mg/L)	10±3	6±0.3 (n=9)
U-Protein (mg/dL)		9±2 (n=3)
Na^+ excretion (mmol/d)	18±6	22±4
P-Na^+ (mmol/L)	140±0.5	140±1
P-K^+ (mmol/L)	3.9±0.1	3.9±0.1
P-ALAT (U/L)	33±6	27±3
P-ALP (U/L)	72±6	62±4

BMI: body mass index. BP: blood pressure. Values are mean ± SEM.

Significance between groups: *$p<0.05$, **$p<0.01$.

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Figure legends

Figure 1

Timeline for acute interventions. Positions: *Sup*: supine position, *Seat*: seated position. Procedures: Positon emission tomography (PET), 4-hour saline infusion (135 mM NaCl, infusion with 12 µmol (kg body mass)$^{-1}$ min^{-1} for 240 min, ≈21 ml/kg), CT: Computed tomography. B: Blood samples. U: Urine samples.

Figure 2

Hemodynamic results at baseline and during volume expansion. (a) Mean arterial blood pressure (MABP) (b) Systemic vascular resistance (SVR) (c) Heart rate (HR) (d) Cardiac index (CI). Significant differences within groups +: $p<0.05$, x: $p<0.01$ (just above individual bar) and between groups with *: $p<0.05$, #: $p<0.01$ (above bars). Values are mean ±SEM, n=6 hypertensives and n=10-12 controls.

Figure 3

Regional renal blood flows at baseline and following volume expansion. (a) Renal medullary blood flow (RMBF), (b) Renal cortical blood flow (RCBF). Significant differences within groups +: $p<0.05$, #: $p<0.01$ (just above individual bar), and between groups +: $p<0.05$, #: $p<0.01$ (above bars). Values are mean ±SEM, n=6 hypertensives and n=12 controls.

Figure 4

Effects of volume expansion on plasma composition and renal excretion rates. (a) Plasma sodium levels (pNa^+), (b) Plasma potassium levels (pK^+), (c) Renal sodium excretion rate (Na^+ excr.), (d) Renal potassium excretion rate (K^+ excr.). Significant differences within groups +: $p<0.05$, #: $p<0.01$ (just above individual bar) and between groups with +: $p<0.05$, #:$p<0.01$ (above bars). Values are mean ±SEM, n=6 hypertensives and n=12 controls.

Figure 5

Effects on GFR, renal clearances and fractional excretion of sodium. (a) Osmolar clearances (C_{Osm}), (b) Free water clearance. Significant differences within groups +: $p<0.05$, #: $p<0.01$ (above individual bars) and between groups +: $p<0.05$, #: $p<0.01$ in (above bars). Values are mean ±SEM, n=6 hypertensives and n=12 controls.

Figure 6

Plasma hormone levels at baseline and during volume expansion. (a) plasma renin activity, (b) plasma aldosterone concentration, (c) plasma AngII concentration, (d) plasma vasopressin concentration. Significant differences within groups +: $p<0.05$, #: $p<0.01$ (above individual bars) and between groups +: $p<0.05$, #: $p<0.01$ (above bars). Values for (a), (b), and (c) are mean ±SEM; n=6 hypertensives or 12 controls; for (d) n=5 in each group.

Figures

Figure 1

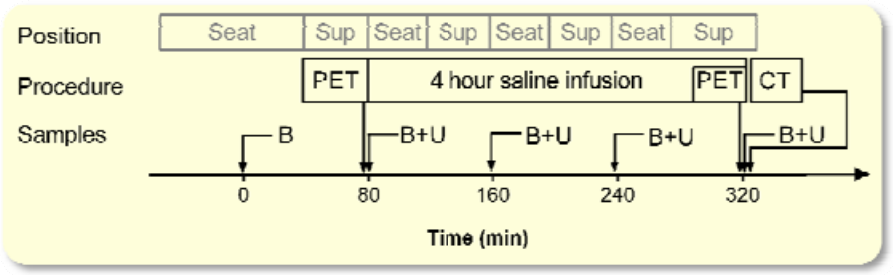

Figure 2

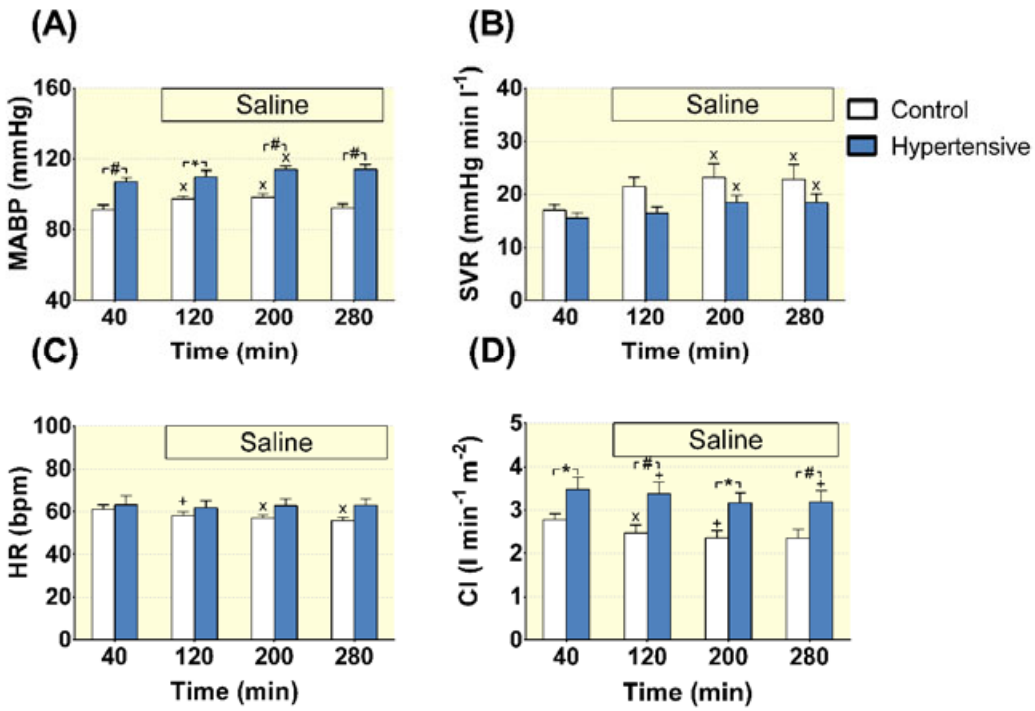

Figure 3

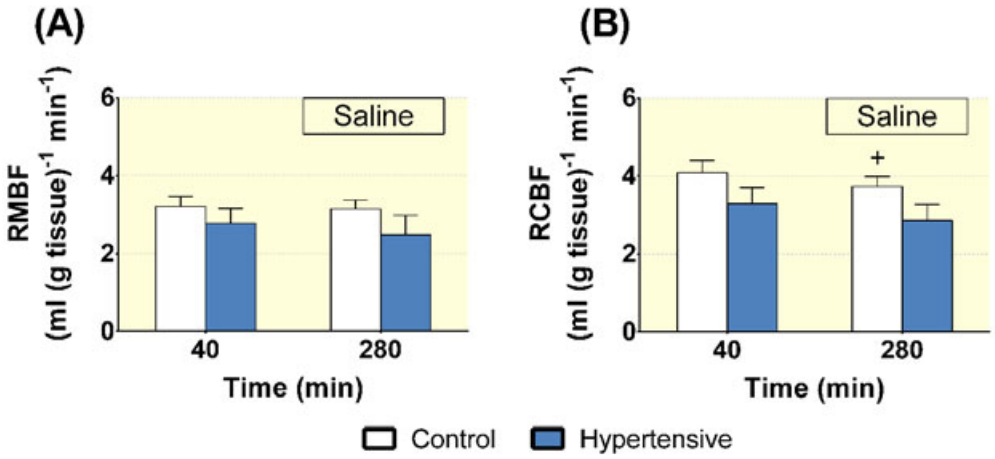

Figure 4

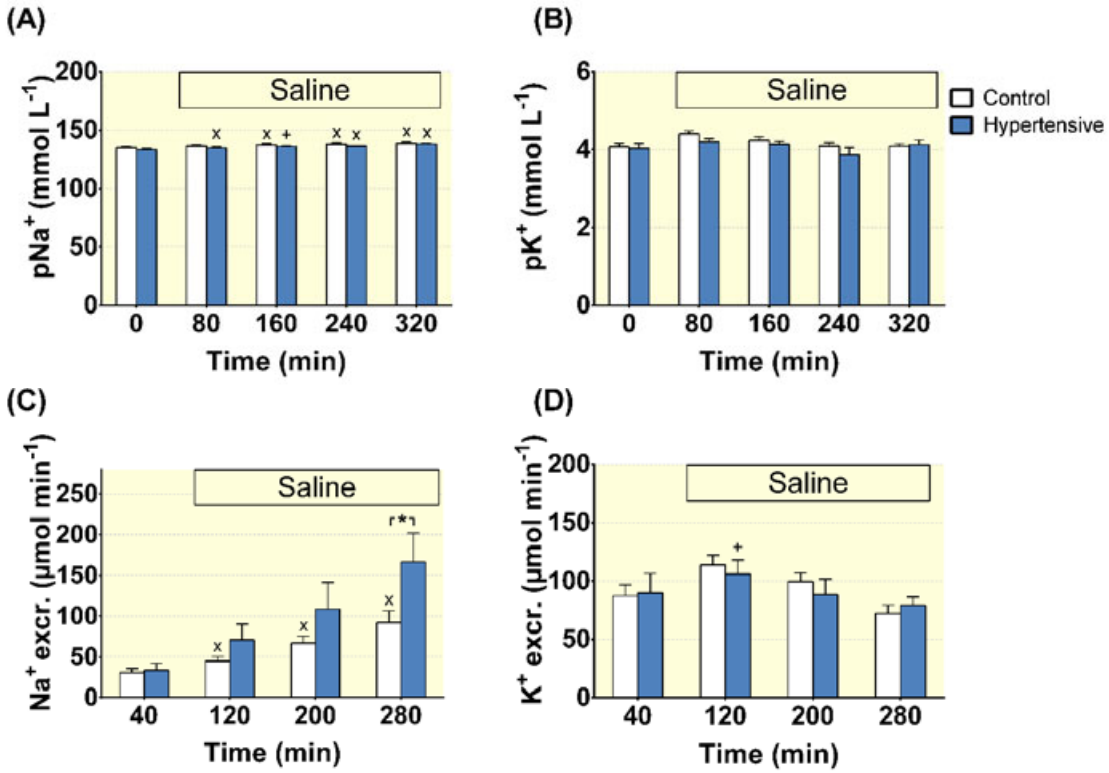

Figure 5

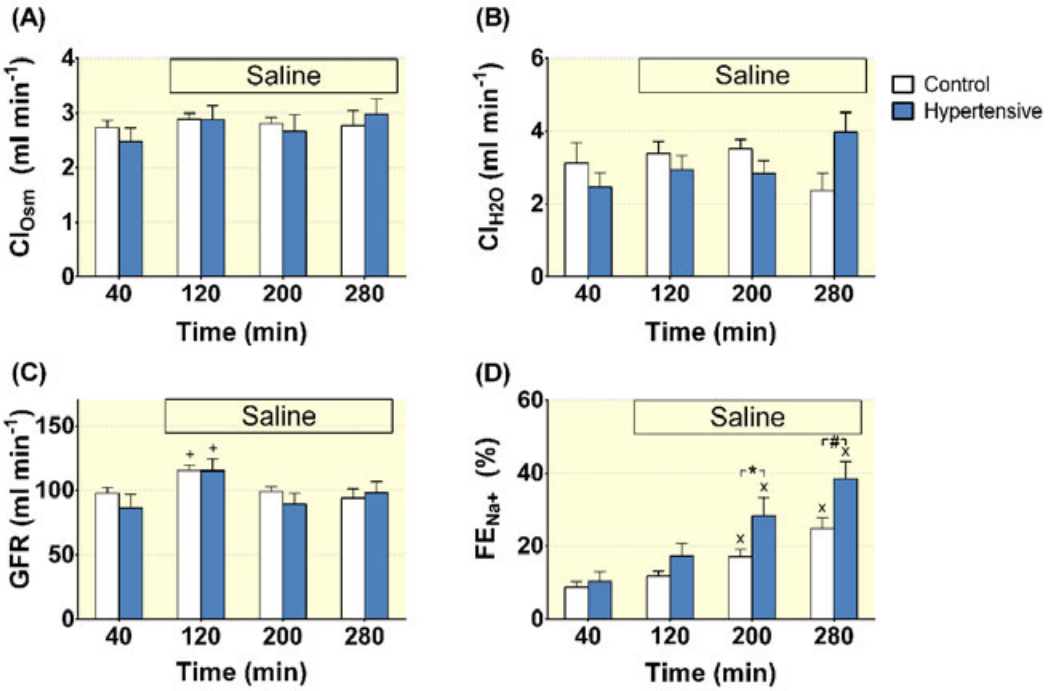

Figure 6