Renal Sodium Excretion and the Peritubular Capillary Physical Factors in Essential Hypertension

Yngvar Willassen, M.D., and Jarle Ofstad, M.D.

SUMMARY Peritubular capillary hydrostatic and oncotic forces and their relationship to the renal excretion of sodium (UNaV) were examined in 19 patients with moderate and uncomplicated essential hypertension (HT) and compared with data from 20 normotensive subjects (NT). Observations were made in hydropenia (C) and during sustained isotonic saline volume expansion (E; 3% increase in body weight). The intrarenal venous pressure (IRVP) was used as an index of peritubular capillary hydrostatic pressure, and the efferent arteriolar colloid osmotic pressure (COPa) was estimated from the arterial COP and the filtration fraction.

C values (mean ± SEM) in HT (and NT) were: arterial pressure (MAP) 110 ± 3 mm Hg (85 ± 1, p < 0.001); glomerular filtration rate (GFR) 122 ± 4 ml/min/1.73 m² (128 ± 3, p > 0.05); renal blood flow (RBF) 1172 ± 38 ml/min/1.73 m² (1298 ± 48, p < 0.05); IRVP 25.0 ± 1.0 mm Hg (24.8 ± 0.8, p > 0.05); COPa 33.0 ± 0.7 mm Hg (31.9 ± 0.6, p > 0.05); and UNaV 140 ± 13 μmole/min (161 ± 12, p > 0.05).

During E, the increase of UNaV in HT was more than double that of NT (p < 0.001) while IRVP did not change in either group (p > 0.05) and COPa fell by 26% (p < 0.001) in both groups. GFR and RBF increased by 18% (p < 0.001) and 19% (p < 0.001) respectively, in HT, but did not change in NT. MAP remained unchanged in both groups.

The results indicate that the peritubular capillary physical factors are normal in established essential hypertension, and that these forces are not involved in the exaggerated natriuretic response to volume expansion in essential hypertension. (Hypertension 2: 771-779, 1980)

KEY WORDS • essential hypertension • renal sodium excretion • renal hemodynamics • intrarenal pressure

The most accepted hypothesis concerning the pathogenetic role of the kidney in essential hypertension is based on the observation that there is, in acute experiments, a positive correlation between the arterial blood pressure (BP) and the renal excretion of sodium. The hypothesis states that this relationship is altered in essential hypertension so that a higher BP is needed for the renal excretion of a given quantity of sodium. The hypothesis states that this relationship is altered in essential hypertension so that a higher BP is needed for the renal excretion of a given quantity of sodium. At normal BP, sodium is therefore retained until the BP has increased enough to establish sodium and water balance. The mediators of this abnormal relationship between kidney perfusion pressure and the renal excretion of sodium — commonly referred to as “resetting” of the pressure natriuresis — have not yet been identified. The hypothesis presupposes factors causing sodium retention as a primary event as well as natriuretic mechanisms associated with the development of hypertension.

In principle, impaired sodium excretion could be caused either by a reduced glomerular filtration rate or increased tubular reabsorption of the filtrate, or both. A subnormal filtration coefficient compensated by increased glomerular capillary hydrostatic pressure has been observed in some hypertensive models in the rat. In one of these models, the peritubular capillary hydrostatic pressure also is elevated, possibly reducing the tubular reabsorption of sodium and water and thus adding to the resetting effect of the increased glomerular capillary pressure. Lowenstein et al. found an elevated intrarenal venous pressure (IRVP) in patients with essential hypertension, and also observed that the augmented natriuretic response to saline volume expansion was associated with an exaggerated increase in IRVP in these patients. These findings have been considered as evidence for an
increased peritubular capillary hydrostatic pressure in human essential hypertension compensating for the postulated sodium retaining mechanisms and partly explaining the "resetting" of the pressure natriuresis.8-11

We have not been able to confirm the findings of Lowenstein et al. that saline volume expansion increases the IRVP in normal man,18 and our preliminary observations in patients with essential hypertension19 did not suggest any abnormality of IRVP. In our present study we examine the IRVP in antidiuresis and during sustained volume expansion in essential hypertension to assess the hydrostatic and oncotic forces acting in the postglomerular capillaries in these experimental conditions.

The results of our study do not support the idea that peritubular capillary physical forces are abnormal in established essential hypertension. We cannot, however, exclude the possibility that changes in these forces are of pathogenetic importance in the initiating phase of the hypertensive process, and that normalization of the physical forces are later events secondary to the development of hypertension.

Materials and Methods

Nineteen patients (13 men, 6 women) with essential hypertension were studied. The patients were without symptoms and signs of hypertensive complications with the exception of slight left ventricular hypertrophy on ECG in two patients. Rapid sequence intravenous urography was normal in all patients, and proteinuria was absent in all. The mean age was 35.3 years (range, 22 to 55 years) and the mean known duration of disease was 3 years (range, 0.5 to 10 years). The patients' consent for participation in the study was obtained after detailed information of the purpose of the study and of the experimental procedure with its inherent risks. The results were compared with our previously reported findings in 20 normal individuals (16 men, 4 women);12 their mean age was 28.9 years (range, 23 to 46 years). All subjects were maintained on an unrestricted salt intake, and antihypertensive drugs were discontinued for 2 weeks or more prior to the study. As the excretion of sodium and water is more labile in hypertensive patients than in normotensive controls and liable to acute changes provoked by emotional reactions4 and alterations in the state of hydration, recorded functional differences between hypertensive and normotensive individuals may express a different reaction to the measuring procedure rather than true basal disparities. To minimize such errors, the control measurements were made in hydropenia after giving the patients time to adapt to the experimental situation.

The observations were made in the morning following food and fluid deprivation for approximately 10 hours. The subjects were studied in the recumbent position on a bed balance with an automatic electronic weight change indicator (J.H. Potter, West Hartford, Connecticut). A Foley catheter was introduced into the urinary bladder after surface anesthesia of the urethra with 2% lidocaine, and the urine was continuously drained from the bladder into flasks placed outside the bed balance. A priming and sustaining infusion of inulin and p-aminohippurate (PAH) diluted in 0.9% saline was then given intravenously to establish and maintain serum concentrations of approximately 0.25 g/liter and 0.05 g/liter respectively. The sustaining infusion was given at a rate of 0.5 ml/min throughout the experiments.

The renal vein catheterization was performed with the technique of Edvall.14 In local anesthesia, a thin-walled radiopaque polyethylene catheter (Kifa, Stockholm) with external diameter of 2.40 mm and a side-hole 3-4 mm from the open end was introduced percutaneously into the right femoral vein and manipulated into the renal vein under fluoroscopic control. A right renal vein position was obtained in 15 hypertensive patients and in 19 normal subjects. In the others, the left renal vein was catheterized. Proper renal vein position was always secured by measurement of the oxygen saturation in the renal venous blood with whole blood photometry. In local anesthesia, a polyethylene catheter was also introduced into the right brachial artery for pressure measurement and blood sampling.

The measurement of IRVP was performed with a method previously tested in the dog.18 A radiopaque polyvinyl catheter (o.d. 0.9 mm) with a softened tip and connected to a pressure transducer was gently advanced under fluoroscopy through the renal vein catheter and retrograde into proper intrarenal venous (wedged) position as previously described.18

Following the vascular catheterizations, about 2½ hours after start of the experiments, control measurements were made during two clearance periods, each lasting 30-45 minutes. The subjects were then volume-expanded with 0.9% NaCl-solution prewarmed to body temperature given intravenously at a rate of 0.5 ml/min/kg body weight to obtain a netto increase of body weight of 3% as indicated by the bed balance. The new weight level was maintained throughout the rest of the experiment by adjustments of the saline infusion rate. Following 30 minutes of sustained volume expansion, the measurements were repeated during two to three clearance periods each lasting 10-15 minutes (experimental periods).

At the midpoint of each clearance period, arterial blood samples were drawn for the determination of serum inulin, PAH, electrolytes, osmolality, total protein, colloid osmotic pressure (COPs) and hematocrit (hct), and renal venous samples for the measurement of the PAH extraction ratio. The IRVP and directly measured mean brachial artery pressure (MAP; obtained by electronic integration) were recorded continuously while renal venous pressure recordings were made intermittently.

The clearance of inulin and PAH were measured according to the principles of Smith.19 The values for the individual clearance periods were corrected to 1.73 m² body surface area, and the mean value for the control periods and the experimental periods were calculated in each subject. Measurements of the intravascular...
pressures were made with Elema Schöndander pressure transducers EMT 35 (Elema Schöndander, Stockholm) and recorded on a Hewlett Packard multichannel recorder (Hewlett Packard, Waltham, Massachusetts). The middle axillary line was used as the zero reference level.

The serum and urine samples were analyzed for inulin and PAH using the methods of Walser et al. and Smith et al. respectively. Sodium and potassium concentrations were measured with a flame photometer (Eppendorf Gerstäubau, Hamburg) and the osmolality with an Advanced osmometer (Advanced Instruments Inc., Needham Heights, Massachusetts). Serum protein concentration was determined by the biuret method. The COP was measured with the colloid osmometer of Auckland and Johnsen using Amicon PM 30 membranes (Amicon Corporation, Lexington, Massachusetts), 0.9% NaCl as reference fluid, and a SEM 4-88 pressure transducer (SE Labs (EMI) Ltd., Feltham, Middlesex).

The renal vascular resistances were calculated as follows:

\[
\text{Total resistance} = \frac{\text{MAP} - \text{RVP (mm Hg)}}{\text{RBF (ml/min)}} \cdot 8 \times 10^4 \text{(dyne sec cm}^{-5})
\]

Precapillary resistance =

\[
\frac{\text{MAP} - \text{IRVP}}{\text{RBF}} \cdot 8 \times 10^4 \text{(dyne sec cm}^{-5})
\]

Postcapillary (venous) resistance =

\[
\frac{\text{IRVP} - \text{RVP}}{\text{RBF}} \cdot 8 \times 10^4 \text{(dyne sec cm}^{-5})
\]

where RBF = renal blood flow, calculated from clearance and extraction ratio of PAH, and RVP = renal venous pressure. The COP of the efferent arterioles (COP\(_{\text{a}}\)) was calculated using the equation of Ladegaard-Pedersen which describes the relation between the volume of a plasma sample (PV) with constant protein mass and the COP of the sample:

\[
\text{PV} \cdot \text{COP}^{0.667} = K
\]

where K is a constant for a given protein mass. The relationship given by the experimental derived factor 0.667 can be shown to be identical with the volume/COP-relation described by Landis and Pappenheimer. Neglecting the protein loss by glomerular filtration, we find that

\[
\text{TRPF} \cdot \text{COP}_{\text{a}}^{0.667} = (\text{TRPF} - \text{GFR}) \cdot \text{COP}_{\text{a}}^{0.667},
\]

and

\[
\text{COP}_{\text{a}} = \text{COP} \cdot \sqrt{1 - \frac{\text{GFR}}{\text{TRPF}}}
\]

The percentage change in total plasma volume (TPV) caused by the saline infusion was calculated in two different ways using the following equations:

\[
\frac{\text{TPV}_E}{\text{TPV}_C} = \frac{\text{hct}_C}{\text{hct}_E} \cdot \frac{1 - \text{hct}_E}{1 - \text{hct}_C} \cdot 100
\]

and

\[
\frac{\text{TPV}_E}{\text{TPV}_C} = \left( \frac{\text{COP}_C}{\text{COP}_E} \right)^{0.667} \cdot 100
\]

where the letter C denotes values in control condition and E denotes values during sustained expansion respectively.

The statistical analysis was performed using the Student's t test for paired and unpaired samples. Statistically significant differences were considered to be present when \(p < 0.05\).

**Results**

The control values for hematocrit, serum protein concentration, and COP\(_{\text{a}}\) were not different in the two groups (table 1). During saline infusion, the hematocrit fell slightly more in the hypertensive patients than in the normal subjects \((p < 0.05)\), while the reduction of serum protein concentration and COP\(_{\text{a}}\), which averaged 15% and 24%, did not differ from the findings in the normotensive group. The increase in plasma volume as calculated from changes in hematocrit and COP\(_{\text{a}}\) averaged 21% in the hypertensives and 20% in the normal subjects \((p > 0.1)\). The control serum sodium concentration was 139.6 mmoles/liter, which did not differ from the values in the normotensives \((p > 0.1)\).

**Response to Saline Infusion**

The renal excretory responses to saline infusion are given in table 2 and figure 1. Control values for diuresis and sodium/potassium excretion were the same in both groups. On average, the urine flow started to increase earlier in the hypertensive patients than in the normal subjects. The urine flow reached a plateau approximately at the time when full volume expansion was obtained, that is, about 60 minutes after start of the infusion, and remained at this level during the sustained volume expansion. The diuretic and natriuretic responses to the volume expansion was significantly greater in the hypertensive patients than in the normotensives \((p < 0.001)\). The filtered load of sodium increased by 18% \((p < 0.001)\) in the hypertensive group, but did not change significantly in the normotensive subjects \((p > 0.10)\). In the hypertensive patients, the fraction of filtered sodium reabsorbed decreased from 99.2 ± 0.1% in the control condition to 95.0 ± 0.1% during volume expansion \((p < 0.001)\), with a corresponding significant increase in fractional...
sodium excretion. The corresponding findings in the normotensive group were 99.1 ± 0.1% in the control condition and 97.2 ± 0.1% during volume expansion (p < 0.001). The increase in potassium excretion observed during volume expansion was the same in both groups. While the increment in osmolar clearance induced by volume expansion was greater in the hypertensives than the normotensives (p < 0.001), the increase in the free water reabsorption during volume expansion did not differ between the two groups.

Renal Hemodynamics During Volume Expansion

The renal hemodynamic findings before and during sustained volume expansion are summarized in table 3. The inulin clearance was similar in the two groups during the control condition, but increased significantly during the volume expansion in the hypertensive individuals. The PAH clearance and renal blood flow, which were significantly lower in the hypertensives than in the normal subjects in the control phase, increased during volume expansion by 28% and 19% respectively, approaching the corresponding values observed in the normotensive individuals. The control values for the PAH extraction ratio averaged 0.86 ± 0.01 in the hypertensives and 0.88 ± 0.01 in the normotensive individuals (p < 0.02) and did not change during volume expansion. The filtration fraction as expressed by the inulin clearance/total renal plasma flow ratio averaged 19.0 ± 0.6 in the hypertensive patients and 17.7 ± 0.6 in the normotensive group.

<table>
<thead>
<tr>
<th>Table 1. Hemodilutional effect of saline volume expansion</th>
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<tbody>
<tr>
<td>Hematocrit (vol %)</td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Essential hypertension</td>
</tr>
<tr>
<td>C</td>
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<td>E</td>
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<td>Δ</td>
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<td>Normotension</td>
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<td>C</td>
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<tr>
<td>E</td>
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<tr>
<td>Δ</td>
</tr>
<tr>
<td>p</td>
</tr>
</tbody>
</table>

C = control condition (hydropenia); E = sustained volume expansion; Δ = difference from control value; Values are mean ± SEM in arterial blood. *Significantly different (p < 0.05) from corresponding value in normotension.

<table>
<thead>
<tr>
<th>Table 2. Renal Excretory Responses to Saline Volume Expansion</th>
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</thead>
<tbody>
<tr>
<td>Urine flow (ml/min)</td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Essential hypertension</td>
</tr>
<tr>
<td>C</td>
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<td>E</td>
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<td>Normotension</td>
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<td>C</td>
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<tr>
<td>E</td>
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<tr>
<td>Δ</td>
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<tr>
<td>p</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Abbreviations are given in Table 1. *Significantly different (p < 0.05) from corresponding value in normotension. †Significantly different (p < 0.001) from corresponding value in normotension.
Table 3. Renal Hemodynamic Values During Saline Volume Expansion

<table>
<thead>
<tr>
<th></th>
<th>Inulin clearance (ml/min)</th>
<th>PAH clearance (ml/min)</th>
<th>Filtration† (%</th>
<th>Renal blood flow (ml/min)</th>
<th>Renal vascular resistance (dyne sec cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Essential hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>122 ± 4</td>
<td>562 ± 21†</td>
<td>22.1 ± 0.8∗</td>
<td>1172 ± 38∗</td>
<td>7840 ± 383†</td>
</tr>
<tr>
<td>E</td>
<td>143 ± 6</td>
<td>714 ± 29</td>
<td>20.2 ± 0.5</td>
<td>1394 ± 60</td>
<td>6554 ± 432†</td>
</tr>
<tr>
<td>∆</td>
<td>21 ± 4*</td>
<td>152 ± 21</td>
<td>-1.9 ± 0.7</td>
<td>222 ± 43</td>
<td>-1087 ± 215*</td>
</tr>
<tr>
<td>p</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.02</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Normotension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>128 ± 3</td>
<td>650 ± 22</td>
<td>20.1 ± 0.7</td>
<td>1298 ± 48</td>
<td>5221 ± 197</td>
</tr>
<tr>
<td>E</td>
<td>134 ± 5</td>
<td>746 ± 36</td>
<td>18.5 ± 0.8</td>
<td>1393 ± 74</td>
<td>4878 ± 271</td>
</tr>
<tr>
<td>∆</td>
<td>5 ± 3</td>
<td>96 ± 28</td>
<td>-1.6 ± 0.6</td>
<td>95 ± 62</td>
<td>-344 ± 189</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>&lt; 0.01</td>
<td>&lt; 0.02</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Significantly different (p < 0.05) from corresponding value in normotension.
†Significantly different (p < 0.001) from corresponding value in normotension.
Filtration fraction = inulin clearance/PAH clearance.
Clearance values are corrected to 1.73 m² body surface area.
Values are mean ± SEM. Abbreviations are given in Table 1.

(p > 0.1) and was significantly reduced during volume expansion (p < 0.02) without any significant difference between the groups. The total and precapillary vascular resistances, which in the control condition were greater in the hypertensive individuals than in the normotensives (p < 0.001), decreased significantly during the volume expansion but were still higher than in the normotensive individuals in the expansion phase (p < 0.02). Volume expansion did not induce any significant change in these resistances in the normal individuals. The postcapillary (venous) resistance in the hypertensive group was significantly higher than in the normotensives in the control period and fell significantly and to the same extent during saline infusion in both groups.

Blood Pressure During Volume Expansion

The intravascular hydrostatic pressures and COP eff are given in table 4 and figure 2. The MAP did not change during volume expansion. Control IRVP ranged from 18.0 to 31.0 mm Hg in the hypertensive patients and from 18.0 to 30.0 mm Hg in the normotensives, with almost identical mean values. In 13 hypertensive patients, the IRVP increased during the saline loading phase, and at the time when full expansion was obtained the mean IRVP in the total hypertensive material had increased from 25.0 ± 1.0 mm Hg in the control periods to 27.8 ± 1.1 mm Hg (p < 0.001). In nine of the 13 patients, the IRVP, however, fell during the phase of sustained expansion, and in the experimental sampling periods IRVP in the hypertensive group averaged 26.4 ± 1.4 mm Hg and did not differ from the preexpansion value (p > 0.1). During the sustained expansion, IRVP in five patients fell to values lower than the control level (fig. 2). Three of these subjects had a temporal increase in IRVP during the saline loading phase. In the normotensive

Figure 1. Individual values for renal sodium excretion (UNaV) in control condition (C) and during sustained saline volume expansion (E) in patients with essential hypertension (n = 19) and in normotensive subjects (n = 20). Horizontal bars represent mean values.
group, mean IRVP increased from 24.8 ± 0.8 to 25.8 ± 0.9 mm Hg (p > 0.05) during the saline loading phase, but fell to the pre-expansion level during sustained expansion.

Renal venous pressure, which in the control period was lower in the hypertensive individuals than in the normotensives (p < 0.05), increased significantly during volume expansion without any difference between the groups.

The mean COPeff in the hypertensive patients did not differ from values observed in the normotensives, and the reduction observed during the volume expansion averaged 26% in both groups. The difference between COPeff and the IRVP averaged 8.0 ± 1.2 mm Hg (p < 0.001) in the control condition in the hypertensive group and fell significantly (p < 0.01) during volume expansion to −2.0 ± 1.5 mm Hg, a value not significantly different from zero (p > 0.1). The COPeff-IRVP differences in the hypertensive group did not differ from those of the normotensive individuals either in the control condition or during sustained volume expansion (p > 0.10).

In the hypertensive group, no significant linear correlation was observed between IRVP and MAP in control condition (r = −0.009, p > 0.1). The increase in sodium excretion caused by the volume expansion did not correlate with either control values of MAP (r = −0.212, p > 0.1), IRVP (r = −0.218, p > 0.1), total renal vascular resistance (r = 0.303, p > 0.1), or the parallel changes in GFR (r = 0.142, p > 0.1), IRVP (r = 0.269, p > 0.1), RVP (r = 0.005, p > 0.1), hct (r = −0.441, p > 0.05) and COPeff (r = −0.061, p > 0.1).

There was, however, a significant positive correlation between the temporal increase of IRVP in the saline loading phase and the increases of urine flow (r = 0.513, p < 0.05) and sodium excretion (r = 0.486, p < 0.05) observed during sustained volume expansion. Similar analysis in the control group did not reveal any significant correlations.

**Discussion**

Under control conditions, the diuresis and sodium excretion as well as the hematocrit and plasma protein concentration in the hypertensive individuals were not different from the normotensive values, indicating that the hydration and sodium balance were similar in the two groups. The observation that the IRVP was the same in both groups in this condition confirms our preliminary findings, but is at variance with the observations of Lowenstein et al. In a study made in mannitol diuresis, these authors observed a substantially increased IRVP in a group of patients with uncomplicated essential hypertension compared with normotensive controls. This discrepancy probably can be explained by the different experimental protocols. As shown by Brodsky and Graubarth the diuretic as well as the natriuretic response to mannitol infusion is augmented in essential hypertension, and the increase in intrarenal pressures provoked by mannitol infusion probably is exaggerated in hypertensive patients due to enhanced volume flow through the collecting ducts. It is therefore possible that the elevated IRVP observed in the hypertensive patients of Lowenstein et al. is best explained as being caused by a greater diuresis in these individuals.

The mean BP as well as renal vascular resistance was higher in the patients studied by Lowenstein et al. than in the present study; this may indicate a more prolonged hypertensive state in their patients. The different IRVP observed in the two studies might thus be comparable to the increase of the end-afferent arteriolar hydrostatic pressure observed during the development of hypertension in the Milan strain of genetically hypertensive rats, this pressure being normal in the slightly hypertensive 35- to 40-day-old rats, but significantly elevated in the more hypertensive 75- to 90-day-old rats compared with age-matched normotensive animals.

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**TABLE 4. Intravascular Hydrostatic and Oncotic Pressures During Saline Volume Expansion**

<table>
<thead>
<tr>
<th></th>
<th>Brachial artery pressure (mm Hg)</th>
<th>Intrarenal venous pressure (mm Hg)</th>
<th>Renal venous pressure (mm Hg)</th>
<th>Different arteriolar colloid osmotic pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Essential hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>110 ± 3†</td>
<td>25.0 ± 1.0</td>
<td>1.0 ± 0.4*</td>
<td>33.0 ± 0.7</td>
</tr>
<tr>
<td>E</td>
<td>111 ± 4†</td>
<td>26.4 ± 1.4</td>
<td>2.0 ± 0.4*</td>
<td>24.4 ± 0.6</td>
</tr>
<tr>
<td>Δ</td>
<td>1 ± 1</td>
<td>1.4 ± 0.9</td>
<td>1.0 ± 0.3</td>
<td>-8.6 ± 0.6</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>&lt; 0.002</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Normotension</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>C</td>
<td>85 ± 1</td>
<td>24.8 ± 0.8</td>
<td>2.3 ± 0.4</td>
<td>31.9 ± 0.6</td>
</tr>
<tr>
<td>E</td>
<td>85 ± 1</td>
<td>25.1 ± 0.9</td>
<td>4.0 ± 0.4</td>
<td>23.6 ± 0.5</td>
</tr>
<tr>
<td>Δ</td>
<td>—</td>
<td>0.3 ± 0.4</td>
<td>1.7 ± 0.3</td>
<td>-8.3 ± 0.4</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*Significantly different (p < 0.05) from corresponding value in normotension.
†Significantly different (p < 0.001) from corresponding value in normotension. Values are mean ± SEM.
Our previous observations in the dog suggest that the IRVP measured with the present technique is a satisfactory expression of the hydrostatic pressure in the smallest peritubular capillaries. Although we cannot completely exclude the possibility that this relationship may not be valid in hypertension, our results indicate that the increased systemic BP is not transmitted to the postglomerular capillaries in this phase of essential hypertension, and present evidence against the hypothesis that the peritubular capillary hydrostatic pressure is involved in the resetting of the pressure diuresis/natriuresis in patients with established hypertension.

The normal IRVP in the hypertensive patients observed in this study corresponds well with the findings of normal peritubular capillary pressure in the spontaneously hypertensive Kyoto-Wistar rats, in which normal glomerular capillary pressures have also been observed. Our results do not exclude the possibility of increased glomerular capillary pressure in essential hypertension. However, evidence for a normal glomerular capillary hydrostatic pressure in hypertensive patients is presented by the findings of Furuyama, revealing that the medial hypertrophy of the renal arteries in patients with essential hypertension is most pronounced in the larger arteries and arterioles, but practically nonexistent in the smallest arterioles. To the extent that medial hypertrophy is produced by increased intravascular hydrostatic pressure, these findings suggest that the arterial hypertension is not transmitted to the smallest preglomerular vessels.

Even normal hydrostatic pressures in the renal microcirculation in established hypertension does not, however, exclude a pathogenetic role for intrarenal pressure-mechanisms in the development of essential hypertension. As in several animal models of hypertension, an increased sympathetic drive seems to be present in human borderline hypertension, which may be the initial phase of essential hypertension. Increased renal vasoconstriction caused by an augmented sympathetic activity may initially reduce the intrarenal pressures provoking sodium retention and hypertension with normalization of the intrarenal pressures and sodium excretion as secondary effects. The recent report of increased renal plasma flow in normotensive children of hypertensive patients does not, however, support the idea of increased renal sympathetic tone in the prehypertensive stage in essential hypertension.

The saline volume expansion clearly provoked an exaggerated diuresis and natriuresis in the hypertensive group as observed by several authors. It is possible that the augmented response was partly due to the increased glomerular filtration rate observed during volume expansion. However, the exaggerated increase in the fractional excretion of filtered sodium suggests an altered tubular reabsorption of sodium with abnormalities in the peritubular capillary hydrostatic and oncotic pressures as possible mediators. As the IRVP was similar during volume expansion in the two groups and not different from that in the control period, an increased peritubular hydrostatic pressure does not seem to be necessary for the sustained increase of sodium and water excretion either in essential hypertension or in normotensive individuals.

In the transitional phase from the control condition to the steady state of sustained volume expansion, the IRVP did not change in six of the 19 patients in the hypertensive group and in nine individuals in the normotensive group. This indicates that increased peritubular capillary hydrostatic pressure is not necessary to initiate the increased excretion rate of sodium and water during moderate volume expansion.
In 13 of the hypertensive patients, a temporal increase of the IRVP was observed, and this pressure change was significantly correlated to the exaggerated diuresis and sodium excretion caused by the saline expansion. Similar temporal changes of the IRVP have been observed in the dog during saline loading. This may indicate that larger increases of the urine flow and sodium excretion rate are dependent on transient increases in the peritubular capillary hydrostatic pressure. However, it is possible that these temporal changes are secondary to the increased urine flow and without any importance for the tubular reabsorption of sodium and water. During saline loading the diuresis in the normotensive individuals was close to the physiological maximum, calculated on a 24-hour basis, and the diuresis in the hypertensive patients was even greater. Our findings indicate that even transient pressure changes in the peritubular capillaries do not play an important part in the establishment of sodium balance either in hypertensive or in normotensive individuals when the diuresis is within physiological limits.

Our findings during saline volume expansion are at variance with those of Lowenstein et al. In their hypertensive patients, IRVP increased from 26.4 to 48.7 mm Hg following an infusion of 1 liter of 2.5% saline given intravenously in 1 hour. A similar but significantly smaller increase of the IRVP was observed in their normotensive individuals. This pressure response should be compared to the initial change in IRVP observed in our study in the transitional phase from the control condition to the stable volume expansion; such a state of sustained volume expansion was not a part of the study of Lowenstein et al. The differences of the IRVP observed were probably caused by a greater and more rapid volume expansion superimposed on a state of mannitol diuresis in the patients of Lowenstein et al.

The filtration fraction expressed as the inulin/PAH-clearance ratio is typically increased in patients with essential hypertension, and an increased peritubular capillary colloid osmotic pressure has therefore been proposed as a possible mediator of increased sodium reabsorption in these patients. Although the inulin/PAH-clearance ratio was significantly elevated in our hypertensive patients, the PAH extraction was slightly decreased, as has also been reported by Reubi et al. The true filtration fraction expressed as the inulin clearance/renal plasma flow ratio was therefore not significantly increased when compared with normotensive individuals, and fell to the same extent in both groups during volume expansion. The calculated post-glomerular oncotnic pressure was the same in both groups in the control condition as well as during sustained saline expansion. In this phase of essential hypertension, abnormalities in peritubular capillary oncotnic pressure therefore cannot readily explain either the "resetting" of pressure natriuresis or the exaggerated natriuretic response to volume expansion.

Although our findings do not suggest any important role for the peritubular physical factors in the exaggerated natriuretic response to sustained volume expansion, the enhanced sodium excretion was associated with a significant hemodynamic alteration in the kidneys: decreased vascular resistance, and increased glomerular filtration rate. As the blood dilution during sustained expansion was similar in the groups, the difference in hemodynamic response cannot be attributed to different alteration in blood viscosity, but must be ascribed to decreased renal vascular tone associated with volume expansion in the hypertensive patients. These findings therefore indicate that the vascular hyperreactivity demonstrated in several vascular circuits in essential hypertension is also present in the renal vascular bed, and confirm the observation that decreased renal blood flow in essential hypertension is at least in part due to functional vasoconstriction. Since the renal perfusion pressure as well as the IRVP was found to be normal during sustained volume expansion, the decreased vascular resistance in this phase probably was not caused by a pressure-mediated autoregulatory dilatation of the afferent arterioles.

Otherwise our study does not give any information as to the mechanisms behind the hemodynamic alterations that might involve both local intrarenal mediators and changes in neurogenic and/or hormonal exogenous stimulation of the renal vasculature. It should, however, be noted that the magnitude of the vasodilatatory response could at least be partly ascribed to altered vascular design due to hypertrophy of the vessel wall. The fact that the volume expansion did not eliminate the difference in precapillary resistance between the hypertensive and normotensive individuals does not imply that structural vascular changes were present. It could mean that the volume expansion was too small to abolish the increased vascular tone in the hypertensive kidneys. The increased postcapillary (venous) resistance in the hypertensive individuals also probably indicates an increased vascular tone in hypertension, as this abnormal resistance is not easily explained by either hypertensive structural changes or increased venous compression.

In conclusion, the present study does not support the hypothesis that the peritubular capillary physical factors are abnormal in established essential hypertension. Our findings suggest that the nephron in moderate and uncomplicated essential hypertension is operating under normal hydrostatic and oncotic pressures, and that the abnormal relationship between kidney perfusion pressure and the renal excretion of sodium and water is due to increased pregglomerular vascular resistance. "Resetting" of pressure natriuresis therefore does not necessarily implicate an abnormal glomerular or tubular handling of sodium. Our study does not give any answer to the question of whether the time-related exaggerated hemodynamic and natriuretic responses to volume expansion are pathogenetically interdependent phenomena. The possibility exists that the factor or factors responsible for the hemodynamic change also mediate the exaggerated natriuretic response by a direct tubular action independent of the peritubular physical factors.
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