Intrarenal Pressure and Sodium Excretion in Hypertension of Chronic Glomerulonephritis in Humans

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

SUMMARY The relationship between the fractional excretion of filtered sodium (FE\text{Na}) and the peritubular capillary physical forces (PCPF) in the hypertension (HT) of chronic glomerulonephritis (GN) was examined in hydropenia (C) and during sustained isotonic saline volume expansion (E; 3% net increase of body weight) in 32 GN patients (16 with HT), and compared with our previous findings in 20 normal individuals (NORM) and 19 patients with essential hypertension (EH). Fourteen GN patients (seven with HT) had a 75% reduction of glomerular filtration rate (GFR), the others (nine with HT) had normal or near normal GFR. The PCPF were estimated from the intrarenal venous (wedged) pressure (IRVP) and the calculated efferent arteriolar protein concentration (EAPC).

In C, IRVP correlated to GFR (r = 0.682, p < 0.001) and (FE\text{Na}) (r = -0.357, p < 0.05), but IRVP and EAPC were similar in HT and normotension at comparable levels of GFR. The increase of FE\text{Na} during E (\Delta FE\text{Na}) was exaggerated in all HT groups even at reduced levels of GFR, and could not be related to changes in renal hemodynamics or PCPF. \Delta FE\text{Na} correlated with mean arterial pressure in C both in GN (r\text{1} = 0.702, p < 0.01) and in the combined NORM/EH group (r\text{2} = 0.478, p < 0.01), with r\text{1} > r\text{2} (p < 0.005). The findings indicate that the pathogenesis of hypertension of chronic glomerulonephritis is independent of changes in the PCPF, and are compatible with the idea that humoral factors are the main mediators of the altered sodium excretion during saline volume expansion in the HT of both chronic GN and EH. (Hypertension 5:375-384, 1983)

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

RETENTION of sodium is considered to be an important pathogenetic factor in the hypertension of primary, nonvascular renal disease. The mechanism of sodium retention as well as the hypertensive mode of action of the sodium ion is, however, still not clear. Changes in the hydrostatic and oncotic pressures in the peritubular microcirculation have been shown to modify the tubular reabsorption of sodium in different experimental animals.\textsuperscript{1-3} By inference, these physical factors have been implicated as mediators of altered tubular sodium transport in physiological and pathological conditions in man, including hypertension.\textsuperscript{4-5}

In previous studies\textsuperscript{6-7} we have examined the postglomerular capillary physical forces in humans by estimating the peritubular capillary hydrostatic pressure from the intrarenal venous (wedged) pressure (IRVP),\textsuperscript{8} and by estimating the colloid osmotic forces from the systemic oncotic pressure and the filtration fraction. Our results indicate that the peritubular capillary physical factors are normal in uncomplicated essential hypertension (EH) both in antidiuresis and during saline volume expansion.\textsuperscript{9}

In the present study we have applied an identical experimental protocol to study the relationship between the peritubular physical forces and the sodium excretion in the renal hypertension of chronic glomerulonephritis (GN) in different stages of the disease.

The results, confirming our earlier preliminary observations,\textsuperscript{9} indicate that the IRVP decreases in parallel with the glomerular filtration rate (GFR) in chronic GN, but the peritubular capillary physical forces are not different in hypertensive and normotensive patients with comparable levels of GFR.

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Abbreviations Used in This Article
C = control condition
E = experimental period
AE = change in experimental period from control
EAPC = efferent arteriolar protein concentration
EH = essential hypertension
EPAH = PAH extraction ratio
FE = fractional excretion
FE\text{H}_{2}O = fractional excretion of filtered water
FE\text{Na} = fractional excretion of filtered sodium
\Delta FE\text{Na} = change of FE\text{Na} during saline volume expansion
FF = filtration fraction
GFR = glomerular filtration rate
GN = glomerulonephritis
hct = hematocrit
HT = hypertension
IgA = immunoglobulin A
IRVP = intrarenal venous (wedged) pressure
MAP = mean arterial pressure
NGFR = normal or near normal glomerular filtration rate
NORM = normal control group
NT = normotension
PAH = para-aminophenylurate
PCPF = peritubular capillary physical factors
PV = plasma volume
RBF = renal blood flow
RGFR = reduced glomerular filtration rate
RVP = renal venous pressure
tprot\text{a} = arterial total protein concentration

Material and Methods

Patients

The studies were made in 32 patients with chronic GN, and the results were compared with our earlier findings in 19 patients with EH$^{7}$ and 20 normal individuals (NORM). Consent for participation in the study was obtained from the patients after detailed information of the purpose of the study and of the experimental procedure with its inherent risks.

The GN patients were referred to the following four groups depending on their GFR and blood pressure: 1) normal or near normal GFR/normotension (NGFR/NT); 2) normal or near normal GFR/hypertension (NGFR/HT); 3) reduced GFR/normotension (RGFR/NT); 4) reduced GFR/hypertension (RGFR/HT). The number of patients, age and sex distribution, and GFR and blood pressure are summarized in table 1. The diagnosis of chronic GN was based on renal biopsy in 25 patients and on the history and the clinical and laboratory findings including intravenous urography in the others. None of the patients had a documented poststreptococcal glomerulonephritis, and the known duration of the disease exceeded 4 years in all cases. In all patients, proteinuria and/or hematuria were present, but none presented a nephrotic syndrome or manifested edema. The hypertensive patients had blood pressure readings of 150/100 mm Hg or more (cuff method) on three or more occasions preceding the study. In two NGFR/HT patients and in four with RGFR/HT, electrocardiography showed slight left ventricular hypertrophy; two of the RGFR/HT patients also had moderate left ventricular enlargement on chest x-ray examination. Manifest cardiac failure was absent in all patients.

At the time of the study, the patients were on an unrestricted salt intake, and all antihypertensive drugs had been discontinued for at least 2 weeks. On clinical examination all patients were volume-repleted.

Renal Histopathology

The renal biopsies were examined by light and immunofluorescence microscopy. In the NGFR group, two patients presented a membranoproliferative GN, one secondary to lupus erythematosus disseminatus, the other idiopathic. In the other NGFR biopsies, the main lesion was a mostly focal, mesangial cell proliferation with granular deposits (IgA, C₃, and occasionally minor quantities of IgG) in the mesangium and along the basement membrane, consistent with a diagnosis of IgA glomerulonephritis. The RGFR kidneys showed an extensive cellular proliferation and deposition of immunoglobulins in the glomerular tufts with obliteration of the capillary loops and hyalinization of a substantial number of glomeruli (end stage kidney).

<table>
<thead>
<tr>
<th>Table 1. Patient Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>NGFR/NT</td>
</tr>
<tr>
<td>NGFR/HT</td>
</tr>
<tr>
<td>RGFR/NT</td>
</tr>
<tr>
<td>RGFR/HT</td>
</tr>
<tr>
<td>NORM</td>
</tr>
<tr>
<td>EH</td>
</tr>
</tbody>
</table>

*Values (means ± SEM) for glomerular filtration rate (GFR = inulin clearance) and directly measured mean arterial pressure (MAP) obtained in control condition during the experiments. No = number of patients (number of patients with renal biopsy in parenthesis). NGFR = normal or near normal GFR; RGFR = reduced GFR; NORM = normal control group; EH = essential hypertension; NT = normotension; HT = hypertension.

$p < 0.05$; $\ddagger p < 0.01$; $\ddagger p < 0.001$, when comparing glomerulonephritis and EH value with corresponding normal value.
Experimental Procedure

The study was carried out in the morning with the patients in the supine position after food and fluid deprivation for approximately 10 hours. The experimental procedure was identical to our earlier description. Measurements were begun about 2½ hours after the start of the experiment and were made during two control periods each lasting 30 to 45 minutes. The subjects were then volume-expanded with 0.9% NaCl solution given intravenously at a rate of 0.5 ml/min/kg body weight to obtain a net increase of body weight of 3% as indicated by a bed balance. The new level of body weight 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 or three experimental periods each lasting 10 to 15 minutes.

The measurements of IRVP were made as previously described. In brief, the main steps in the procedure were renal vein catheterization with a wide bore radiopaque polyethylene catheter introduced percutaneously into a femoral vein followed by the introduction of a radiopaque vinyl catheter (0.9 mm o.d.) with a softened tip through the renal vein catheter retrograde into occluded position in an intrarenal vein. IRVP and the directly measured mean brachial artery pressure (MAP; obtained by electronic integration) were recorded continuously during the experiments, while renal venous pressure recordings (RVP, measured in nonoccluded position in the main renal vein) were made intermittently. In each observation period, measurements were made of inulin and para-aminohippurate (PAH) clearance, PAH extraction ratio (EPAH) from one kidney, hematocrit (hct), serum and urine sodium concentration and osmolality, and serum total protein concentration. In each patient mean values for the control periods (C) and the experimental periods (E) were calculated.

Analytical Procedures and Calculations

The analytical procedures and calculations were performed as previously described. The increase of plasma volume (PV) during saline infusion was computed from the decrease of hct using the following equation:

\[
P_{\text{Vf}} = \frac{hct (1 - hct)}{Pv_c}
\]

The efferent arteriolar total protein concentration (tprot_e) was calculated from the arterial total protein concentration (tprot_a) and the filtration fraction (FF = GFR/total renal plasma flow) as follows:

\[
tprot_e = \frac{tprot_a}{1 - FF}
\]

The following equations were used for the renal vascular resistances:

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

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

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

Statistical Analysis

The statistical analysis was performed with the Student's t test for paired samples within the groups and the Newman-Keuls multiple comparison test for comparisons between the groups. Statistically significant differences were considered to be present when \( p < 0.05 \). Values reported are means ± SEM.

Results

Hemodilution and Change of Plasma Volume

The mean hct and tprot_a in control condition and during the saline volume expansion are summarized in table 2. The control hct was significantly lower than normal in RGFR/HT, while tprot_a was similar in all groups. During volume expansion, both hct and tprot_a fell significantly in all groups without any differences between the groups (p > 0.05). The plasma volume expansion during saline infusion calculated from the change of hct, averaged 18% in the GN as well as NORM patients, compared with 20% in EH patients (p > 0.05). No difference of volume expansion was observed between the GN groups.

Renal Sodium and Water Excretion

The control urine flow and absolute sodium excretion (table 3) were the same in all groups. The fractional excretions of filtered water (FE_{w,0}) and sodium (FE_{Na,0}) were significantly increased from normal in the RGFR groups (table 3). While FE_{Na,0} was similar in these two groups, FE_{w,0} was significantly increased in RGFR/HT when compared with RGFR/NT (p < 0.05). The filtration of GFR reabsorbed as solute-free water (TC_{H2O/GFR}) averaged 0.71 ± 0.07% in NGFR/NT and 0.91 ± 0.12% in NGFR/HT, which did not differ from the values of 0.84% ± 0.08% (p > 0.10) in NORM or 0.86% ± 0.07% (p > 0.10) in EH. The corresponding values were -0.10% ± 0.54% in RGFR/NT and -0.10% ± 0.29% in RGFR/HT, which were significantly less than normal (p < 0.005).

During saline volume expansion, mean urine flow and absolute sodium excretion increased significantly in all groups (table 3). When compared with NORM,
these responses were enhanced in NGFR/HT to the same extent as in EH, while the changes in the RGFR groups did not differ from normal. Exaggerated increases of mean \( FE_{\text{H}2\text{O}} \) and \( FE_{\text{N}} \) were seen in NGFR/HT compared with NGFR/NT \((p < 0.05)\) (table 3) and were similar to the responses seen in EH. In RGFR the increase of \( FE_{\text{H}2\text{O}} \) and \( FE_{\text{N}} \) were greater than normal both in NT and HT, but were clearly exaggerated in HT when compared with NT \((p < 0.05)\).

Renal Hemodynamics

The values for GFR (inulin clearance), RBF, and FF are given in table 4. Mean GFR and RBF were slightly reduced in NGFR/HT. In the two renal failure groups, GFR and RBF were approximately 25% of normal values without any difference between the groups \((p > 0.05)\). During volume expansion, GFR increased significantly in both hypertensive GN groups and in EH. RBF also increased significantly in RGFR/HT, while the 12% increase observed in NGFR/HT did not reach a level of statistical significance. FF was significantly lower than normal only in RGFR, and fell during volume expansion in all groups except RGFR/NT. The fall, however, was significant only in the non GN groups.

### Table 2. Hemodilutional Effects of Saline Volume Expansion

<table>
<thead>
<tr>
<th>Group</th>
<th>C</th>
<th>ΔE</th>
<th>p</th>
<th>C</th>
<th>ΔE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGFR/NT</td>
<td>41.6±1.3</td>
<td>-4.6±0.5</td>
<td>&lt; 0.001</td>
<td>7.02±0.11</td>
<td>-1.08±0.11</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NGFR/HT</td>
<td>44.9±1.1</td>
<td>-4.3±0.4</td>
<td>&lt; 0.001</td>
<td>7.20±0.23</td>
<td>-0.99±0.12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RGFR/NT</td>
<td>39.3±2.4</td>
<td>-3.7±0.4</td>
<td>&lt; 0.001</td>
<td>7.10±0.20</td>
<td>-1.02±0.15</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RGFR/HT</td>
<td>35.0±2.3*</td>
<td>-2.9±0.7</td>
<td>&lt; 0.001</td>
<td>6.82±0.30</td>
<td>-0.73±0.12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NORM</td>
<td>42.9±0.7</td>
<td>-3.9±1.5</td>
<td>&lt; 0.001</td>
<td>6.99±0.13</td>
<td>-0.99±0.04</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>EH</td>
<td>44.7±1.1</td>
<td>-4.8±0.3</td>
<td>&lt; 0.001</td>
<td>7.21±0.12</td>
<td>-1.06±0.06</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are means ± SEM in control condition (C) and change from control (ΔE) during sustained saline volume expansion, with corresponding \( p \) values. Other abbreviations are given in table 1.

*\( p < 0.001 \).

### Table 3. Effect of Sustained Saline Volume Expansion on Renal Water and Sodium Excretion

<table>
<thead>
<tr>
<th>Group</th>
<th>Urine flow (ml/min)</th>
<th>Fractional excretion of filtered water (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>ΔE</td>
</tr>
<tr>
<td>NGFR/NT</td>
<td>0.9±0.1</td>
<td>1.6±0.3</td>
</tr>
<tr>
<td>NGFR/HT</td>
<td>1.0±0.1</td>
<td>5.1±1.7*</td>
</tr>
<tr>
<td>RGFR/NT</td>
<td>1.4±0.2</td>
<td>2.4±0.7</td>
</tr>
<tr>
<td>RGFR/HT</td>
<td>1.4±0.2</td>
<td>3.4±0.4</td>
</tr>
<tr>
<td>NORM</td>
<td>1.1±0.1</td>
<td>2.0±0.4</td>
</tr>
<tr>
<td>EH</td>
<td>0.9±0.1</td>
<td>5.0±0.9*</td>
</tr>
</tbody>
</table>

Values are means ± SEM. Abbreviations are given in tables 1 and 2.

*\( p < 0.05 \); † \( p < 0.01 \); £ \( p < 0.001 \), when comparing glomerulonephritis and EH value with corresponding normal value.

Blood Pressure, Peritubular Capillary Physical Factors, and Intrarenal Resistances

MAP in control condition (table 1) was only moderately increased in NGFR/HT and EHT. No change of MAP was observed during volume expansion in any group.

The arterial pulsations characteristic for the IRVP in NORM and EH were clearly visible also in the GN patients, although somewhat damped in the RGFR kidneys. Mean IRVP was significantly lower than normal in RGFR (table 5). The observed pressure range was 9 to 20 (mean 13.9) mm Hg in RGFR/NT and 8 to 28 (mean 13.5) mm Hg in RGFR/HT compared with a range of 18 to 30 (mean 24.8) mm Hg in NORM and 18 to 31 (mean 25.0) mm Hg in EH. No significant differences of IRVP were observed between hypertensive and normotensive GN groups at the same level of GFR or between NORM and EH.

During volume expansion, IRVP increased significantly in the hypertensive GN groups, but remained unchanged in the GN patients with normal blood pressure and in NORM and EH.

Values for \( t_{prot} \) and RVP were similar in all groups in control condition; \( t_{prot} \) decreased and RVP increased significantly during volume expansion without any differences between the groups.
SODIUM EXCRETION AND BLOOD PRESSURE IN GLOMERULONEPHRITIS/Willassen and Ofstad

The calculated precapillary and postcapillary renal vascular resistances were significantly increased in RGFR (table 6), and both resistances were higher in RGFR/HT than in RGFR/NT (p < 0.05). Mean precapillary resistance was also increased in NGFR/HT. In NORM the precapillary resistance was 73% of the total renal vascular resistance, while the corresponding figures were 75% in NGFR/NT, 83% in NGFR/HT, 86% in RGFR/NT, 91% in RGFR/HT, and 78% in EHT. During saline loading, the precapillary resistance fell significantly in the RGFR/HT group and in EH.

**Regression Analysis**

By analysis of the GN material (32 patients), highly significant linear correlations (p < 0.001) were observed between control values of IRVP and GFR (r = 0.682; fig. 1), RBF (r = 0.651; fig. 1), total calculated renal vascular resistance (r = −0.559) and precapillary resistance (r = −0.574), while postcapillary resistance did not correlate significantly with IRVP (r = −0.263; p > 0.10). A weak but significant negative correlation was present between control MAP and IRVP (r = −0.389; p < 0.05), and negative correlations (p < 0.001) were also found between control

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**TABLE 3. (Continued)**

<table>
<thead>
<tr>
<th>Na excretion (μmol/min)</th>
<th>C</th>
<th>ΔE</th>
<th>p</th>
<th>Fractional excretion of filtered Na (%)</th>
<th>C</th>
<th>ΔE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>123 ± 9</td>
<td>318 ± 65</td>
<td>&lt; 0.002</td>
<td>0.7 ± 0.1</td>
<td>1.4 ± 0.3</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>158 ± 32</td>
<td>888 ± 375*</td>
<td>&lt; 0.05</td>
<td>0.9 ± 0.2</td>
<td>5.0 ± 2.3*</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>125 ± 18</td>
<td>311 ± 89</td>
<td>&lt; 0.02</td>
<td>2.5 ± 0.6*</td>
<td>5.2 ± 1.7*</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>114 ± 23</td>
<td>439 ± 68</td>
<td>&lt; 0.001</td>
<td>3.6 ± 1.5*</td>
<td>9.9 ± 2.3*</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>161 ± 12</td>
<td>390 ± 61</td>
<td>&lt; 0.001</td>
<td>0.9 ± 0.1</td>
<td>1.9 ± 0.3</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>140 ± 13</td>
<td>906 ± 132*</td>
<td>&lt; 0.001</td>
<td>0.8 ± 0.1</td>
<td>4.2 ± 0.6*</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>
### Table 4. Renal Hemodynamic Values During Sustained Saline Volume Expansion

<table>
<thead>
<tr>
<th>Group</th>
<th>Glomerular filtration rate</th>
<th>Renal blood flow</th>
<th>Filtration fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C (ml/min/1.73 m²)</td>
<td>ΔE (%)</td>
<td>p</td>
</tr>
<tr>
<td>NGFR/NT</td>
<td>139 ± 5</td>
<td>8.5 ± 4.5</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>NGFR/HT</td>
<td>107 ± 7</td>
<td>9.3 ± 3.5*</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>RGFR/NT</td>
<td>38 ± 45</td>
<td>7.2 ± 6.4</td>
<td>&gt; 0.10</td>
</tr>
<tr>
<td>RGFR/HT</td>
<td>32 ± 10†</td>
<td>24.1 ± 5.1†</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>NORM</td>
<td>128 ± 3</td>
<td>4.1 ± 2.5</td>
<td>&gt; 0.10</td>
</tr>
<tr>
<td>EH</td>
<td>122 ± 4</td>
<td>17.6 ± 3.6*</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Absolute values (means ± SEM) in control condition (C) and percent change from C (ΔE) are given for glomerular filtration rate and renal blood flow. Filtration fraction = glomerular filtration rate/total renal plasma flow. Other abbreviations are given in tables 1 and 2.

* p < 0.05; † p < 0.01; ‡ p < 0.001, when comparing glomerulonephritis and EH value with corresponding normal value.

### Table 5. Intrarenal and Renal Venous Pressure and Efferent Arteriolar Total Protein Concentration during Sustained Saline Volume Expansion

<table>
<thead>
<tr>
<th>Group</th>
<th>Intrarenal venous pressure (mm Hg)</th>
<th>Renal venous pressure (mm Hg)</th>
<th>Efferent arteriolar protein concentration (g/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>ΔE</td>
<td>p</td>
</tr>
<tr>
<td>NGFR/NT</td>
<td>23.9 ± 1.7</td>
<td>0.4 ± 0.7</td>
<td>&gt; 0.10</td>
</tr>
<tr>
<td>NGFR/HT</td>
<td>20.4 ± 2.4</td>
<td>3.7 ± 1.6†</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>RGFR/NT</td>
<td>13.9 ± 1.3</td>
<td>1.6 ± 0.9</td>
<td>&gt; 0.10</td>
</tr>
<tr>
<td>RGFR/HT</td>
<td>13.5 ± 2.6</td>
<td>2.4 ± 0.9*</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>NORM</td>
<td>24.8 ± 0.8</td>
<td>0.3 ± 0.4</td>
<td>&gt; 0.10</td>
</tr>
<tr>
<td>EH</td>
<td>25.0 ± 1.0</td>
<td>1.4 ± 0.9</td>
<td>&lt; 0.10</td>
</tr>
</tbody>
</table>

Values are means ± SEM. Abbreviations are given in tables 1 and 2.

* p < 0.05; † p < 0.01; ‡ p < 0.001, when comparing glomerulonephritis and EH value with corresponding normal value.

### Table 6. Renal Vascular Resistances during Sustained Saline Volume Expansion

<table>
<thead>
<tr>
<th>Group</th>
<th>Precapillary</th>
<th>Postcapillary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C (dyne sec/cm²)</td>
<td>ΔE (%)</td>
</tr>
<tr>
<td>NGFR/NT</td>
<td>3788 ± 408</td>
<td>-4.6 ± 4.2</td>
</tr>
<tr>
<td>NGFR/HT</td>
<td>6634 ± 1299*</td>
<td>-7.7 ± 5.7</td>
</tr>
<tr>
<td>RGFR/NT</td>
<td>14341 ± 1750†</td>
<td>3.1 ± 7.6</td>
</tr>
<tr>
<td>RGFR/HT</td>
<td>33988 ± 6835‡</td>
<td>-20.6 ± 5.6*</td>
</tr>
<tr>
<td>NORM</td>
<td>3804 ± 153</td>
<td>-5.3 ± 3.4</td>
</tr>
<tr>
<td>EH</td>
<td>5967 ± 344*</td>
<td>-14.8 ± 3.1*</td>
</tr>
</tbody>
</table>

Absolute values (means ± SEM) in control condition (C) and percent change from C (ΔE) during volume expansion are given. Abbreviations are given in tables 1 and 2.

* p < 0.05; † p < 0.01; ‡ p < 0.001, when comparing glomerulonephritis and EH value with corresponding normal value.
MAP and GFR \( (r = -0.670) \) and between MAP and RBF \( (r = -0.776) \). In the combined NORM/EHT group (39 individuals), no significant correlation was present either between MAP and IRVP or between MAP or GFR.

In the control condition an inverse curvilinear relationship appeared to be present between GFR and \( \Delta F_{ENa} \) (fig. 2). A weak negative linear correlation was observed between IRVP and \( \Delta F_{ENa} \) \( (r = -0.357; p < 0.05) \). Control tpro\(_t\) did not correlate significantly to \( \Delta F_{ENa} \) \( (r = -0.289; p > 0.10) \). Control MAP and \( \Delta F_{ENa} \) also correlated significantly with each other \( (r = 0.512; p < 0.01) \); this relationship was not present in the NORM/EH group \( (r = -0.047; p > 0.10) \).

The natriuretic response to volume expansion as expressed by the increases of \( \Delta F_{ENa} \) \( (\Delta F_{ENa}) \) appeared to increase curvilinearly with decreasing GFR (fig. 2). A significant linear correlation was present between control MAP and \( \Delta F_{ENa} \) in the GN patients \( (r = 0.702; p < 0.001) \) as well as in the combined NORM/EH group \( (r = 0.478; p < 0.01) \) with a significantly smaller regression coefficient in the latter group \( (p < 0.005) \) (fig. 3). The regression coefficient for the MAP/\( \Delta F_{ENa} \) relationship in group NGFR did not differ significantly from that of RGFR \( (p > 0.10) \).

During saline loading, \( \Delta F_{ENa} \) did not correlate to the associated changes in any of the following parameters either in GN or the combined NORM/EH group (NORM/EH-values in parenthesis); GFR: \( r = 0.311; p > 0.05 \) \( (r = 0.146; p > 0.10) \); RBF: \( r = 0.08; p > 0.10 \) \( (r = 0.152; p > 0.10) \); IRVP: \( r = 0.180; p > 0.10 \) \( (r = 0.310; p > 0.05) \); tpro\(_t\): \( r = -0.285; p > 0.10 \) \( (r = 0.02; p > 0.10) \); plasma volume: \( r = -0.316; p > 0.05 \) \( (r = -0.278; p > 0.10) \); RVP: \( r = 0.266; p > 0.10 \) \( (r = -0.014; p > 0.10) \).

**Figure 2.** Control values of fractional excretion of filtered sodium \( (F_{ENa}) \) and change of \( F_{ENa} \) \( (\Delta F_{ENa}) \) during saline volume expansion related to control GFR in glomerulonephritis. Other abbreviations are given in figure 1.

**Figure 3.** Relationships between the increase of fractional excretion of sodium during saline volume expansion and the control mean arterial blood pressure (MAP). NORM = normal control group; EH = essential hypertension; other abbreviations as in figure 1.
Discussion

Comparability of the Patient Groups

The natriuretic effect of saline loading is enhanced in volume-expanded individuals and reduced during sodium depletion. All patients in the present study were clinically volume repleted, and the renal excretion of sodium and water in the control periods was similar in all groups. The degree of hydration thus seems comparable in all patient groups.

The slight increase of FE\textsubscript{Na} in the RGFR groups confirms the decreased free water reabsorption in kidneys with nephron loss observed earlier.\footnote{17}

Relationship of the IRVP to the Peritubular Capillary Pressure in Diseased Kidneys

There are reasons to believe that the IRVP is an adequate expression of the average pressure in the smallest peritubular capillaries in normal kidneys\footnote{8} and therefore probably also in the NGFR groups, where changes of the postglomerular vascular anatomy probably were minor. In severely damaged GN kidneys, the postglomerular vascular anatomy is not well known. As withdrawal of the IRVP catheter from wedged to free renal venous position caused an abrupt pressure drop, and the arterial pulse pressure waves were visible in the IRVP curves also in RGFR, the catheter position undoubtedly was intrarenal also in these kidneys.

The reduced IRVP in the RGFR groups corresponds with micropuncture measurements of the peritubular capillary pressure in chronic glomerulonephritic rats with moderately reduced GFR; the lowest pressures were found in the most severely damaged kidneys and were considerably below the normal range.\footnote{13}

The vascular pressure condition in the fibrotic scar tissue in the damaged kidneys probably did not influence the pressure readings substantially; this blood flow must have been small as the tissue fibrosis is caused by hypoperfusion due to occlusion of the glomerular capillaries or the small arteries.

Additional evidence in favor of a decreased peritubular capillary pressure in chronic GN with reduced GFR is the abundant and often dilated renal capsular arteries considered characteristic for chronic GN kidneys.\footnote{14} These vessels communicate with the renal parenchymal arteries\footnote{15} and probably function as collaterals in analogy with what is found in renal artery stenosis,\footnote{16} where the IRVP is also decreased both in acute animal experiments\footnote{8} and in chronic stenosis in humans (Y. Willassen, unpublished observations).

Vascular Resistances in the Control Condition

While the calculated values for total renal vascular resistance (organ resistance) in the NGFR groups may be considered to express the condition of the resistance vessels, the interpretation of this resistance is difficult in kidneys with severe structural alterations such as in the RGFR groups. In these kidneys with reduced nephron population, the resistance of the vessels perfusing the remaining functioning tissue cannot be quantified by the methods used in this study. A decreased number of nephrons by itself induces arteriolar dilatation and greatly increased renal vascular conductivity.\footnote{17, 18} The relevance of the different resistance data reported in acute models of GN\footnote{19-21} to long-standing human chronic GN is uncertain. In human chronic GN, increased vessel wall thickness and narrowing of preglomerular vessels including the interlobular arteries and the afferent arterioles have been described,\footnote{22, 23} suggesting an increased preglomerular resistance in these kidneys. In short, the question whether the resistance vessels in the RGFR groups were dilated or constricted must be left unanswered. However, if an unaltered or reduced preglomerular resistance was present in the severely damaged kidneys in this study, a constriction of the efferent arterioles would have to be implicated to explain the reduction of the peritubular capillary hydrostatic pressure in these kidneys. Furthermore, the total resistance was significantly greater in the RGFR group with hypertension than in the normotensive RGFR patients, although GFR and probably the renal mass were the same in these groups. Thus, hypertension seems to constrict the resistance vessels also in kidneys with severe organic lesions.

Relationship Between IRVP, Blood Pressure, and Sodium Excretion in the Control Condition

Corresponding with our earlier findings of almost identical IRVP values in normal individuals and in patients with EH, the IRVP in patients with chronic GN did not appear to be directly related to the systemic arterial pressure. The weak negative correlation between IRVP and MAP in the GN patients probably is best explained as secondary to the correlation between MAP and GFR.

FE\textsubscript{Na} was similar in normotensive and hypertensive GN groups at comparable levels of GFR as well as in the normotensive control group and the patients with essential hypertension. In addition, the inverse covariation observed between GFR and FE\textsubscript{Na} appeared to agree closely with the curvilinear relationship predicted on the basis of a constant and equal sodium intake\footnote{26} in both the normotensive and hypertensive GN groups. This indicates that there is no direct functional relationship between the blood pressure and the FE\textsubscript{Na} in individuals with chronic renal failure and, that the significant positive correlation between MAP and FE\textsubscript{Na} probably was secondary to the reciprocal relation between MAP and GFR.

The weak but significant negative correlation between IRVP and FE\textsubscript{Na} was possibly secondary to the association of both IRVP and FE\textsubscript{Na} to GFR. Any functional relationship between IRVP and FE\textsubscript{Na} must for obvious reasons have been indirect as a reduced postglomerular hydrostatic pressure is supposed to initiate a sodium retention and a decrease of FE\textsubscript{Na}. Such an indirect effect may well exist. Studies both in patients with chronic glomerulonephritis and renal failure\footnote{26} and...
in animals with reduced renal mass\textsuperscript{37} show that the $FE_{\text{Na}}$ may be kept normal on a low sodium diet. This indicates a connection between sodium retention and $FE_{\text{Na}}$, and suggests that the relationship between $FE_{\text{Na}}$ and both IRVP and GFR may be explained by sodium retention induced by decreasing values of these hemodynamic parameters.

There is good evidence that $FE_{\text{Na}}$ both in normal\textsuperscript{28} and diseased kidneys\textsuperscript{29} is influenced by a circulating natriuretic factor which might be directly correlated to $FE_{\text{Na}}$ in the patient studied. This factor has recently been thought to produce vasoconstriction of smooth muscle cells and arterial hypertension.\textsuperscript{30} If a natriuretic principle caused the increased $FE_{\text{Na}}$ in our patients, the sensitivity toward its hypertensive effect may have varied widely from one patient to another, as the $FE_{\text{Na}}$ was similar in hypertensive and normotensive individuals with comparable GFR.

Renal Excretory and Hemodynamic Responses to Saline Loading

The six groups studied differed with respect to the presence of GN, hypertension, and reduced GFR. Neither in the hypertensive nor normotensive patients did the presence of GN alter the pattern of changes provoked by the saline volume expansion in renal hemodynamics, $FE_{\text{Na}}$ and $FE_{\text{H2O}}$. Furthermore, exaggerated hemodynamic and excretory responses were present both in NGFR/HT and in EHT. This indicates that the exaggerated natriuresis was related to the elevated blood pressure per se or some pressure-associated factor, and that it is not a unique feature of patients with EH. In fact, the MAP/$\Delta FE_{\text{Na}}$ regression lines show that the exaggerated natriuresis was substantially potentiated in GN when compared with the NORM/EH group. The amplified response was not dependent on the reduced GFR in the GN group as it was present also in NGFR.

The finding of an exaggerated $\Delta FE_{\text{Na}}$ with decreasing GFR corresponds with the observations of Slatopolsky et al.\textsuperscript{31} in uremic humans and with the results obtained by Gutman and Rieselbach\textsuperscript{32} in unilateral kidney disease in nonuremic humans and dogs. Our observation that the presence of hypertension significantly amplified $\Delta FE_{\text{Na}}$ and $\Delta FE_{\text{H2O}}$ even at low levels of GFR is only seemingly in disagreement with the findings of Cottier\textsuperscript{33} and of Sasamori.\textsuperscript{34} When measuring the absolute sodium excretion, these authors did not see any exaggerated responses in hypertensive patients with low GFR, which was found also in the present study. However, if the sodium excretion is calculated as $FE_{\text{Na}}$ and thus corrected for the variation of the GFR in the experimental groups, the effect of the volume expansion on the remaining functioning nephrons is revealed.

Schacht et al.\textsuperscript{35} have reported an exaggerated natriuresis during saline volume expansion in the course of poststreptococcal glomerulonephritis independent of the level of GFR and the presence of hypertension, which contrasts with the normal natriuresis observed in our NGFR/NT group. There is no obvious explanation of this discrepancy, however, neither the patient material nor the experimental procedure (hypertonic saline loading with more than 30% expansion of the plasma volume) is comparable with the present study.

The natriuretic responses to saline loading may in part be explained by an increased filtered load of sodium. However, as the increase of $FE_{\text{Na}}$ was significantly correlated neither to GFR nor to RBF, hemodynamic changes were probably not the most important factors. On the other hand the enhanced natriuresis in the hypertensive GN patients was associated with a significant increase of the IRVP, suggesting an increased peritubular capillary hydrostatic pressure during saline loading. The increase of $FE_{\text{Na}}$ did not, however, correlate with the changes of IRVP, and this pressure did not increase significantly during saline loading in the patients with essential hypertension. The increased IRVP therefore was probably not a mediator of the exaggerated natriuresis, but rather an expression of reduced compliance in the diseased kidneys during the high urine flow rate. As the changes of the efferent arteriolar colloid osmotic pressure were identical in the normotensive and hypertensive individuals in all corresponding groups, it may be concluded that changes in neither renal hemodynamic nor intrarenal physical factors seem to explain the increased $FE_{\text{Na}}$ in the hypertensive patients in the present study. Our findings are compatible with the presence of an increased production of circulating natriuretic substance\textsuperscript{36} during volume expansion assuming an altered sensitivity of the volume control system\textsuperscript{26} when the blood pressure is increased.

The finding of active vasomotion in severely damaged hypertensive kidneys during saline loading is at variance with the study of Hollenberg et al.\textsuperscript{38} who observed a subnormal increase of blood flow following an intraarterial injection of vasodilators in diseased kidneys of patients with essential and secondary hypertension. On the other hand, there is good evidence that the diameter of the afferent arteriole has retained its ability to contract and dilate in chronically diseased kidneys in chronic DOCA-salt hypertensive rats.\textsuperscript{39} As far as segmental resistance changes are concerned, the findings of decreased total renal vascular resistance and increased GFR, but only minor changes in the peritubular capillary pressure, indicate that the increased conductance during saline loading was mainly preglomerular. The vasodilatation observed during saline loading argues against the presence of a circulating natriuretic factor with the capability of contracting smooth muscle cells in the resistance vessels.\textsuperscript{30} An alternate explanation is that the vasoconstrictive property of this factor is a long-term effect not present in acute experiments.

References

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