INTRARENAL PRESSURE AND EXAGGERATED NATRIURESIS IN ESSENTIAL HYPERTENSION

J. LOWENSTEIN, E. R. BERANBAUM, H. CHASIS AND D. S. BALDWIN

Departments of Medicine and Radiology, New York University School of Medicine

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SUMMARY

1. Intrarenal pressure, estimated by measurement of wedged renal vein pressure, was elevated in patients with essential hypertension. Despite increased afferent arteriolar resistance, glomerular pressure was elevated indicating that the higher systemic pressure in essential hypertension is transmitted beyond the arterioles and accounts for elevation of intrarenal pressure.

2. During hypertonic saline loading in hypertensives, renal arteriolar resistance falls, resulting in further increase in intrarenal pressure. Increments in intrarenal pressure paralleled increases in sodium excretion in patients with essential hypertension during the exaggerated natriuresis and in normotensive subjects after the prolonged infusion of hypertonic saline.

3. The marked increase in intrarenal pressure which appears to be responsible for exaggerated natriuresis in essential hypertension is attributable to an altered (exaggerated) response of the renal arterioles. The data suggest that elevated intrarenal pressure may play a role in the regulation of sodium balance in patients with essential hypertension.

While many investigators have noted that patients with essential hypertension excrete more sodium than normotensive subjects in response to the infusion of hypertonic saline, the mechanism for this exaggerated natriuresis is not known (Baldwin et al., 1958; Farnsworth, 1946; Ulrych, Hofman & Hejl, 1964; Hanenson et al., 1959; Birchall et al., 1953; Brodsky & Graubarth, 1953; Cottier, Weller & Hoobler, 1958). The observation that increased peritubular capillary hydrostatic pressure may accompany natriuresis during volume expansion in the experimental animal (Lewy & Windhager, 1968; Koch, Aynedjian & Bank, 1968; Martino & Earley, 1968) suggested a possible renal haemodynamic basis for exaggerated natriuresis and

Correspondence: Dr Jerome Lowenstein, New York University School of Medicine, 550 First Avenue, New York, 10016, U.S.A.
prompted us to measure intrarenal pressure and to examine its relation to sodium excretion in patients with essential hypertension.

In the rat, wedged renal vein pressure closely approximates proximal tubular and peritubular capillary pressures (Gottschalk & Mylle, 1956, 1957; Wirz, 1955). While it seems likely that pressure gradients exist, at least transiently, between the proximal tubules and the peritubular capillaries, micropuncture studies have failed to measure a consistent difference between proximal tubular pressure and peritubular capillary pressure, and in this discussion the term intrarenal pressure is used to indicate these pressures.

In the dog, wedged renal vein pressure measurements are comparable to values obtained by direct needle measurements of intrarenal pressure (Swann et al., 1952b). Brun et al. (1956) and Stahl (1966) demonstrated the feasibility of measuring wedged renal vein pressure (WRVP) in man and proposed that it might provide an estimate of renal interstitial pressure.

We have found that changes in WRVP in man during osmotic diuresis, elevation of ureteropelvic pressure, renal vasoconstriction and renal vasodilatation correspond to changes in proximal tubular and peritubular capillary pressures measured directly by others in experimental animals under the same conditions, suggesting that WRVP provides a measure of intrarenal pressure in man.

We have found that WRVP is significantly elevated in hypertensive patients, and during saline infusion exaggerated natriuresis was accompanied by further increases in WRVP. In normotensives, lesser changes in sodium excretion were accompanied by smaller increases in wedged renal vein pressure. These observations are in accord with the hypothesis that increased intrarenal pressure mediates decreased tubular reabsorption of sodium in man, and suggest that exaggerated natriuresis may be related to an alteration in the regulation of intrarenal pressure in essential hypertension.

METHODS

Observations have been made in twenty-one patients with essential hypertension and eighteen normotensive subjects free of cardiovascular and renal disease. The patients with essential hypertension were aged 28–55 years (mean 39.5), and had no cardiomegaly, congestive heart failure or proteinuria. The normotensive subjects were 20–46 years (mean 36.1). Directly measured systemic arterial pressures and full control data are contained in Table 38/9 (Clinical Science Table) which has been deposited with the Librarian, Royal Society of Medicine, 1 Wimpole St., London, W.1 from whom copies are available on application. All subjects were hospitalized in the wards of the New York University Medical Division of Bellevue Hospital or its Clinical Research Center and gave informed consent before participating in the studies. All subjects were receiving a regular ward diet. Antihypertensive medications and diuretics were omitted for at least 2 weeks prior to studies.

Observations were made in the fasting state following 12–16 hr of fluid restriction. In most instances an infusion of 5% mannitol was administered at 2 ml/min to ensure adequate urine flow for collections. Following catheterization of bladder or ureters, glomerular filtration rate (GFR), renal plasma flow (RPF) and extraction ratio of p-aminohippurate (EpAH) were measured utilizing inulin and p-aminohippurate clearance techniques previously described (Baldwin et al., 1960). Percutaneous retrograde catheterization of the right renal vein was performed by the method of Seldinger (1953), and a polyethylene catheter (outside diameter
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0.9 mm) was manipulated through the renal vein catheter into a small division of the renal vein. Arterial, venous and wedged renal vein pressures were measured with a Statham pressure transducer and recorded on a multichannel photographic recorder.

The recording of wedged renal vein pressure

A typical recording of wedged renal vein pressure is shown in Fig. 1. When the catheter was wedged and could be advanced no further, pressure rose abruptly to a new stable level and the form of the pressure trace changed from a venous pulse to one resembling an arterial wave. In the representative study shown in Fig. 1, pressure in the main renal vein was 5.8 mmHg and wedged renal vein pressure measured 19.2 mmHg. Withdrawal and reinsertion of the catheter from this position resulted in an abrupt fall and rise in pressure with the maximum and minimum stable levels being reached within 1–2 sec. The value of WRVP recorded when the catheter is repeatedly withdrawn and reinserted is reproduceable, 20.3, 19.2, and 19.2 mmHg in the example shown. With the catheter in the wedged position it was observed that diatrozoate sodium ("Hypaque") injected through it filled venous channels corresponding in position and direction of flow to the arcuate and interlobar veins (Fig. 2), suggesting that the catheter tip is located at the corticomedullary junction near the junction of the interlobar and arcuate veins. Gottschalk & Mylle (1956, 1957) found that WRVP closely approximates arcuate vein pressure and hydrostatic pressure in the proximal tubule and peritubular capillaries in the rat. The relatively high pressure in the arcuate veins and renal parenchyma is maintained by resistance in the venous (post-capillary) segment. This has been
attributed to compression of the interlobar veins at the point where they enter the renal cortex (Gottschalk & Mylle, 1957) or to sphincters within the interlobar veins near the point of entry into the arcuate vein (Koester, Locke & Swann, 1955). The abrupt increase in pressure as the catheter is advanced within the renal vein might result from passage of the catheter tip directly into an arcuate vein or from occlusion of an interlobar vein. In either instance, a measure of arcuate vein pressure would still be obtained since occlusion of an interlobar vein would result in equalization of pressure between the arcuate vein and the occluded interlobar vein. As the arcuate vein is drained by a number of interlobar veins, occlusion of a single interlobar vein would not significantly alter arcuate vein hydrostatic pressure. We have occasionally observed a further increase in recorded pressure when the catheter is advanced beyond the position where an abrupt increase in pressure was first recorded, and similar observations were made in the dog by Hinshaw (1964). Since our purpose was to measure arcuate vein pressure, and a lower pressure can be read with partial occlusion of a interlobar vein, we have recorded WRVP at the deepest point in the venous system to which the catheter could be advanced.

Osmotic diuresis. In six studies in normotensive subjects, following control measurement of WRVP, mannitol (10%, 20 ml/min) was infused intravenously over a period of 60–90 min while serial measurements of GFR, RPF and WRVP were made.

Increased ureteropelvic pressure. In one normotensive subject and two patients with essential hypertension the ureters were occluded with tightly fitting catheters (No. 7 and No. 8F), and following control measurements of WRVP, the outflow level of the right ureteral catheter was elevated 40–50 cm in order to achieve an applied hydrostatic pressure of 30–37 mmHg. Serial measurements of WRVP were made during elevation of ureteropelvic pressure.

Renal vasodilatation. In two normotensive subjects, following ureteral catheterization and control measurements, acetylcholine chloride was infused into the right renal artery at rates of 100–188 μg/min. Arterial pressure and WRVP were recorded continuously; GFR, RPF, and sodium excretion were measured after urine flow stabilized.

Renal vasoconstriction. In two normotensive subjects, renal haemodynamics and sodium excretion were measured before and during the intravenous administration of adrenaline (3–14 μg/min).

Saline loading. The effect of rapid intravenous administration (18 ml/min) of 2.5% NaCl on sodium excretion and renal haemodynamics was studied in six normotensive subjects and nine patients with essential hypertension. In six of nine hypertensive subjects the infusion was discontinued after 1 litre of saline was administered. In three hypertensive subjects and in four normotensive subjects, saline administration was continued until 2 litres of saline had been infused.

Measurement of cardiac output in duplicate by indicator dilution utilizing indocyanine green was performed before and immediately after saline administration; cardiac output was calculated in the manner described by Hamilton et al. (1932), and corrected to 1.73 m² body surface area.

RESULTS

1. WRVP as a measure of intrarenal pressure

Osmotic diuresis. WRVP increased during osmotic diuresis induced by the rapid infusion of hypertonic mannitol in each of six studies in three normotensive subjects (Table 1). Control
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Fig. 2. Location of the catheter for measurement of wedged renal vein pressure. In the panel at the left, the catheter is at the cortico-medullary junction. At the right, radiocontrast material injected through the catheter outlines interlobar veins and a segment of arcuate vein.
## Table 1. Effect of osmotic diuresis on WRVP and intrarenal haemodynamics*

<table>
<thead>
<tr>
<th>Patient</th>
<th>WRVP (mmHg)</th>
<th>C&lt;sub&gt;OSM&lt;/sub&gt; (ml/min)</th>
<th>C&lt;sub&gt;N&lt;/sub&gt; (ml/min)</th>
<th>Renal blood flow (ml/min)</th>
<th>E&lt;sub&gt;PAH&lt;/sub&gt;</th>
<th>R&lt;sub&gt;T&lt;/sub&gt; dyne sec cm&lt;sup&gt;-1&lt;/sup&gt;</th>
<th>R&lt;sub&gt;R&lt;/sub&gt; dyne sec cm&lt;sup&gt;-1&lt;/sup&gt;</th>
<th>R&lt;sub&gt;V&lt;/sub&gt; dyne sec cm&lt;sup&gt;-1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.K.</td>
<td>15 0 26 0</td>
<td>2 6 12 2</td>
<td>130 95</td>
<td>1265 1440</td>
<td>0 830 0 788</td>
<td>4970 4550</td>
<td>1915 1675</td>
<td>3060 2120</td>
</tr>
<tr>
<td>H.K.</td>
<td>25 8 40 0</td>
<td>3 1 13 2</td>
<td>137 114</td>
<td>1190 1160</td>
<td>0 865 0 885</td>
<td>6700 6680</td>
<td>2300 1560</td>
<td>3400 2930</td>
</tr>
<tr>
<td>H.K.</td>
<td>17 1 41 5</td>
<td>3 5 13 0</td>
<td>127 105</td>
<td>1170 1225</td>
<td>0 655 0 649</td>
<td>5200 5040</td>
<td>1160 208</td>
<td>3420 2730</td>
</tr>
<tr>
<td>H.K.</td>
<td>17 0 26 4</td>
<td>3 8 23 4</td>
<td>130 110</td>
<td>1730 1920</td>
<td>0 830 0 810</td>
<td>3760 3590</td>
<td>1170 897</td>
<td>2120 1850</td>
</tr>
<tr>
<td>V.P.</td>
<td>22 7 34 8</td>
<td>3 5 11 4</td>
<td>123 103</td>
<td>1200 1320</td>
<td>0 780 0 830</td>
<td>6900 6500</td>
<td>2630 2320</td>
<td>3380 2600</td>
</tr>
<tr>
<td>E.E.</td>
<td>21 4 55 7</td>
<td>2 4 12 2</td>
<td>117 87</td>
<td>1370 1070</td>
<td>0 890 0 920</td>
<td>5430 8390</td>
<td>2140 2230</td>
<td>2350 2520</td>
</tr>
</tbody>
</table>

* Clearance values are corrected to 1.73 m<sup>2</sup> body surface area; C = control observations, D = observations at the height of osmotic diuresis; WRVP = wedged renal vein pressure; C<sub>OSM</sub> = osmolar clearance; C<sub>N</sub> = inulin clearance; E<sub>PAH</sub> = extraction ratio for PAH; R<sub>T</sub>, R<sub>A</sub>, R<sub>E</sub>, R<sub>V</sub> = total renal, afferent segmental, efferent segmental, and venous segmental resistances.
WRVP averaged 19.9 mmHg and rose progressively to a mean value of 37.4 mmHg with parallel increases in solute clearance. GFR was reduced during osmotic diuresis in all studies; maximal reduction averaged -20.3% (P < 0.01). Renal blood flow increased in three (+14%, +11%, +10%), decreased in one (-11%) and was unchanged in two studies during maximal reduction in GFR. Extraction ratio for PAH averaged 0.808 before and 0.809 at the height of osmotic diuresis. Since the fall in GFR during mannitol diuresis was not associated with significant changes in renal blood flow or extraction of PAH (Table 1), it is unlikely that vasoconstriction or redistribution of intrarenal blood flow was responsible for decreased filtration (Baldwin, Lowenstein & Chasis, 1967). If WRVP is equal to proximal tubular hydrostatic pressure, glomerular filtration rate would be reduced as a consequence of the increase in pressure opposing filtration (i.e. proximal tubular hydrostatic pressure). Miles & de Wardener (1954) recorded increases in interstitial pressure by direct needle measurements in the dog undergoing mannitol diuresis. Gottschalk (1964) found that wedged renal vein, peritubular capillary and proximal tubular hydrostatic pressures increased equally in the rat during osmotic diuresis with glucose, and attributed the increase in intrarenal pressure to increased volume flow through the collecting ducts. Koch et al. (1967) also found an increase in proximal tubular pressure in rats undergoing mannitol diuresis and were able to account for the observed decrease in GFR by increased tubular hydrostatic pressure. If the increase in WRVP is taken as a measure of the increase in proximal tubular pressure during osmotic diuresis in man, the resultant decrease in net filtration pressure (see below) and fall in GFR are seen to be attributable to the increase in intrarenal pressure. Calculated glomerular pressure was not decreased, indicating that the fall in GFR cannot be attributed to the decrease in efferent resistance which results from decreased blood viscosity during infusion of mannitol.

**Increased ureteropelvic pressure.** WRVP increased when ureteropelvic pressure was elevated in three subjects. Control wedged renal vein pressures were 20.5, 25.5 and 26.4 mmHg. When ureteropelvic pressure was increased (30–37 mmHg), WRVP increased steadily to levels which approximated the applied ureteral pressure (35.9, 31.3 and 39.4 mmHg) and returned slowly, over a period of 25–50 min to control levels as applied ureteral pressure was decreased. Changes in glomerular filtration rate, renal plasma flow, p-aminohippurate extraction and fractional excretion of sodium during the period of elevated ureteropelvic pressure were small.

In the rat, elevation of ureteropelvic pressure resulted in an increase in pressure both in the proximal tubule and peritubular capillary to levels approaching the applied ureteropelvic pressure (Gottschalk & Mylle, 1956). In the dog, Swann et al. (1952b) and Gilmore (1964) observed that intrarenal (needle) pressure increased when ureteropelvic pressure was elevated.

**Renal vasodilatation and renal vasoconstriction** (Tables 2 and 3). Renal arterial infusion of acetylcholine in two normotensive subjects resulted in ipsilateral increase in renal plasma flow from 234 to 370 and from 288 to 326 ml/min/kidney. Wedged renal vein pressure in the infused kidney increased from 17.5 to 34.1 and from 26.6 to 43.8 mmHg (Table 2). Small increases in arterial pressure were observed in both subjects. The observed fall in total renal resistance and the decrease in efferent segmental resistance evidenced by the fall in filtration fraction during renal vasodilatation would be expected to result in greater transmission of systemic pressure to the postglomerular capillaries and elevation of peritubular capillary pressure. The observed increases in WRVP during renal vasodilatation is in accord with this prediction and with the observations of Hayslett, Kashgarian & Epstein (1968) who found an increase in proximal tubular hydrostatic pressure during aortic infusion of acetylcholine in the rat.
The intravenous infusion of adrenaline in two normotensive subjects resulted in a decrease in renal plasma flow from 730 to 584 and from 478 to 313 ml/min. Since renal resistance at the afferent and efferent arteriole, proximal to the peritubular capillaries, was increased by adrenaline a reduction in peritubular capillary pressure was anticipated and the observed fall in wedged renal vein pressure, from 29.7 to 20.5 mmHg and from 36.0 to 28.3 mmHg (Table 3), is in accord with this prediction.

**Table 2. Effect, in two normotensive subjects, of acetylcholine infusion into the right renal artery on WRVP, renal haemodynamics and sodium excretion**

<table>
<thead>
<tr>
<th></th>
<th>V (ml/min)</th>
<th>WRVP (mmHg)</th>
<th>C_{IN} (ml/min)</th>
<th>C_{PAH} (ml/min)</th>
<th>FF (%)</th>
<th>U_{Na}V (μEq/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>L</td>
<td>R</td>
<td>L</td>
<td>R</td>
<td>L</td>
</tr>
<tr>
<td>H.K.</td>
<td>Control</td>
<td>1.71</td>
<td>17.5</td>
<td>69</td>
<td>76</td>
<td>234</td>
</tr>
<tr>
<td>ACH</td>
<td>188 μg/min</td>
<td>20.8</td>
<td>34.1</td>
<td>80</td>
<td>85</td>
<td>370</td>
</tr>
<tr>
<td>D.B.</td>
<td>Control</td>
<td>0.85</td>
<td>26.6</td>
<td>71</td>
<td>66</td>
<td>288</td>
</tr>
<tr>
<td>ACH</td>
<td>100 μg/min</td>
<td>4.95</td>
<td>43.8</td>
<td>61</td>
<td>58.5</td>
<td>326</td>
</tr>
</tbody>
</table>

*Clearances corrected to 1.73 m² body surface area; ACH = acetylcholine chloride; V = urine flow rate; C_{PAH} = PAH clearance; FF = filtration fraction; U_{Na}V = sodium excretion rate. Other abbreviations as in Table 1.

**Table 3. Effect of intravenous infusion of adrenaline on WRVP, renal haemodynamics and sodium excretion**

<table>
<thead>
<tr>
<th></th>
<th>V (ml/min)</th>
<th>WRVP (mmHg)</th>
<th>C_{IN} (ml/min)</th>
<th>C_{PAH} (ml/min)</th>
<th>FF (%)</th>
<th>U_{Na}V (μEq/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>L</td>
<td>R</td>
<td>L</td>
<td>R</td>
<td>L</td>
</tr>
<tr>
<td>C.H.</td>
<td>Control</td>
<td>1.61</td>
<td>29.7</td>
<td>123.5</td>
<td>730</td>
<td>16.9</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>4.2 μg/min</td>
<td>1.73</td>
<td>20.5</td>
<td>129.0</td>
<td>584</td>
<td>22.1</td>
</tr>
<tr>
<td>J.W.</td>
<td>Control</td>
<td>5.2</td>
<td>36.0</td>
<td>104</td>
<td>478</td>
<td>21.8</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>14.4 μg/min</td>
<td>7.7</td>
<td>28.3</td>
<td>105</td>
<td>313</td>
<td>33.6</td>
</tr>
</tbody>
</table>

*Clearances corrected to 1.73 m² body surface area.

The observed changes in WRVP in man are in accord with the changes in intrarenal pressure measured directly in experimental animals examined under comparable conditions and indicate that WRVP may be taken as an estimate of intrarenal pressure. Further, values of WRVP in normotensive man (mean = 20.9 mmHg: full values given in Clinical Science Table 38/9 at the Royal Society of Medicine) are in reasonably good agreement with estimates of intrarenal pressure obtained by direct needle measurements in man by Ferris (1951) and Reubi (1956). With a method of estimating intrarenal (peritubular capillary and proximal tubular)
pressures the calculation of glomerular pressure and afferent and efferent arteriolar resistance can be made using a measured, rather than an assumed, value for intrarenal pressure (see below).

II. Intrarenal pressure in normal and hypertensive man (Clinical Science Table 38/9 at Royal Society of Medicine, Fig. 3)

WRVP was measured in twenty-nine studies in eighteen normotensive subjects and in twenty-three studies in twenty-one patients with essential hypertension. WRVP averaged 20.9 ± 4.05 mmHg (range, 12.7–29.8 mmHg) in normotensives and in patients with essential hypertension averaged 28.7 ± 6.46 mmHg (range, 17.4–43.2 mmHg, P < 0.001) (Fig. 3). Examination of the relationship between WRVP and mean arterial pressure in hypertensive patients revealed a weak correlation (r = 0.49, P < 0.01).

Glomerular hydrostatic pressure ($P_G$) was estimated from the filtration equation,

$$GFR = \lambda (P_G - [P_T + P_{ONC}])$$

(1)

where $P_T$ is proximal tubular hydrostatic pressure given by the measured WRVP, $P_{ONC}$ is glomerular oncotic pressure calculated from the plasma concentrations of albumin and globulin, corrected for the loss of water by filtration, and $\lambda$ is a permeability constant. The term ($P_G - [P_T + P_{ONC}]$) defines net filtration pressure.
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Glomerular pressure averaged $62.6 \pm 5.2$ mmHg in normotensive subjects and $72.4 \pm 7.3$ mmHg in patients with essential hypertension ($P < 0.001$) (Fig. 3). Utilizing the measured value of WRVP as peritubular capillary pressure and the value for glomerular pressure derived from formula (1) the resistance across the preglomerular (afferent), postglomerular (efferent), and postcapillary (venous) segments of the renal vascular bed may be estimated.

Segmental renal resistances were calculated as follows:

\[
\text{afferent resistance} = \frac{P_A - P_G}{RBF} \times 1336 \quad (2)
\]

\[
\text{efferent resistance} = \frac{P_G - P_{\text{cap}}}{RBF - \text{GFR}} \times 1336 \quad (3)
\]

\[
\text{venous (postcapillary) resistance} = \frac{P_{\text{exp}} - P_V}{RBF} \times 1336 \quad (4)
\]

where $P_A$, $P_G$, $P_{\text{cap}}$, and $P_V$ are the pressures in the aorta, glomerulus, peritubular capillaries (WRVP) and renal vein or inferior vena cava. This formulation differs from that previously proposed by Gomez (1951) in that peritubular capillary pressure is estimated directly by WRVP rather than as the sum of oncotic pressure and an assumed value for interstitial pressure. Calculated values for segmentary renal resistance are given in *Clinical Science* Table 38/9 at the Royal Society of Medicine. Total renal resistance was increased by 35% in hypertensive patients (mean = 10210 dyne sec cm$^{-5}$, compared with a value of 6759 in normotensives). The predominant increment in resistance is at the preglomerular segment or afferent arteriole, as reported by Gomez (1951).

III. The renal and systemic response to saline loading in normotensive and hypertensive subjects

Fig. 4 shows the natriuretic response to the infusion of 2.5% saline in six normotensive and nine hypertensive subjects. Control sodium excretion rates differed only slightly (normotensives: 200 μEq/min, range 126–282; hypertensives: 277 μEq/min, range 107–496). However, after the rapid infusion of 1 litre of hypertonic saline, in normotensives the average rate of sodium excretion increased to 361 μEq/min (range 169–605) while the average rate of sodium excretion in the six patients with essential hypertension who exhibited exaggerated natriuresis ranged from 1720 to 3710 μEq/min. Sodium excretion in the remaining three hypertensive subjects (W.J., H.H and R.P.) did not exceed that observed in normotensive subjects. In these three hypertensives and in four normotensive subjects, after the infusion of a second litre of saline, average sodium excretion rate increased to 1404 μEq/min, a value similar to that observed after infusion of 1 litre of saline in hypertensives manifesting exaggerated natriuresis.

The renal haemodynamic changes in response to saline infusion are summarized in Table 4. The full data are available in *Clinical Science* Table 38/10, which has been deposited with the Librarian, Royal Society of Medicine. In six hypertensive patients manifesting 'exaggerated natriuresis' control WRVP averaged 26.4 mmHg and rose to a mean of 48.7 mmHg, while little change occurred in the three hypertensive subjects in whom exaggerated natriuresis did not occur. In normotensive subjects, control WRVP averaged 22.5 mmHg and was
30.6 mmHg after administration of 1 litre of hypertonic saline. Glomerular filtration rate rose slightly at the peak of exaggerated natriuresis in both hypertensives and normotensives. Renal blood flow rose greatly in hypertensives, but only slightly in normotensives. In hypertensive patients exhibiting exaggerated natriuresis, total renal resistance fell by 37%. Utilizing the measured values of WRVP to estimate segmental renal resistance, afferent segmental resistance was found to decrease in five or six hypertensives; the mean change was from 4625 to 2893 dyne sec cm⁻⁵ (−37%). Efferent segmental resistance fell from 4945 dyne sec cm⁻⁵ to 3094 dyne·sec·cm⁻⁵ (−37%) at the height of natriuresis. Glomerular pressure increased from an average control value of 72.3 mmHg to 88.3 mmHg during exaggerated natriuresis. In hypertensive subjects who did not manifest exaggerated natriuresis and in normotensive

![Graph showing natriuretic response to hypertonic saline](image)

**Fig. 4.** The natriuretic response to the infusion of hypertonic saline in normotensive subjects and patients with essential hypertension.

**Table 4. Summary of renal haemodynamic changes during saline loading**

<table>
<thead>
<tr>
<th></th>
<th>Essential hypertension</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Saline</td>
</tr>
<tr>
<td>WRVP (mmHg)</td>
<td>26.4</td>
<td>48.7</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>106</td>
<td>119</td>
</tr>
<tr>
<td>Renal blood flow (ml/min)</td>
<td>919</td>
<td>1444</td>
</tr>
<tr>
<td>Renal arteriolar resistance (dyne sec cm⁻⁵)</td>
<td>9660</td>
<td>6050</td>
</tr>
<tr>
<td>Glomerular pressure (mmHg)</td>
<td>72</td>
<td>88</td>
</tr>
<tr>
<td>Afferent arteriolar resistance (dyne sec cm⁻⁵)</td>
<td>4625</td>
<td>2893</td>
</tr>
</tbody>
</table>
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subjects, afferent arteriolar resistance was unchanged and efferent arteriolar resistance fell by only 15%. When sodium excretion was increased by prolongation of the saline infusion (2 litres) in these subjects, the changes in WRVP, renal arteriolar resistance and glomerular pressure were comparable to those observed in hypertensive patients who exhibited exaggerated natriuresis after 1 litre of saline (Clinical Science Table 38/10 at Royal Society of Medicine).

The systemic haemodynamic response to infusion of 1 litre of saline was examined in five hypertensive patients who exhibited exaggerated natriuresis (Clinical Science Table 38/10). Mean arterial pressure rose from 125 to 136 mmHg and vena caval pressure from 5-1 to 7-6 mmHg. Cardiac output averaged 6875 ml per mm per 1·73 m² body surface area during control periods. At the peak of exaggerated natriuresis, cardiac output was increased in two and decreased in three. The mean cardiac output after volume expansion was 6801 ml per min per 1·73 m². Mean systemic vascular resistance averaged 1541 dyne sec cm⁻⁵ during control observations and 1555 dyne sec cm⁻⁵ during natriuresis.

DISCUSSION

We have found that intrarenal pressure, measured as wedged renal vein pressure, is elevated in essential hypertension. Miles & de Wardener (1953) observed that some hypertensive subjects manifest sodium diuresis in response to emotional stress. Since sodium excretion measured simultaneous with the recording of WRVP did not differ in hypertensive and normotensive subjects, it seems unlikely that the observed elevation of WRVP in hypertensives can be attributed to the emotional stress of the procedure itself.

Although renal arteriolar resistance was increased, as expected in patients with essential hypertension, glomerular pressure was also elevated, indicating that the greater systemic pressure in hypertensives is transmitted beyond the afferent arteriole and accounts, at least in part, for increased intrarenal pressure. Autoregulation of glomerular filtration rate is maintained despite greater transmission of pressure, since increases in glomerular pressure are paralleled by increases in proximal tubular hydrostatic pressure and net filtration pressure remains unchanged. Koch et al. (1968) found that intrarenal (proximal tubular) pressure and glomerular hydrostatic pressure increased in the anaesthetized rat following acute elevation of arterial pressure by carotid ligation, and Stahl (1965) found that intrarenal pressure (WRVP) increased under similar conditions in the dog. Swann, Moore & Montgomery (1952a) observed that intrarenal (needle) pressure rose when arterial pressure was increased by carotid clamping in the anaesthetized dog. Thurau & Wober (1962) failed to find a change in proximal tubular or peritubular capillary pressures when arterial pressure was varied by carotid clamping in the anaesthetized rat; however, following paralysis of smooth muscle with papaverine, elevation of arterial pressure resulted in increase in both proximal tubular and peritubular capillary pressure. These observations in the experimental animal and the present data suggest that, although renal resistance is increased and renal blood flow may be decreased in essential hypertension, greater pressure is transmitted across the renal arterioles to the glomerular and peritubular capillaries.

During saline infusion, exaggerated natriuresis in hypertensive subjects was associated with an increase in WRVP from 26·4 mmHg to 48·7 mmHg. While solute diuresis by itself may have contributed to the increase in WRVP, as during mannitol diuresis, the renal haemodynamic data suggest that renal vasodilatation was the major cause of increased intrarenal
pressure during saline loading. In contrast to the fall in GFR which occurred during mannitol diuresis, glomerular filtration rate increased during exaggerated natriuresis. This increase in GFR suggests that net filtration pressure increased and, in light of the elevated pressure in the proximal tubule (inferred from the change in WRVP), provides evidence that glomerular pressure increased during exaggerated natriuresis. Increased glomerular pressure is the result of decreased afferent arteriolar resistance as well as increased mean arterial pressure. Since efferent arteriolar resistance also decreased during exaggerated natriuresis, there was greater transmission of systemic pressure to the peritubular capillaries. Increased resistance distal to the peritubular capillaries (Rv in Table 1), the predominant renal haemodynamic alteration during mannitol diuresis, played only a small role in the increase in WRVP during natriuresis. Thus, while elevation of WRVP was observed during diuresis induced by mannitol or saline loading, the mechanism underlying the change in intrarenal pressure appeared to differ. That is, while increase in solute and water excretion appear to result in increased intrarenal pressure during mannitol diuresis, the changes in intrarenal pressure associated with exaggerated natriuresis appear to be due primarily to renal vasodilatation.

During saline loading, increases in sodium excretion were regularly associated with increments in wedged renal vein pressure. In hypertensive patients exhibiting exaggerated natriuresis, the increase in WRVP averaged 22-4 mmHg while changes in WRVP in normotensives and hypertensives who failed to demonstrate exaggerated natriuresis were smaller (mean increase, 7-7 mmHg). When natriuresis was evoked by prolongation of saline infusion, sodium excretion and WRVP rose to levels comparable to those seen during 'exaggerated natriuresis'. Further, parallel increases in WRVP and sodium excretion were observed during renal vasodilatation with acetylcholine and parallel decreases in WRVP and sodium excretion were observed during renal vasoconstriction with adrenaline.

During elevated ureteropelvic pressure, fractional excretion of sodium was unchanged despite elevated WRVP. Brenner, Bennett & Berliner (1968) found unchanged proximal tubular fractional reabsorption of filtrate during ureteral occlusion of the rat. The role of tubular dilatation and increased transit time in the nephron in the maintenance of sodium reabsorption is not clear.

Lewy & Windhager (1968) observed decreased fractional reabsorption of sodium during partial renal venous occlusion in the rat and Wathen & Selkurt (1969) confirmed this observation in the dog. Wathen & Selkurt (1969) found that sodium excretion fell during renal vein occlusion in animals undergoing saline diuresis, as reported previously by Blake et al. (1949) and attributed this to reduction in GFR.

Lewy & Windhager (1968) and Earley & Friedler (1966) postulated that the net rate of sodium reabsorption by the renal tubular epithelium might be effected by the rate of removal of fluid by the peritubular capillaries, and suggested that increase in the interstitial fluid volume of the kidney might be responsible for decreased tubular reabsorption of sodium under some experimental conditions.

Natriuresis or decreased proximal tubular reabsorption of sodium has been observed to occur in response to a variety of manoeuvres which would be expected to increase renal interstitial volume and/or pressure according to the Starling hypothesis, viz. acute elevation of arterial pressure in the rat (Koch et al., 1968), partial renal venous occlusion in the rat and dog (Lewy & Windhager, 1968; Wathen & Selkurt, 1969), renal vasodilatation in the dog (Martino & Earley, 1967), and volume expansion with hypo-osmotic (Eknoyan et al., 1967), iso-osmotic
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(Dirks, Cirksena & Berliner, 1965; Watson, 1966), and hypo- or iso-ontotic solutions (Martino & Earley, 1967; Levinsky, Lalone & Moss, 1963) and plasmapheresis (Vereerstraeten & Toussaint, 1969) in the dog. Wedged renal vein pressure is elevated during volume expansion with saline in the dog (Martino & Earley, 1968).

The observed elevation of wedged renal vein pressure (and, by inference, of peritubular capillary pressure) and decrease in oncotic pressure in the peritubular capillary blood during saline infusion might be expected to bring about redistribution of fluid between the peritubular capillaries and the renal interstitium and result in increased interstitial volume. Our data, demonstrating an association between elevation of wedged renal vein pressure (attributable to increased transmission of arterial pressure to the peritubular capillaries), and decreased fractional reabsorption of sodium during saline infusion, are consistent with the hypothesis that increased renal interstitial volume may have mediated natriuresis during saline loading. Although filtered load of sodium was generally increased during saline loading, this factor does not of itself appear sufficient to account for the observed natriuresis since the increment in excreted sodium was seen to exceed that in filtered sodium in some subjects, both in this study and in our previous experience with saline loading (Baldwin et al., 1958), and volume expansion with saline has been shown to result in natriuresis when filtered load of sodium is decreased experimentally in animals (Dirks et al., 1965). The data do not exclude the possibility that a circulating natriuretic hormone also participates in the natriuretic response to saline loading.

Our data indicate that natriuresis during saline infusion is associated with increased intrarenal pressure both in normals and hypertensives; exaggerated natriuresis in patients with essential hypertension is associated with a greater increase in intrarenal pressure. During saline loading, resistance proximal to the peritubular capillaries, that is, the sum of afferent and efferent arteriolar resistance, fell from 9660 to 6050 dyn sec cm\(^{-5}\) during exaggerated natriuresis in hypertensives and from 6470 to 5380 dyn sec cm\(^{-5}\) in normotensive subjects. Afferent arteriolar resistance decreased by 37\% in hypertensive patients and was unchanged in normotensive subjects. As a result of the greater fall in renal arteriolar resistance, the increment in intrarenal pressure during saline infusion in patients with essential hypertension far exceeds that observed in normotensive subjects, and might provide an explanation for exaggerated natriuresis in hypertensive subjects.

The mechanism by which renal arteriolar reactivity is altered in patients with essential hypertension is not known. Elevated systemic arterial pressure per se might result in altered arteriolar reactivity. This thesis is supported by the occurrence of 'exaggerated natriuresis' in other forms of hypertension, viz. phaeochromocytoma, hyperaldosteronism, Cushing's syndrome, and in the contralateral kidney in renovascular hypertension (Hanenson et al., 1959; Birchall et al., 1953; Birchall, Madsen & Anderson, 1964), and after elevation of blood pressure by the infusion of metaraminol (Vaamonde et al., 1964; Eisinger, 1966). Increased blood pressure, by virtue of changes in the compliance characteristics of the systemic vascular bed, might alter the systemic haemodynamic response to volume expansion (Ulrych et al., 1964). We have found that systemic arteriolar resistance was unchanged and changes in cardiac output were small during exaggerated natriuresis, suggesting that the altered renal arteriolar response was not part of an exaggerated systemic haemodynamic response to volume expansion, but the possibility remains that renal arteriolar reactivity is specifically altered by local changes in compliance in the kidney of the hypertensive. The increased intrarenal pres-
sure, which we have found to be characteristic of essential hypertension, might be common to other forms of hypertension as well: we have observed increased intrarenal pressure in hypertension induced by metaraminol infusion (unpublished observations). Increased intrarenal pressure then, reflecting increased systemic pressure, may be responsible for altered renal arteriolar reactivity.

If acute elevation of intrarenal pressure mediates natriuresis, as suggested by our studies during saline loading, chronic elevation of intrarenal pressure, as found in essential hypertension, may play a role in the maintenance of sodium homeostasis in hypertensive patients. Our previous studies demonstrated that proximal tubular reabsorption of sodium is excessive in patients with essential hypertension (Baldwin et al., 1960; Steinmetz et al., 1964; Baldwin, Gombos & Chasis, 1965) and increased proximal tubular reabsorption of sodium is characteristic of the kidney with significant artery stenosis (Baldwin, 1961), while, paradoxically, in both instances sodium balance is maintained. The present data indicate that increased systemic arterial pressure is transmitted across the renal arterioles and results in increased intrarenal pressure in essential hypertension. As a result, sodium excretion might be increased in some nephrons, compensating for excessive reabsorption in others, or tubular reabsorption of sodium might be decreased at more distal sites of nephrons in which proximal reabsorption is excessive. In this way, increased intrarenal pressure may play a role in the regulation of sodium excretion in patients with essential hypertension and the occurrence of hypertension itself may be viewed as a mechanism for the maintenance of sodium homeostasis.

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