ROLE OF THE KIDNEY IN 'SALT AND WATER DEPENDENT HYPERTENSION' OF END-STAGE RENAL DISEASE

G. BIANCHI, C. PONTICELLI, U. BARDI, B. REDAELLI, L. CAMPOLO, C. DE PONTI AND G. GRAZIANI

Istituto di Patologia Speciale Medica and
Sezione di Nefropatologia dell'Istituto di Urologia dell'Università di Milano,
Laboratori di Farmacologia della Lepetit, Milan, Italy

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SUMMARY

1. Blood pressure, plasma renin concentration, exchangeable body sodium, plasma volume and extracellular fluid volume were measured in five patients on maintenance haemodialysis for end-stage renal disease in whom hypertension was relatively easy to control by the combination of dialysis and restriction of salt intake. Measurements were made on three occasions: on a free salt intake the day before dialysis; on a low salt intake the day after dialysis; on a free salt intake the day before dialysis after nephrectomy.

2. The fall of blood pressure after haemodialysis and salt intake restriction was accompanied by a decrease of exchangeable body sodium and body fluids while plasma renin concentration increased. The fall of blood pressure after bilateral nephrectomy was accompanied by a fourfold decrease of plasma renin without any change of the other variables.

3. The hypertension of these patients might thus be considered 'salt and water dependent' or 'renin dependent' according to the means used to decrease blood pressure.

There is now general agreement that in the majority of patients with end-stage renal disease and hypertension, haemodialysis and salt intake restriction decrease blood pressure to normal; in a small group of patients, however, this treatment does not decrease blood pressure but tends to increase it (Vertes, Cangiano, Berman & Gould, 1969; Brown, Curtis, Lever, Robertson, de Wardener & Wing, 1969; British Medical Journal, 1969; Safar, Fendler, Weil, Beuven-Mary, Brissey, Idatte, Meyer & Milliez, 1970; Wilkinson, Scott, Uldall, Kerr & Robson, 1970). The finding that patients with hypertension resistant to dialysis have plasma renin activities higher than those in the majority of patients who are not resistant has led some authors to conclude that whereas in most patients hypertension is 'water and salt dependent' there is a small group in whom it is 'renin dependent' (Vertes et al., 1969) or that renin is...
an important pathogenic factor in hypertension resistant to dialysis (Safar et al., 1970; Brown, Düsterdieck, Fraser, Lever, Robertson, Tree & Weir, 1971).

The pressor role of renin in patients with hypertension resistant to dialysis is also supported by the response to bilateral nephrectomy. The blood pressure fall observed after bilateral nephrectomy in these patients is accompanied by a marked decrease of plasma renin activity without any change of total body sodium or body fluids (Hampers, Zollinger, Skillman, Gumpert, Baily & Merrill, 1969; Safar et al., 1970; Wilkinson et al., 1970).

The effect of nephrectomy in patients whose hypertension can be controlled by haemodialysis, has been studied in relation to plasma renin concentration and blood pressure (Gleadle, Brown, Curtis, Fraser, Lawson, Lever, Linton, McVeigh, Robertson, de Wardener & Wing, 1969; Verniory, Potvliege, Van Geertruyden, Vereerstraeten, Kinnaert, Lotteau & Toussaint, 1970) and also exchangeable sodium and blood pressure (Onesti, Schwartz, Ramirez & Brest, 1968). The purpose of the present investigation was to study in parallel in the same patient the changes in renin, exchangeable sodium and body fluids produced by bilateral nephrectomy. Patients were selected in whom it was possible to control hypertension by haemodialysis and moderate sodium intake restriction, and nephrectomy was undertaken in preparation for renal transplantation.

MATERIAL AND METHODS

Patients

Five patients on maintenance haemodialysis for end-stage renal disease were studied with simultaneous measurement of plasma renin concentration, exchangeable sodium, plasma and extracellular fluid volumes. All patients were hypertensive at the time of starting maintenance haemodialysis (arterial hypertension was arbitrarily defined as being present when blood pressure was 145 mmHg systolic and 95 mmHg diastolic or more on at least five occasions). In all the hypertensive patients it was relatively easy to normalize blood pressure by weight decrease with haemodialysis and restriction of salt intake (see Fig. 1). At the time of the study no patient was receiving antihypertensive treatment, or had hypertensive retinopathy, haemorrhages, exudates or papilloedema.

In each patient, two sets of measurements were carried out before bilateral nephrectomy at intervals ranging from 20 to 30 days; the first study was on the day before haemodialysis during a period of relatively free salt intake; the second study was on the day after haemodialysis during a period of salt intake restriction at which time a significant change of blood pressure, body weight and exchangeable sodium had been produced.

Another set of measurements was carried out after bilateral nephrectomy on the day before haemodialysis during a period of relatively free salt intake; this enabled the effect of nephrectomy to be assessed by comparing the results of the periods during which total body sodium was approximately the same.

Table 1 shows the time-interval of these measurements in relation to the starting of maintenance haemodialysis.

Techniques

All measurements were started between 8 and 9 a.m., the patient having rested in the supine position for at least 1 h. Blood pressure was recorded by sphygmomanometer from the start of the study until noon at intervals of approximately 1 h while the other measurements were being taken, and the average blood pressure value was used in the analysis.
The other measurements were carried out in the following order: withdrawal of blood from the arterial cannula of a Scribner shunt for estimation of plasma renin and electrolytes, plasma volume, extracellular fluid volume and exchangeable body sodium. Plasma renin concentration was measured by the method of Brown, Davies, Lever, Robertson & Tree (1964) without modifications. The recovery of renin and the error of the method used by us are described elsewhere (Bianchi & Riva, 1965; Bianchi, Campolo, Vegeto, Pietra & Piazza, 1970). The normal values of plasma renin concentration ranged from 4.5 to 21 units/l. Plasma volume was estimated by the Evans Blue dye method. To avoid the interference of plasma turbidity, the dye was extracted from the plasma on Solkafloc according to Campbell, Frohman & Reeve (1958). Preliminary studies (Bianchi et al., 1970) demonstrated no significant difference between plasma volume estimated by this method and with \( ^{131}I \)-labelled albumin. Extracellular volume was measured by the thiocyanate method. Total exchangeable sodium was determined by the isotope-dilution technique with \( ^{24}Na \); 24 h were allowed for equilibration. Haemodialysis was performed twice a week with a Kiil apparatus for a total of 22–24 h a week.

### RESULTS

Some clinical data on the five patients studied are shown in Table 1. In all patients it was possible to decrease the arterial pressure to normal when body weight was decreased by haemodialysis and restriction of salt intake.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>24 h Urine volume (ml)*</th>
<th>Work capacity</th>
<th>Time (months) from the beginning of haemodialysis</th>
<th>First set of measurements</th>
<th>Nephrectomy</th>
<th>Measurements after nephrectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>M</td>
<td>Chronic glomerulonephritis</td>
<td>200</td>
<td>Active</td>
<td>19</td>
<td>19</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>M</td>
<td>Chronic glomerulonephritis</td>
<td>0</td>
<td>Active</td>
<td>23</td>
<td>23</td>
<td>29</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>M</td>
<td>Chronic glomerulonephritis</td>
<td>0</td>
<td>Active</td>
<td>13</td>
<td>13</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>M</td>
<td>Chronic glomerulonephritis</td>
<td>0</td>
<td>Restricted</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>9.5</td>
</tr>
<tr>
<td>5</td>
<td>39</td>
<td>F</td>
<td>Chronic glomerulonephritis</td>
<td>100</td>
<td>Active</td>
<td>1.5</td>
<td>1.5</td>
<td>6.5</td>
<td>8.5</td>
</tr>
</tbody>
</table>

* Value for the day of the first set of measurements.
The linear regression lines of mean blood pressure on body weight for each patient with 95% confidence limits are shown in Fig. 1. These lines have been calculated from all the paired values of blood pressure and body weight obtained before and after haemodialysis over a period of approx. 1 month between the first two sets of measurements. It is clear that for each patient there is a certain value of body weight at which the blood pressure is within the normal range.

![Graph showing linear regression lines for each patient](image)

**FIG. 1.** Linear regression with 95% confidence limits of mean blood pressure on body weight before bilateral nephrectomy in the five patients studied. The number of paired observations in each patient was 21, 16, 18, 18 and 20, for patients 1, 2, 3, 4 and 5 respectively.

**Effect of haemodialysis and salt intake**

The changes of renin, sodium, plasma volume and extracellular fluid volume accompanying the fall of blood pressure produced by haemodialysis and moderate restriction of salt intake are shown in Table 2. The values for plasma and extracellular fluid volumes of patient 4 were not included in the table since the determinations performed after haemodialysis were not reliable owing to a technical failure.

Apart from decreasing blood pressure, this treatment also decreases exchangeable body sodium, plasma and extracellular fluid volumes and body weight, while increasing plasma renin concentration. The changes of weight, blood pressure, exchangeable sodium and renin are statistically significant.

**Effect of bilateral nephrectomy**

The results in Table 3 demonstrate that the fall of blood pressure caused by bilateral nephrectomy is accompanied by a fourfold decrease of plasma renin concentration without any significant modification of the other variables. The changes of blood pressure and renin are statistically significant.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Systolic blood pressure (mmHg)</th>
<th>Diastolic blood pressure (mmHg)</th>
<th>Plasma volume (ml)</th>
<th>Body wt. (kg)</th>
<th>Exchangeable sodium (mEq)</th>
<th>Body fluids (ml)</th>
<th>Extracellular fluid volume (ml)</th>
<th>Plasma renin concentration (units/l)</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>182</td>
<td>108</td>
<td>91.0</td>
<td>61.0</td>
<td>56.0</td>
<td>47.3</td>
<td>66.0</td>
<td>628</td>
<td>32.5</td>
<td>15.2</td>
</tr>
<tr>
<td>2</td>
<td>146</td>
<td>97</td>
<td>54.0</td>
<td>35.0</td>
<td>53.5</td>
<td>46.8</td>
<td>65.0</td>
<td>737</td>
<td>2.4</td>
<td>1.8</td>
</tr>
<tr>
<td>3</td>
<td>178</td>
<td>112</td>
<td>88.0</td>
<td>68.0</td>
<td>86.0</td>
<td>73.5</td>
<td>75.0</td>
<td>872</td>
<td>1.9</td>
<td>0.6</td>
</tr>
<tr>
<td>4</td>
<td>171</td>
<td>118</td>
<td>92.0</td>
<td>62.0</td>
<td>95.0</td>
<td>78.0</td>
<td>57.0</td>
<td>935</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Mean</td>
<td>169.8</td>
<td>106.2</td>
<td>90.5</td>
<td>60.0</td>
<td>88.0</td>
<td>70.5</td>
<td>70.5</td>
<td>872</td>
<td>2.0</td>
<td>1.5</td>
</tr>
<tr>
<td>SE (paired comparisons)</td>
<td>6.28</td>
<td>4.68</td>
<td>5.53</td>
<td>3.53</td>
<td>5.35</td>
<td>4.53</td>
<td>2.32</td>
<td>1.41</td>
<td>&lt;0.05</td>
<td>&lt;0.2</td>
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</tbody>
</table>

* Before haemodialysis and on free salt intake.
† After haemodialysis and on salt intake restriction.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Systolic blood pressure (mmHg)</th>
<th>Diastolic blood pressure (mmHg)</th>
<th>Body wt. (kg)</th>
<th>Plasma volume (ml)</th>
<th>Extracellular fluid volume (ml)</th>
<th>Exchangeable body sodium (mEq)</th>
<th>Plasma renin concentration (units/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before*</td>
<td>After*</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>1</td>
<td>182</td>
<td>158</td>
<td>108</td>
<td>98</td>
<td>61.0</td>
<td>56.8</td>
<td>3225</td>
</tr>
<tr>
<td>2</td>
<td>146</td>
<td>126</td>
<td>97</td>
<td>69</td>
<td>53.0</td>
<td>53.0</td>
<td>4070</td>
</tr>
<tr>
<td>3</td>
<td>178</td>
<td>132</td>
<td>112</td>
<td>83</td>
<td>59.3</td>
<td>58.0</td>
<td>4917</td>
</tr>
<tr>
<td>4</td>
<td>171</td>
<td>124</td>
<td>118</td>
<td>72</td>
<td>57.0</td>
<td>57.6</td>
<td>21558</td>
</tr>
<tr>
<td>5</td>
<td>172</td>
<td>131</td>
<td>96</td>
<td>77</td>
<td>47.3</td>
<td>44.6</td>
<td>2900</td>
</tr>
<tr>
<td>Mean</td>
<td>169.8</td>
<td>134.2</td>
<td>106.2</td>
<td>79.8</td>
<td>55.5</td>
<td>54.0</td>
<td>3778</td>
</tr>
<tr>
<td>SE</td>
<td>6.28</td>
<td>6.13</td>
<td>4.27</td>
<td>5.13</td>
<td>2.45</td>
<td>2.51</td>
<td>452</td>
</tr>
<tr>
<td>t</td>
<td>6.26</td>
<td>4.40</td>
<td>1.73</td>
<td>1.54</td>
<td>-1.74</td>
<td>0.74</td>
<td>-0.96</td>
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<tr>
<td>P</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>&gt;0.1</td>
<td>&gt;0.2</td>
<td>&gt;0.4</td>
<td>&gt;0.3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Before and after bilateral nephrectomy.
DISCUSSION

A pressor role of renin has been suggested in end-stage renal disease with hypertension resistant to dialysis and salt intake restriction (Brown et al., 1969; Vertes et al., 1969; Safar et al., 1970; Wilkinson et al., 1970; Brown et al., 1971). Gleadle et al. (1969), however, found no significant change in blood pressure after bilateral nephrectomy in two patients whose hypertension was controlled by haemodialysis. No information is available in that paper on exchangeable sodium.

The results reported here demonstrate that bilateral nephrectomy can decrease blood pressure without significant change of exchangeable sodium and body fluids in patients whose hypertension could be controlled by haemodialysis before nephrectomy. Thus the kidney would appear to have a primary hypertensive role in these patients too, in agreement with the results of Onesti et al. (1968) who demonstrated that blood pressure was higher for a given concentration of exchangeable sodium before bilateral nephrectomy than after. Changes in plasma renin concentration may be responsible for this difference (see Ledingham, 1971; Brown et al., 1971).

In our patients the average fall of blood pressure of 35 mmHg systolic and 25 mmHg diastolic was accompanied by a fourfold decrease of plasma renin concentration. In normal rabbits (Imbs, Brown, Davies, Lever & Robertson, 1967) and dogs (Bianchi, Brown, Lever, Robertson & Roth, 1968) an approximate 4–5-fold increase of plasma renin concentration produced by infusion of exogenous renin increased mean blood pressure 30–40 mmHg. Renin infusion data in man are not available. With this proviso, the correspondence between the changes in blood pressure and plasma renin concentration observed in rabbits and dogs and the changes observed in our patients, is in favour of the hypothesis that renin has a pressor role in the salt-dependent hypertension of end-stage renal disease.

Thus the hypertension of these patients might have two components: one 'salt and water' dependent, since it is relieved by salt and water restriction, and another 'renin' dependent, since the fall of blood pressure after bilateral nephrectomy is accompanied by a marked decrease of plasma renin concentration without significant modification of the other variables.

The apparent conflict between the two observations might be explained by considering the interdependence between renin and sodium balance in influencing blood pressure. Previous reports (Brown, Davies, Lever & Robertson, 1966; Laragh, 1967; Bianchi et al., 1968; Brown et al., 1971; Ledingham, 1971) indicate that the pressor effect of a given plasma renin concentration is dependent on the state of sodium balance, being greater when sodium is retained in the body and less when sodium depletion occurs. Conversely, sodium retention decreases and sodium depletion increases plasma renin concentration. Moreover, sodium balance per se may influence blood pressure (Onesti et al., 1968; Carlberger & Collste, 1968) through either an alteration of body fluids (Dustan & Page, 1964) or a direct effect on the arterial wall smooth muscle (Tobian, 1960). Thus both factors must be measured simultaneously if the pressor role of either sodium or renin is to be assessed.

In our patients it is possible that the fall of exchangeable body sodium produced by haemodialysis and salt intake restriction was so marked as to decrease blood pressure in spite of the increase in plasma renin concentration, whereas the decrease of plasma renin concentration caused by nephrectomy resulted in the fall of blood pressure without changing exchangeable sodium.
If we admit a pressor role of renin in salt dependent hypertension, a sharp separation of patients with end-stage renal disease hypertension into those with 'salt and water-dependent hypertension' and those with 'renin-dependent hypertension' (Vertes et al., 1969) may not be justified since, as already suggested (British Medical Journal, 1969), the two groups may merge into each other.

REFERENCES


Dustan, H.P. & Page, I.H. (1964) Some factors in renal and renoprival hypertension. Journal of Laboratory and Clinical Medicine, 64, 948-959.


