ABNORMAL RENAL HAEMODYNAMICS AND RENIN SUPPRESSION IN HYPERTENSIVE PATIENTS

M. A. D. H. SCHALEKAMP, M. P. A. SCHALEKAMP-KUYKEN AND W. H. BIRKENHÄGER

Department of Internal Medicine, Zuiderziekenhuis, Rotterdam, Netherlands

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SUMMARY

1. Intra-arterial pressure, renal plasma flow and glomerular filtration rate were estimated in thirty-two patients with benign essential hypertension. In twenty cases plasma renin concentrations were also determined. Variability of blood pressure was estimated by automatic indirect pressure recording.

2. There was an even distribution between high and low values of renal vascular resistance and filtration fraction. Variability of blood pressure was inversely related to renal vascular resistance.

3. In five patients plasma renin concentration was found to be abnormally low both in the recumbent and in the 45° tilt position.

4. Plasma renin concentration was related to renal blood flow, renal vascular resistance, filtration fraction and variability of blood pressure.

5. The results suggest that in hypertension renin release is suppressed by an increase in intravascular pressure at the level of the juxtaglomerular cells. The extent of renin suppression seems to be related to the stage of hypertensive disease.

Although plasma renin concentrations in benign essential hypertension are generally within normal limits, some patients have abnormally low values. A low plasma renin concentration is an important criterion in the diagnosis of primary hyperaldosteronism, but recent studies have failed to demonstrate hypersecretion of aldosterone in normokalaemic hypertensive patients with low plasma renin activity (Küchel et al., 1967; Ledingham, Bull & Laragh, 1967; Helmer & Judson, 1968; Weinberger et al., 1968; Channick, Adlin & Marks, 1969; Jose & Kaplan, 1969).

In the present study an attempt was made to relate plasma renin concentration in patients with benign essential hypertension to renal blood flow, renal vascular resistance, glomerular filtration rate, filtration fraction, lability of blood pressure and severity of hypertension.

Correspondence: Dr W. H. Birkenhager, Zuiderziekenhuis, Groeneveld 15, Rotterdam, Netherlands.

101
Thirty-two hypertensive patients, eighteen men and fourteen women, aged 19–60, were studied. In all of them the diagnosis of uncomplicated essential hypertension was made after examination followed by intravenous pyelography, radio-isotope renography and ophthalmoscopic examination of the optic fundi. Plasma electrolytes were normal in all cases (Table 1), and plasma creatinine did not exceed 1.5 mg/100 ml. The patients were taken into hospital and received a diet containing 3 g NaCl daily, which was checked by the analysis of 24 hr urine specimens. In patients receiving therapy, treatment had been stopped before the investigations were started. The interval was at least 20 days in patients who were treated with guanethidine, methyldopa and diuretics, and 10 days in the case of bethanidine. Other drugs were not used.

Renal plasma flow and glomerular filtration rate were estimated by measurement of the clearances of \(^{131}\)I-Hippuran (sodium ortho-iodohippurate) and endogenous creatinine, respectively. For determinations of renal plasma flow a constant infusion technique was used. Blood samples were taken at 15 min intervals and urine was collected at hourly intervals without catheterization. In twelve patients the estimation of glomerular filtration rate was carried out at the same time by measurement of the \(^{57}\)Co-cyanocobalamin clearance. In these cases we used \(^{125}\)I-Hippuran instead of \(^{131}\)I-Hippuran for estimation of renal plasma flow, as described by Cutler & Glatte (1965). Radioactivity of that part of the plasma samples not bound to protein was determined by subtracting the activity after exhaustive dialysis against 0.9% NaCl. The fraction of dialysable \(^{57}\)Co-cyanocobalamin varied from 70 to 85%. Renal blood flow was calculated from renal plasma flow by using the venous haematocrit and assuming 90% renal extraction of Hippuran. Probably the latter assumption means that renal blood flow was underestimated, particularly in those cases with very low renal plasma flow values.

Plasma volume was estimated by determining the dilution of \(^{131}\)I-human serum albumin injected intravenously. Blood samples were drawn after 10, 20, 30 and 40 min. Blood volume was calculated from plasma volume by using the venous haematocrit.

Variability of blood pressure was computed from automatic indirect blood pressure recordings as described by Birkenhager et al. (1968). In eighteen patients mean arterial pressure was measured by direct manometry from an indwelling needle; in two others, mean pressure was calculated indirectly (see Table 1).

Plasma renin determination. Plasma renin was determined in the same twenty patients. Blood samples were taken between 09.00 and 10.00 hours, after the patients had been kept in bed throughout the night. A second blood sample was taken 2 hr later after the patients had remained on a tilting table at 45° for 1 hr. In twelve patients additional blood samples were obtained at noon and in the afternoon, after they had been recumbent for at least 1 hr. In twenty-six control subjects plasma renin determinations were carried out under comparable circumstances. Plasma renin concentration was determined according to the method of Skinner (1967). We made use of an excess of exogenous renin substrate prepared from sheep plasma as described by the same author. Two ml aliquots of plasma containing 20 I.U. heparin/ml were treated by dialysis at 4° against a buffer solution pH 3.3 containing 0.005 M EDTA for 24 hr, followed by warming to 32° for 60 min. This treatment causes a destruction of angiotensinase activity and endogenous renin substrate. The treated plasma was dialysed at 4° in a buffer solution, pH 7.5, containing 0.001 M EDTA for 24 hr, and incubated with standard renin substrate at 37° for up to 15 hr. The concentration of substrate in the incubation mixture was 600 ng/ml,
Repeated determinations

- Indirect recordings BP mean being calculated as BP diastolic + 0.4 (BP systolic - BP diastolic).

- Est. BV: estimated blood volume.
- BP var.: variability of arterial pressure.
- RVR: renal vascular resistance (BP mean/Est. RBF).

- GFR: glomerular filtration rate.
- FF: filtration fraction.
- BP: arterial pressure.
- PRC: plasma renin concentration.

### Table 1: Physical and Laboratory Data on the Twenty Intensively Studied Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (y)</th>
<th>BSA (m²)</th>
<th>Est. RBF† (ml/min)</th>
<th>GFR (ml/min)</th>
<th>FF (%)</th>
<th>BP (mmHg)</th>
<th>PRC (ng/ml/hr)</th>
<th>Est. BV (ml)</th>
<th>Plasma (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>35</td>
<td>1.21</td>
<td>282</td>
<td>136</td>
<td>0.26</td>
<td>113</td>
<td>93</td>
<td>3</td>
<td>160/110</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>41</td>
<td>1.52</td>
<td>282</td>
<td>136</td>
<td>0.26</td>
<td>113</td>
<td>93</td>
<td>3</td>
<td>160/110</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>42</td>
<td>1.21</td>
<td>282</td>
<td>136</td>
<td>0.26</td>
<td>113</td>
<td>93</td>
<td>3</td>
<td>160/110</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>44</td>
<td>1.21</td>
<td>282</td>
<td>136</td>
<td>0.26</td>
<td>113</td>
<td>93</td>
<td>3</td>
<td>160/110</td>
</tr>
</tbody>
</table>

(Not all values are listed for simplicity.)

**Legend:**
- BSA: body surface area.
- Est. RBF: estimated renal blood flow.
- GFR: glomerular filtration rate.
- FF: filtration fraction.
- BP: arterial pressure.
- PRC: plasma renin concentration.

- Indirect recordings being calculated as BP diastolic + 0.4 (BP systolic - BP diastolic).
- BP var.: variability of arterial pressure.
- RVR: renal vascular resistance (BP mean/Est. RBF).

Values between 3.5 and 5.4 (mg/dl) were considered to be normal in our laboratory.
as determined by the maximum amount of angiotensin which could be produced in the presence of great excess of plasma renin. In plasma renin assays angiotensin concentration of the incubation mixture never exceeded 120 ng/ml. With these precautions angiotensin was produced at a constant rate during incubation. Angiotensin was assayed in anephric rats after administration of pentobarbitone and pentolinium. Injection of $0.025-0.1$ ml aliquots of the incubation mixture were compared with injections of known amounts of synthetic val-5-angiotensin II-asp-$\beta$-amide (Hypertensin, Ciba). All samples were assayed in at least two rats.

Fig. 1. Distribution of values of renal vascular resistance, glomerular filtration rate and filtration fraction with respect to estimated renal blood flow in thirty-two hypertensive patients.
Plasma renin concentration was expressed in ng of angiotensin produced by 1 ml of plasma during an incubation period of 1 hr. Recovery of synthetic angiotensin was at least 95%. After repeating dialysis at pH 3.3 and warming to 32° before incubation no loss of plasma renin could be detected. From a series of thirty double-plasma renin determinations performed within 1 month the 95% confidence limits for reproducibility of results were calculated to be the mean ± [0.2 × mean].

RESULTS

Renal haemodynamics

The results are summarized in Fig. 1. Renal blood flow ranged from 321 to 1184 ml min⁻¹ 1.73 m⁻². Mean arterial blood pressure varied between 115 and 160 mmHg. In all cases renal vascular resistance was elevated, between 7500 and 32 000 dynes sec cm⁻⁵. Glomerular filtration rate varied between 73 and 152 ml min⁻¹ 1.73 m⁻². Filtration fraction values were between 0.18 and 0.40. Variability of blood pressure was found to be inversely related to renal vascular resistance (Fig. 2).

![Fig. 2. Relationship between renal vascular resistance and variability of arterial pressure in twenty hypertensive patients \( r = -0.77; P<0.05 \).](image)

Plasma renin concentration

Control renin values were between 5.6 and 17 ng ml⁻¹ hr⁻¹ (Fig. 3). In hypertensives the concentrations ranged from 2.0 to 16. Five patients showed renin levels below 4.0 ng ml⁻¹ hr⁻¹. The values remained subnormal even after tilting to 45° during 1 hr (Fig. 3). In twelve cases, including all patients whose morning renin levels were subnormal, additional plasma samples were obtained at noon and in the afternoon during recumbency. The differences between the morning values and the levels at noon and in the afternoon did not exceed 1.6 ng ml⁻¹ hr⁻¹.
Abnormally large blood volumes were not observed in patients with low renin values. On the contrary, in some the blood volume was found to be relatively small. No clear correlation could be demonstrated between plasma renin concentration and plasma sodium concentration \((r = -0.42; 0.1 > P > 0.05)\).
Relationships between plasma renin concentration and renal haemodynamics

Table 1 summarizes the results obtained in twenty patients whose plasma renin levels were determined together with estimations of renal blood flow, renal vascular resistance and filtration fraction. Fig. 4 shows that a significant relationship appeared between plasma renin concentration and these measures of renal function. Plasma renin concentration was related to renal blood flow and showed a negative correlation with the total renal vascular resistance. On the other hand, plasma renin concentration and glomerular filtration rate were not related. A very obvious negative relationship appeared between plasma renin concentration and filtration fraction values.

![Graphs showing relationships between plasma renin concentration and various renal parameters.](image)

*Fig. 4. Relationships between plasma renin concentration and estimated renal blood flow, renal vascular resistance, glomerular filtration rate and filtration fraction respectively in twenty hypertensive patients during recumbency. Significance levels indicated for each relationship.*

Relationships between plasma renin and variability of blood pressure

Plasma renin concentrations were related to variability of blood pressure, the latter being estimated during a period of several successive days before and after blood sampling for plasma renin determinations (Fig. 5). We found no correlation with the severity of hypertension.
DISCUSSION

Several factors have been implicated in the control of renin release. In early experimental studies in animals the perfusion pressure within the kidney was indicated as a sensitive regulating mechanism. Tobian, Tomboulian & Janecek (1959) discovered a relationship between renal perfusion pressure and degranulation of juxtaglomerular cells in the isolated rat kidney. Skinner, McCubbin & Page (1964) actually demonstrated a release of renin during reduction of perfusion pressure and a suppression of renin release during high perfusion pressure in the canine kidney. Recently Kaneko et al. (1968) observed increased renin secretion rates after acute lowering of systemic arterial blood pressure by sodium nitroprusside infusions in normotensive and hypertensive patients.

Attention has mainly been directed towards the effects of sodium intake (Brown et al., 1963, 1964), plasma sodium concentration (Brown et al., 1965) and fluid balance (Fraser et al., 1965; Newsome & Bartter, 1968). Although the sympathetic nervous system appears to modify the renin response to volume expansion and depletion (Vander, 1967), transplanted kidneys react in a similar way to intact donor kidneys (Blaufox et al., 1969).

Many authors have demonstrated a so-called 'suppressed', i.e. subnormal, plasma renin activity in a significant number of hypertensive patients. Plasma renin levels were not only low during basal conditions. The 'suppression' remained when patients were submitted to manoeuvres designed to stimulate renin release by means of a modest shrinkage of effective plasma volume. This is accomplished by keeping the patient standing for several hours while on a low salt diet and/or treatment with diuretics. The incidence of subnormal plasma renin activity was between 10 and 40% (Gunnells et al., 1967; Küchel et al., 1967; Helmer & Judson, 1968; Channick et al., 1969; Jose & Kaplan, 1969). Suppression of plasma renin activity is an important feature of primary hyperaldosteronism (Conn, Cohen & Rovner, 1964; Ledingham et al., 1967; Davis & Newsome, 1967). However, hyperaldosteronism has a much lower incidence than...
Renin suppression in hypertension

suppressed renin activity. In the great majority of cases the cause of suppressed renin activity in hypertension remains unknown (Helmer & Judson, 1968; Channick et al., 1969; Jose & Kaplan, 1969; Woods et al., 1969).

Surprisingly the original concept of a pressure feedback control mechanism has not been applied to the exploration of this group of hypertensive patients. Intravascular pressure at the level of the juxtaglomerular cells cannot be estimated in a direct way by measurement of the systemic arterial blood pressure, because of autoregulatory and adrenergic intrarenal mechanisms. An alternative approach is the evaluation of the maintenance of glomerular filtration rate in the face of a progressive decrease of renal blood flow (Goldring & Chasis, 1944). The discrepancy found between these two variables appears to be a reflection of the amount of pressure exerted in the glomerular loops. Probably this pressure is also applied to the preglomerular vascular segment. If this hypothesis is correct, the inverse relationship between filtration fraction and plasma renin concentration in the present series suggests that suppression of renin activity is due to an increased intravascular pressure at the level of the juxtaglomerular cells.

The standard stimulus used in this study to provoke renin release was rather weak, because restriction of salt intake was only moderate. However, renin levels remained relatively low when a much stronger stimulus (tilting to 45°) was used. We feel that the 45° tilt is a more standardized procedure than the upright position because of differences in calf muscle contractions in the latter. In most experimental protocols conditions are not clearly defined. Quiet walking causes the cardiac output to rise above the level in the prone posture (Wang, Marshall & Shepherd, 1960). We therefore prefer the passive 45° tilt as a standard procedure.

It could be argued that some of our patients have primary hyperaldosteronism. Even if this were the case in one or two patients, this would not be pertinent to our argument that a relationship exists between renal haemodynamics, particularly filtration fraction, and plasma renin.

The significance of this finding is that plasma renin may be related to the stage of hypertensive disease. This hypothesis is supported by the correlation which could be demonstrated between variability of arterial blood pressure, as defined in a previous study from our department (Birkenhager et al., 1968), and plasma renin concentration.

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REFERENCES


