Plasma renin levels and systemic haemodynamics in essential hypertension

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Summary
1. Plasma renin concentration, intra-arterial pressure, cardiac output and total peripheral resistance have been studied in 50 patients with essential hypertension and normal renal function.  
2. Total peripheral resistance and plasma renin were negatively correlated ($r = -0.45$), indicating that 'high-renin' essential hypertension is not necessarily associated with arteriolar vasoconstriction.  
3. The inverse relation between mean arterial pressure and plasma renin ($r = -0.46$) suggests a role for the renal baroreceptor mechanism in the suppression of renin in 'low-renin' hypertension.  
4. Cardiac output was positively related to plasma renin concentration ($r = +0.42$).  
5. Multiple regression analysis indicates that the described relationships were independent of age.

Key words: arterial pressure, cardiac output, essential hypertension, renin, total peripheral resistance.

Introduction
The bipolar vasoconstriction-volume analysis of hypertension postulates that arteriolar vasoconstriction is responsible for the blood pressure elevation in patients with 'high-renin' essential hypertension and that low renin values indicate a volume-expanded state with relatively dilated arterioles (Laragh, 1973). However, no haemodynamic measurements have been presented to support this hypothesis. The present paper tests the application of the vasoconstriction–volume analysis to essential hypertension, by studying the relation between plasma renin concentration, total peripheral resistance, arterial pressure and other haemodynamic variables. Since it is not possible to measure arteriolar vasoconstriction and dilatation directly in humans, the total peripheral resistance, calculated from mean arterial pressure and cardiac output, has been used as a measure of overall arteriolar vasomotor tone.

Patients and methods
Fifty white hypertensive patients (29 men and 21 women), aged 20–65 years (mean: 42.6, SD 11.0, years), mean weight 70.5 (SD 13.0) kg, were studied. None was judged to have secondary hypertension on the basis of history, physical examination and appropriate laboratory tests. Intravenous pyelogram was performed in all, and renal arteriography if indicated. Severity of hypertension was assessed by the World Health Organisation criteria. Uncomplicated hypertension was present in 23 patients (stage I), left ventricular hypertrophy on ECG and/or eye-fundus grade 2 (Keith-Wagener) in 19 (stage II). The severity was classified as stage III in eight patients, because of ECG criteria of an old myocardial infarction in two, a cerebrovascular accident with recovery.
in two, and an eye-fundus grade 3 in four. None
had renal failure or heart failure.

The patients were taken into the hospital and
received a diet containing 130 mmol of sodium/
day, which was checked by the analysis of
24 h urine specimens. In patients receiving
therapy, treatment had been stopped at least
3 weeks before admission; the patients in
whom the severity was classified as stage III
were not on treatment when referred to our
hospital. None of the female patients was
taking oral contraceptive drugs.

The patients were in hospital for at least 4
days before the study. Blood for determination
of plasma renin concentration was withdrawn
at 08.00 hours, recumbent, before rising.
Plasma renin concentration was determined by
the method of Skinner (1967), but the generated
angiotensin I was measured by radioimuno-
assay (Lijnen, Amery & Fagard, 1976). The
normal range in our laboratory was 6.2-19.3
pmol h$^{-1}$ ml$^{-1}$. Plasma renin concentration
was related to renin activity (Vallotton, 1971)
in 84 plasma samples of hypertensive patients,
of whom 30 were on a daily sodium intake of
130 mmol, and 54 were sodium volume-
depleted by low-sodium diet and chlorthalidone
(50 mg daily for 3–5 days). The relation be-
tween plasma renin concentration and renin
activity was significant in the total group
($r = +0.84; P<0.001$) as well as in the sodium-
replete patients ($r = +0.59; P<0.001$) (Fig. 1).

Haemodynamic measurements were carried
out between 09.00 and 10.00 hours in the labora-
tory, where room temperature was 18–22°C
and humidity 40–60%. The brachial artery
was punctured with a Teflon needle (Dameco
model, 1.10 mm by 82 mm) to measure intra-
arterial pressure and for sampling of arterial
blood. A venous catheter (Swan–Ganz 93.110.
5F) was introduced in the antecubital vein and
positioned in the pulmonary artery for sampling
of mixed venous blood. After introduction of
the catheter, uptake of oxygen was measured
continuously by the open-circuit method; oxygen
was determined by a paramagnetic
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Gas analyser (Sirengnost, Siemens). The brachial artery pressure was registered on a recorder (Mingograph 81) with an Elema-Schonander EMT 34 pressure transducer. Cardiac output was determined by the direct-oxygen Fick method 30 min after introduction of the catheters, and expressed as litres/min, and as l min\(^{-1}\) m\(^{-2}\) (cardiac index) for comparisons of the results (body surface area ranged from 1·43 to 2·20 m\(^2\)). Total peripheral resistance was calculated from mean arterial pressure and cardiac output, and is expressed as kPa l\(^{-1}\) s (10\(^{-1}\) dynes s cm\(^{-5}\)) and also from mean pressure and cardiac index (expressed as kPa l\(^{-1}\) s m\(^{-1}\)). Heart rate was recorded from the ECG. Stroke volume (ml) and stroke index (ml/m\(^2\)) were calculated from cardiac output (index) and heart rate.

Results

Regression equations and correlation coefficients, obtained by regression analysis of the data, are given in Table 1.

Plasma renin concentration

Plasma renin concentration ranged from 2·6 to 46·6 pmol h\(^{-1}\) ml\(^{-1}\). Its distribution curve was positively skewed but was Gaussian for log plasma renin concentration (mean 1·040, SD 0·295). In 12 patients plasma renin concentration was <6·2 pmol h\(^{-1}\) ml\(^{-1}\) and ≥19·3 pmol h\(^{-1}\) ml\(^{-1}\) in 10. log Plasma renin concentration tended to decrease with age, but the correlation was not significant (Table 1).

Systemic haemodynamics

Mean intra-arterial pressure ranged from 108 to 180 mmHg, cardiac output from 3·14 to 11·49 l/min, cardiac index from 1·99 to 6·18 l min\(^{-1}\) m\(^{-2}\), calculated total peripheral resistance from 75·2 to 346·5 kPa l\(^{-1}\) s, and resistance index from 140·0 to 546·4 kPa l\(^{-1}\) s m\(^{-1}\). Heart rate averaged 81·6 (SD 13·0) beats/min, and mean creatinine clearance was 82·4 (SD 20·6) ml min\(^{-1}\) 1·73 m\(^{-2}\).

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Mean intra-arterial pressure (Fig. 2), systolic

| Table 1. Regression equations between age, log plasma renin concentration and systemic haemodynamics |
|---------------------------------|---------------------------------|-------------------------------|-----------------|
|                                 |                                 | Regression equation           | r               | P                 |
| log PRC (pmol h\(^{-1}\) ml\(^{-1}\)) |                                 |                               |                 |                   |
| MAP (mmHg)                      | 163·0 – 25·3x                   | –0·46                         | <0·001          |
| SAP (mmHg)                      | 230·3 – 38·8x                   | –0·47                         | <0·001          |
| DAP (mmHg)                      | 120·1 – 15·3x                   | –0·37                         | <0·01           |
| TPR (kPa l\(^{-1}\) s)          | 296·8 – 102·5x                  | –0·45                         | <0·001          |
| TPR(l) (kPa l\(^{-1}\) s m\(^{-2}\)) | 506·5 – 170·8x                  | –0·48                         | <0·001          |
| CO (l/min)                      | 3·59 – 2·62x                    | +0·42                         | <0·01           |
| CI (l min\(^{-1}\) m\(^{-2}\))   | 2·32 – 1·23x                    | +0·38                         | <0·01           |
| SV (ml)                         | 38·3 – 39·3x                    | +0·46                         | <0·001          |
| SI (ml/m\(^2\))                 | 25·8 – 18·2x                    | +0·44                         | <0·01           |
| HR (min\(^{-1}\))              | 85·1 – 3·4x                     | –0·08                         | >0·1            |
| C\(_{\text{creatinine}}\) (ml min\(^{-1}\) 1·73 m\(^{-2}\)) | 82·6 – 0·2x                    | 0·00                          | >0·1            |
| Age (years)                     |                                 |                               |                 |                   |
| log PRC                         | 1·234 – 0·005x                  | –0·17                         | >0·1            |
| MAP (mmHg)                      | 128·4 – 0·19x                   | +0·13                         | >0·1            |
| SAP (mmHg)                      | 160·1 – 0·70x                   | +0·32                         | <0·05           |
| DAP (mmHg)                      | 113·5 – 0·22x                   | –0·19                         | >0·1            |
| TPR (kPa l\(^{-1}\) s)          | 75·39 – 2·71x                   | +0·44                         | <0·01           |
| TPR(l) (kPa l\(^{-1}\) s m\(^{-2}\)) | 152·54 – 4·1x                   | +0·43                         | <0·01           |
| CO (l/min)                      | 9·42 – 0·073x                   | –0·43                         | <0·01           |
| CI (l min\(^{-1}\) m\(^{-2}\))   | 5·13 – 0·036x                   | –0·41                         | <0·01           |
| SV (ml)                         | 106·4 – 0·65x                   | –0·28                         | <0·05           |
| SI (ml/m\(^2\))                 | 57·8 – 0·31x                    | –0·28                         | <0·05           |
| HR (min\(^{-1}\))              | 90·7 – 0·21x                    | –0·18                         | >0·1            |
and diastolic pressures (Table 1) were inversely related to log plasma renin concentration. Fig. 3 shows the negative relationship between total peripheral resistance index and log plasma renin concentration, which is similar for total peripheral resistance (Table 1). Cardiac index (Fig. 4) and output (Table 1) were highest in the higher renin patients, although heart rate was not related to log plasma renin concentration. Also creatinine clearance was not related to log plasma renin concentration (Table 1).

Age and systemic haemodynamics

Systolic intra-arterial pressure was significantly related to age; diastolic and mean arterial pressure were not. Resistance (index) and age were positively correlated, and negative relationships were found between cardiac output (index) and age, and stroke volume (index) and age (Table 1).

Plasma renin, age and systemic haemodynamics

To examine the possibility that the relationships between plasma renin concentration and the haemodynamic variables were influenced by age, multiple regression analysis was used with log plasma renin concentration (PRC) and age as independent variables. The following equations were obtained (partial correlation coefficients are given in parentheses).
For mean arterial pressure:

\[ 159.1 - 24.84 \log \text{PRC} (r = -0.45; \ P = 0.001) + 0.08 \text{years (} r = +0.06; \ P > 0.1) \]

For total peripheral resistance index:

\[ 336.4 - 149.0 \log \text{PRC} (r = -0.45; \ P = 0.001) + 3.46 \text{years (} r = +0.40; \ P < 0.01) \]

For cardiac index:

\[ 3.85 + 1.03 \log \text{PRC} (r = +0.34; \ P < 0.05) - 0.031 \text{years (} r = -0.38; \ P < 0.01) \]

The partial regression coefficients for arterial pressure, resistance index and cardiac index, in relation to log plasma renin concentration, are close to the single regression coefficients given in Table 1.

Discussion

The plasma renin values of subjects with essential hypertension have been found to be within the range observed in normotensive subjects in only about 60% of patients (Brunner, Laragh, Baer, Newton, Goodwin, Krakoff, Bard & Bühler, 1972). In the present study we did not subdivide the patients into three subgroups according to plasma renin, because, first, it has not been definitely established that these groups correspond to three different entities, and, secondly, different methods for subclassifying patients do not identify exactly the same patients in the three subgroups (Woods, Pittman, Pulliam, Werk, Waidir & Allen, 1976). Instead the data were analysed by regression analysis.

The present study tests one aspect of the vasoconstriction–volume analysis of essential hypertension, which suggests that arteriolar vasoconstriction is responsible for the blood pressure elevation in patients with 'high-renin' essential hypertension, and relatively dilated arterioles in 'low-renin' hypertension (Laragh, 1973). Arteriolar vasoconstriction and dilatation cannot, however, be measured directly in humans. Total peripheral resistance (index), derived from mean arterial pressure and cardiac output (or cardiac index) has been used for studying the vasomotor tone of the arterioles, though it does not distinguish between the different vascular beds, nor give information on the underlying mechanisms, which may represent both structural change and the effects of circulating humoral agents. The present analysis of sodium-replete essential hypertensive subjects with normal renal function shows that the patients with the lowest renin concentration have a high total peripheral resistance (index), whereas this is lowest in patients with higher renin concentration (Table 1; Fig. 3). The relation holds at any age. This is in striking contrast to the suggestion that marked arteriolar vasoconstriction is responsible for the blood pressure elevation in 'high-renin' essential hypertension, and that arteriolar dilatation accompanies low renin values. The present conclusions do not, however, bear on secondary forms of hypertension, essential hypertension with impaired renal function, nor on malignant hypertension.

The inverse relation between arterial pressure and plasma renin (Fig. 2) even suggests that arterial pressure is a determinant of plasma renin in essential hypertension. Indeed, it is not clear how lower plasma renin values can lead to higher pressures, and a more likely explanation of the inverse correlation is that the elevated arterial pressure suppresses renal renin secretion through the renal baroreceptor mechanism. The suggestion that, in 'low-renin' essential hypertension, renin release is suppressed by an increase in intravascular pressure at the level of the juxtaglomerular cells has been put forward by Schalekamp, Schalekamp-Kuyken & Birkenhager (1970) and Birkenhager, Schalekamp, Krauss, Kolsters, Schalekamp-Kuyken, Kroon & Teulings (1972), and was based on the finding of an inverse relation between filtration fraction and plasma renin concentration in benign essential hypertension. Since the elevated systemic arterial pressure is transmitted throughout the renal vascular bed in essential hypertension (Löwenstein, Beranbaum, Chasis & Baldwin, 1970), the observation of a higher arterial pressure in 'low-renin' patients is also consistent with the hypothesis that the renal pressure feedback control mechanism of renin secretion is at least partly responsible for the low renin values. An inverse relation between arterial pressure and plasma renin has been found in some studies (Bloomfield, Gould, Cangiano & Vertes, 1970; Tuck, Williams, Cain, Sullivan & Dluhy, 1973; Stroobandt, Fagard, Roussel-Deruyck & Amery, 1973; Kolsters, Schalekamp, Birkenhager & Lever, 1975), but not in others (Dustan, Tarazi & Frohlich, 1970; Birkenhager et al., 1972;
Brunner et al., 1972; Wisenbaugh, Garst, Hull, Freedman, Matthews & Hadady, 1972; Lucas, Occobock, Stern, Haskell, Holzwarth, Sozen, Wood & Farquhar, 1974). The selection of patients and methods of measuring plasma renin and blood pressure may account for this discrepancy together with several factors known to affect plasma renin values (Davis, 1973) and arterial pressure, such as sodium balance, posture and time of the day when samples were obtained. We attempted to relate 'basal' plasma renin concentration, obtained at 08.00 hours in recumbent patients ingesting 130 mmol of sodium/day, to systemic haemodynamics in similar conditions. Also age has to be considered since a decrease of plasma renin with age has been reported by several authors (Birkenhager et al., 1972; Tuck et al., 1973; Woods et al., 1976), but not by others (Jose, Crout & Kaplan, 1970; Wisebaugh et al., 1972). In our study plasma renin concentration tended to be lower in the older patients. Multiple regression analysis indicated, however, that the inverse relation between plasma renin concentration and arterial pressure was independent of age. It thus seems that the height of the arterial pressure is a determinant of the plasma renin level in essential hypertension. This finding may contribute to the understanding of abnormally low renin values present in approximately 25% of hypertensive subjects. This is consistent with the absence of persuasive evidence that 'low-renin' essential hypertension is a distinct disease entity (Dunn & Tannen, 1974), since normal plasma and extracellular fluid volumes have been observed in 'low-renin' hypertension (Schalekamp, Beevers, Kolsters, Lebel, Fraser & Birkenhager, 1974). Sympathetic nervous underactivity has recently been demonstrated as a common feature of 'low-renin' essential hypertension and has also been interpreted as a secondary phenomenon, related to the severity of the hypertension (Esler, Randall, Bennett, Zweifler, Julius, Rydelek, Cohen & DeQuattro, 1976). Defective nervous stimulation of renin release may thus be another determinant of the low plasma renin value.

It is probable that about 20% of our patients have abnormally elevated plasma renin values. Their mean arterial pressure was in the lower range of the total group (Fig. 2), and cardiac output (index) (Fig. 4) and stroke volume (index) (Table 1) were increased. Calculated total peripheral resistance (index) was within normal limits (Fig. 3), which has been considered 'inappropriately' normal because of its inability to decrease in response to the high cardiac output (Julius & Conway, 1968; Wallace, 1975). Heart rate was not related to plasma renin concentration (Table 1), but was abnormally high in the hypertensive patients; this has been reported previously (Frohlich, Tarazi, Ulrych, Dustan & Page, 1967) and attributed to parasympathetic inhibition (Wallace, 1975). Patients with higher renin values tended to be younger (Table 1). This pattern may suggest that these patients, with normal renal function, represent individuals with 'early' hypertension and overactivity of the autonomic nervous system. Since patients with renal hypertension, with essential hypertension and renal failure, and with malignant hypertension were not studied, the higher renin patients of the present study represent a selected group and the results may not apply to the other categories. An increased cardiac index has been shown before in relation to high plasma renin values (Dustan et al., 1970), whereas peripheral plasma renin was greater in a subgroup of hypertensive patients with an enhanced sympathetic nervous activity (Esler & Nestel, 1973). Sympathetic overactivity may explain the higher plasma renin values (Vander, 1965), the higher stroke volume and cardiac output (Guyton, Jones & Coleman, 1973). The observation that heart rate is elevated but not different from patients with 'normal' and 'low-renin' essential hypertension may be due to the observed parasympathetic defect in heart-rate control in essential hypertensive patients (Wallace, 1975).

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