Renal haemodynamics and plasma renin in patients with essential hypertension

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Summary

1. Blood pressure, glomerular filtration rate (GFR) and renal plasma flow (RPF) were measured in twenty-three patients with essential hypertension and in twenty-one control subjects. Plasma renin concentration was measured in all the hypertensive patients and in fifteen control subjects.

2. GFR and RPF were similar in the hypertensive group and in the control group, whereas the renal vascular resistance was significantly higher in the hypertensive patients. GFR and RPF decreased with increasing blood pressure in both groups. Increasing age induced a further reduction in GFR and RPF in the control subjects but not in the hypertensive patients.

3. Plasma renin concentration in the hypertensive group did not differ from that in the control subjects. The concentration was not correlated to age in either the hypertensive or normal group.

4. Plasma renin index was positively correlated to GFR and RPF and inversely correlated to filtration fraction and renal vascular resistance.

5. It is concluded that GFR and RPF depend on blood pressure in both hypertensive patients and normotensive control subjects. In contrast to the control group, the age effect was negligible in the hypertensive group. It is suggested that renin release depends on changes in renal vascular resistance in the arterioles at the glomerulus and the results support the baroreceptor theory of renin release.

Key words: age, essential hypertension, renal haemodynamics, renin.

Introduction

In many patients with essential hypertension renal haemodynamics are abnormal. A decrease in renal plasma flow and an elevation in both filtration fraction and renal vascular resistance have been demonstrated in earlier studies (Goldring, Chasis, Ranges & Smith, 1941; Ladefoged, 1968; Hollenberg, Epstein, Basch, Cough, Hickler & Merrill, 1969). Several patients with uncomplicated essential hypertension have, however, normal renal haemodynamics (Hollenberg, 1972).

It is well known that plasma renin activity and plasma renin concentration are within normal limits in most patients with essential hypertension. In about 20-30% of patients, however, plasma renin activity is abnormally high or low (Laragh, Baer, Brunner, Bühler, Sealy & Vaughan, 1972).

It has been reported that plasma renin concentration correlates positively with RPF(1) and inversely with filtration fraction and renal vascular resistance in patients with essential hypertension (Schalekamp, Schalekamp-Kuyken & Birkenhäuser, 1970; Molzahn, Dissman, Halim, Lohmann & Oelkers, 1972). Contrary to these results, Hollenberg et al. (1969) found that renin secretion increased in parallel to decreases in renal blood flow. This discrepancy prompted us to study renal haemodynamics and plasma renin concentration simultaneously in patients with essential hypertension.

(1) Abbreviations: RPF, renal plasma flow; GFR, glomerular filtration rate.
Materials and methods

Plasma renin concentration, GFR and RPF were measured in twenty-three hypertensive patients consecutively admitted to our outpatient clinic. The mean age was 41 years (range 21–59 years). There were sixteen males and seven females. All patients had essential hypertension. Aortic coarctation and diseases of the renal arteries or suprarenal glands were excluded by clinical examination, measurement of serum electrolytes, creatinine clearance, intra-venous urography and the renal excretion of adrenaline, noradrenaline and vanillyl mandelic acid. None of the females was taking oral contraceptive tablets. Thirteen patients had never been treated with antihypertensive medicaments. In the remaining ten patients antihypertensive treatment had been withdrawn at least 4 weeks before the investigation. Four patients had no retinal changes, whereas five had grade I changes, thirteen had grade II changes and one had grade III (grading of Keith–Wagner). In twelve patients hypertrophy or strain was seen on electrocardiography. Creatinine clearance was 103 ml/min ± 22 (1 sd) and none of the patients had proteinuria.

Two groups of normotensive healthy control subjects were studied: (1) GFR and RPF were measured in twenty-one control subjects (mean age 42 years, range 23–73 years: thirteen males and eight females); (2) plasma renin concentration was measured in fifteen control subjects (mean age 28 years, range 17–58 years: eleven males and four females). All of the patients and control subjects were on a liberal sodium intake. They were all informed of the nature of the tests before the start of the study and all agreed to participate.

Blood pressure was measured after at least 1 h rest in the supine position. Blood pressure measurements were carried out with the same sphygmomanometer and were measured several times on each occasion. The lowest reading has been used.

Blood samples for determination of plasma renin concentration were obtained by venous puncture in the morning, at 09.00 hours, immediately after the blood pressure measurements and before the clearance studies. The subjects had fasted for approximately 8 h. Plasma renin concentration was measured by the method described by Giese, Jørgensen, Nielsen & Lund (1970). This involves the radio-immunoassay of angiotensin I after previous dialysis of plasma, incubation at 37°C and pH 7.4 with and without addition of an internal standard of human renin and extraction of the angiotensin I produced. The Medical Research Council (Division of Biological Standards, National Institute for Medical Research, Mill Hill, London) has made Renin (Human) 68/356 available to us. Plasma renin concentrations are given in Goldblatt units/ml of plasma, the above-mentioned standard human renin being used as reference. Plasma renin index was calculated by dividing renin concentration by the urinary Na/K ratio. The calculation of the index was performed in order to smooth out variations of plasma renin concentration due to differing sodium and potassium balance. The urinary Na/K ratio is inversely related to plasma renin concentration as shown by Brown, Davies, Lever & Robertson (1964).

GFR and RPF were measured by a constant infusion technique. The reference substances employed were [131I]hippuran and [125I]iothalamate and were obtained from The Radiochemical Centre (Amersham, Bucks., U.K.). The labelled substances were stored in the dark at 4°C for a maximum of 2 weeks. The amount of free iodine was less than 2%. A priming dose was given so that the radioactivity in plasma was between 300 and 600 c.p.m./ml for [131I]hippuran and 800 and 1600 c.p.m. for [125I]iothalamate. Plasma radioactivity was kept stable by constant infusion with aid of a Holter infusion pump. The measurement of radioactivity was performed in a dual-channel analyser to a statistical accuracy of less than 1%. Each patient was examined for three or four clearance periods each of approximately 30 min. Blood specimens were taken 5 min before the middle of each period. Bladder catheterization was not performed. The patients urinated in either the standing or sitting positions. In the course of 1 h immediately before collection of urine 1000 ml of water was given to each patient, in addition to a further 500 ml/h during the clearance periods. Coefficient of variation between the clearance periods was less than 10% for all patients. Earlier investigations (Mogensen, 1971; Skov & Hansen, 1974) have shown that [131I]hippuran and [125I]iothalamate are reliable substances for the measurements of RPF and GFR.

The Mann–Whitney test was used for comparison of mean values. Regression analyses were performed according to the method described by Nie, Bent & Hull (1970).
Results

Renal haemodynamics

Table 1 shows mean renal haemodynamic values and blood pressure in the control subjects and in the hypertensive patients.

Blood pressure was considerably elevated in the hypertensive group in comparison with the control patients. GFR, RPF and filtration fraction were similar in the two groups, so that, necessarily, the renal vascular resistance was significantly higher in the hypertensive group ($P<0.01$).

In the control subjects, there was a significant negative correlation between age and both GFR ($r = -0.715, n = 21, P<0.001$) and RPF ($r = -0.760, n = 21, P<0.001$); mean blood pressure was positively correlated with age ($r = 0.803, n = 21, P<0.001$) and negatively with GFR ($r = -0.636, n = 21, P<0.01$) and RPF ($r = 0.674, n = 21, P<0.001$).

Multiple regression analysis was carried out with the GFR or RPF as the dependent variables and age and mean blood pressure as the two independent variables. The partial regression coefficients were statistically significant between GFR and age [$b_1 = -0.252 \pm 0.545$ (SEM), $n = 21, P<0.001$] and between GFR and mean blood pressure [$b_2 = 2.036 \pm 0.247$ (SEM), $n = 21, P<0.001$]. The partial regression coefficients were also statistically significant between RPF and age [$b_1 = 9.499 \pm 2.143$ (SEM), $n = 21, P<0.001$] and between RPF and mean blood pressure [$b_2 = 8.113 \pm 0.970$ (SEM), $n = 21, P<0.001$].

In the hypertensive group no correlation was found between age and GFR ($r = -0.380, n = 23, P>0.05$) or RPF ($r = -0.379, n = 23, P>0.05$). The mean blood pressure was correlated to age ($r = 0.487, n = 23, P<0.05$) and also to GFR ($r = -0.493, n = 23, P<0.05$) and RPF ($r = -0.539, n = 23, P<0.01$).

Multiple regression analysis was also performed in the hypertensive group using the same dependent and independent variables as were used in the control group. The partial regression coefficients between GFR and age were not significant [$b_1 = -1.002 \pm 0.513$ (SEM), $n = 23, P>0.05$], whereas the partial regression coefficients between GFR and mean blood pressure were significant [$b_2 = 1.022 \pm 0.157$ (SEM), $n = 23, P<0.001$]. The partial regression coefficient between RPF and age was not significant [$b_1 = -4.125 \pm 2.163$ (SEM), $n = 23, P>0.05$], whereas the partial regression coefficient between RPF and mean blood pressure was significant [$b_2 = 3.868 \pm 0.663$ (SEM), $n = 23, P<0.001$].

Plasma renin concentration

The mean plasma renin concentration was 37 μunits (Goldblatt)/ml ± 16 (1 SD) in the control subjects. In the hypertensive group this was 31 μunits/ml ± 9 (1 SD) and was not different from the control group.

No relationship could be demonstrated between plasma renin concentration or plasma renin index and age.

Relation between renal haemodynamics and plasma renin index

In Fig. 1 a significant correlation is demonstrated between plasma renin index and RPF ($r = 0.613,$...
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FIG. 1. Relation between plasma renin index and renal plasma flow in patients with essential hypertension.

\( n = 23, \ P < 0.01 \). The index was also positively correlated to GFR \( (r = 0.447, n = 23, P < 0.05) \) and inversely to filtration fraction \( (r = -0.483, n = 23, P < 0.05) \) and renal vascular resistance \( (r = -0.514, n = 23, P < 0.05) \).

No correlation could be demonstrated between RPF and plasma renin concentration \( (r = 0.123, n = 23, P > 0.05) \).

Discussion

In the present study normal values of GFR, RPF and filtration fraction were found in the hypertensive patients. Renal vascular resistance, however, was considerably elevated.

Goldring et al. (1941) and Ladefoged (1968) demonstrated a reduction in RPF and an increase in filtration fraction in patients with essential hypertension. Renal haemodynamics vary greatly, however, in patients with essential hypertension and are often within the normal range (Hollenberg, 1972). It is likely that this large variation is due to differences in the severity of the hypertension-induced abnormalities in the renal vessels in the patients examined.

The elevated renal vascular resistances we have observed are in good agreement with results of earlier investigations (Goldring et al., 1941; Löwenstein, Beranbaum, Chasis & Baldwin, 1970). The exact nature of the increased renal vascular resistance is obscure. Structural changes have been demonstrated (Ljungqvist, 1962), but functional factors also seem important, since both pyrogen (Goldring et al., 1941) and loading with saline (Löwenstein et al., 1970) are able to reduce renal vascular resistance. It is conceivable that both morphological alterations and changes in the vascular tone in the renal vessels are important. The studies of Folkow (1971) and Hollenberg, Adams, Solomon, Chenitz, Burger, Abrams & Merrill (1975) have shown that functional renal vascular abnormalities are important in patients with mild essential hypertension, whereas organic vascular change is associated with severe degrees of hypertension.

The renal vascular abnormalities in essential hypertension have been interpreted as reflecting the effects of an increased intravascular pressure on a normal ageing process (Hollenberg, 1972). Our results show that GFR and RPF decrease with increasing blood pressure in both hypertensive and control subjects. On multiple regression analysis increasing age was shown to be associated with a further reduction in GFR and RPF in the control subjects. In the hypertensive group, however, the ageing effect is negligible, and changes in GFR and RPF are mainly determined by the effect of the increased blood pressure.

It is well known that plasma renin concentration is often elevated in hypertension associated with renovascular disease and in malignant hypertension. Most patients with essential hypertension, however, have normal plasma renin concentration, as was the case with the patients in our study. We found no relation between blood pressure and plasma renin concentration and this agrees with the results of Lucas, Holzwarth, Oocobock, Sozen, Stern, Wood, Haskel & Farquhar (1974).

Plasma renin concentration was not related to age in either the control or the hypertensive group. This contrasts with earlier reports which describe a progressive decline in plasma renin activity with increasing age in both normal subjects and hypertensive patients (Sambhi, Crane & Genest, 1973). This discrepancy, however, could be attributed to the fact that our study group include fewer patients with a narrower age range.

In the present study a relationship was demonstrated between plasma renin index and RPF, filtration fraction and renal vascular resistance. RPF was positively and filtration fraction and renal vascular resistance were inversely correlated to plasma renin index, suggesting that an increase of filtration frac-
tion and renal vascular resistance suppresses renin release. According to earlier views (Goldring et al., 1941), an increase in filtration fraction and renal vascular resistance in patients with essential hypertension was supposed to be due to an elevated resistance in the efferent arterioles. Recently, however, it has been shown (Löwenstein et al., 1970) that renal vascular resistance is also increased in the preglomerular vessels. Renin release may thus be dependent on resistance in the afferent arterioles at the level of the juxtaglomerular cells.

Our results concerning the relationship between RPF and plasma renin index agree with earlier studies (Schalekamp et al., 1970; Molzahn et al., 1972), but contrast with Hollenberg et al. (1969), who found a low rate of renin secretion in patients with uncomplicated essential hypertension with a normal renal blood flow, as determined by $^{133}$Xe wash-out. In patients with essential hypertension and moderate hypertensive disease, however, the renal blood flow was reduced in parallel to an elevation of the rate of renin secretion. The differences between the results of Hollenberg et al. (1969) on the one hand and those of Schalekamp et al. (1970) and ours on the other, seem difficult to explain. In a later study (Schalekamp, Krauss, Kolsters, Schalekamp & Birkenhäger, 1973), however, it was shown that an inverse relationship between renal vascular resistance or filtration fraction and plasma renin concentration does not exist when renal vascular resistance is very high. The difference in the conclusions may thus be due to differences in renal vascular resistance in the patients in the different studies.

Apart from renal haemodynamics, plasma renin concentration is influenced by several other factors, e.g. posture and salt balance (Cohen, Grim, Conn, Blough, Guyer, Kem & Lucas, 1971; Laragh et al., 1972). All the measurements in the present study were made after the subject had rested for at least 1 h in the supine position. Brown et al. (1964) have shown a significant correlation between the urinary Na/K ratio and plasma renin activity in subjects on different sodium and potassium intakes.

The present results suggest that using the plasma renin index may be a way of allowing for the variation in plasma renin concentration due to differences in sodium and potassium intakes.

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References


