Plasma Renin Levels and Vascular Complications in Hypertension

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Summary

Plasma renin levels, measured in 39 untreated patients in 1967, under conditions of sodium loading and sodium depletion have been related to the incidence of stroke and myocardial infarction. Renin levels were not significantly different in patients with or without vascular complications. Out of 13 patients with persistently low renin levels 6 had suffered either a stroke or a myocardial infarction and 7 had not. Plasma renin levels were also measured in 116 treated hypertensive patients. There was no relation between plasma renin level and vascular complications. It is concluded that levels of plasma renin are not a reliable index of the probability of hypertensive patients suffering a stroke or myocardial infarction.

Introduction

The claim has recently been made that plasma renin levels may be useful in distinguishing hypertensive patients at risk from vascular disease from those with a smaller risk. Brunner *et al.* (1972) found that patients with high or normal levels of plasma renin in relation to sodium excretion had a higher incidence of stroke or myocardial infarction than patients with low levels. They concluded that patients with low renin levels appeared to be protected from these incidents and claimed that plasma renin activity could be regarded as a potential risk factor in hypertension.

About 25-30% of patients with essential hypertension have been reported to have low levels of plasma renin which fail to increase on sodium depletion (Creditor and Loschky, 1968; Helmer and Judson, 1968; Jerums and Doyle, 1969). While the reason for this low renin activity in these patients is not clear, the possibility that these patients may in some way be protected from vascular disease would be important if confirmed.

We report here studies on the relation between plasma renin levels and vascular complications of hypertension.

Subjects and Methods

Fifty patients with essential hypertension were studied in 1967 (Jerums and Doyle, 1969). Briefly, untreated patients were admitted to hospital, given a full diet with added sodium

chloride (100 mEq) daily, and kept in bed for five days. On the fifth day urinary sodium output, plasma renin, and aldosterone were measured. The patients were then given a diet containing 10 mEq of sodium for four days and allowed out of bed. On the fifth day of sodium depletion measurements of plasma renin and urinary sodium were repeated. Plasma renin was measured by a biological assay using the method of Skinner (1967). Thirty-nine of these patients were traced in August 1972 for follow-up; the remaining 11 could not be contacted. Of the 39 patients 19 had never had either a stroke or a myocardial infarction before or after the 1967 study, and these remained alive and well. Of the remaining 20 patients 15 had suffered either a stroke or a cardiac infarction before the 1967 study. Ten of these had a further stroke or myocardial infarction between 1967 and 1972, and eight of the 15 died. In addition, five patients had a stroke or myocardial infarction after the study, and of these one died.

In a separate group of 116 patients plasma was drawn for estimation of plasma renin concentration during routine visits to the hypertensive clinic for assessment of the effects of therapy. At the same time 24-hour specimens of urine were collected and the sodium excretion was measured. Plasma renin concentration in this group was measured by radioimmunoassay (Mendelsohn *et al.*, 1971), which gives a different numerical value to bioassay but is similar in reproducibility.

Results

Details of the two groups of patients—20 with vascular incidents and 19 without—are given in table I. In the original study 14 of the 50 patients had persistently low levels of plasma renin which failed to rise after sodium depletion and when in the erect posture. Of the 39 patients available for follow-up 13 were in this low renin group. Of these, six were among the 20 who had had a stroke or a myocardial infarction. The remaining seven low renin patients were in the group of 19 without a stroke or myocardial infarction. Of the five patients who did not have vascular incident before the 1967 study but who subsequently developed one two were in the low renin group and three had normal renin levels.

The initial blood pressure levels in the patients with and without vascular incidents were almost identical; the mean levels of plasma renin concentration in the two groups when sodium loaded were 8.57 ± 1.25 (S.E.) ng/ml/hr in the group who had vascular incidents and 6.97 ± 1.04 ng/ml/hr in the group who had never had myocardial infarction or a stroke. The mean levels when sodium deplete were 14.99 ± 1.70 in the group with incidents and 12.91 ± 1.76 in the other group. In neither situation were the differences between the two groups statistically significant.

The larger group of 116 patients had estimations of plasma renin performed by radioimmunoassay. These patients were receiving treatment for hypertension. The results were very similar to those in the closely controlled untreated group. Thirty-three of the 116 patients had had a myocardial infarction or a stroke and 83 had not. In the former group the mean value for plasma renin was 2.89 ± 0.34 ng/ml/hr, while in the group without vascular complications the mean value was 2.88 ± 0.19 ng/ml/hr.

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TABLE I—Details of 39 Patients Who did or did not have Stroke

	M.	F.	Mean Age (years)	Mean Blood Pressure (mm Hg)	Mean P.R.C. (1)	Mean P.R.C. (2)	Low Renin*
Patients with vascular complications (n = 20)	14	6	65	213/128	8.57 ± 1.247	14.99 ± 1.70	6
Patients with no vascular complications (n = 19)	7	12	50	210/128	6.97 ± 1.04 (t = 0.987; N.S.)	12.91 ± 1.76 (t = 0.855; N.S.)	7

*Low renin refers to patients whose plasma renin levels were below 5 ng/ml/hr when sodium loaded and failed to rise when sodium depleted (Jerums and Doyle, 1969).
P.R.C.(1) = Plasma renin concentration after five days of sodium loading.
P.R.C.(2) = Plasma renin concentration after five days of low sodium diet.

An arbitrary classification into low, normal, and high renin groups was made in this series, taking the levels of plasma renin in relation to 24-hour sodium excretion. The results, shown in table II, indicate that almost 20% of both groups had low levels of plasma renin in relation to their sodium excretion. Low levels of plasma renin therefore appeared not to be a reliable index of the presence or absence of vascular complications.

TABLE II—Relation between High, Normal, and Low Plasma Renin Values and Vascular Complications in Treated Hypertensive Patients

	No. of Patients with Vascular Incidents	No. of Patients with no Vascular Incidents	Total
High renin (above 4.5 ng/ml/hr)	3	15	18
Normal renin (1.5–4.5 ng/ml/hr)	24	52	76
Low renin (below 1.5 ng/ml/hr)	6	16	22
Total	33	83	116

Discussion

These results do not support the claim that hypertensive patients with low plasma renin levels have an appreciably lower incidence of stroke or myocardial infarction than patients with normal or high values. The results obtained in untreated patients studied under closely controlled conditions of sodium balance, similar to those described by Brunner *et al.* (1972), indicate that low levels of plasma renin occurred as often in patients who had stroke or myocardial infarction as in those who had not, whether renin levels were measured before or after the incident. The patients in this group may have differed from those described by Brunner *et al.* Although they stated that patients with malignant hypertension or primary renal disease were excluded from their study they referred to a group of patients with high renin values who had "high diastolic blood pressures, hypokalaemia, azotaemia, proteinuria and severe vascular changes in the optic fundi." As they say, "in this setting it may not be surprising that cardiovascular complications were frequent." None of our patients had any of these manifestations. On the other hand, the incidence of low renin values in our patients was 28%, which agrees

closely with those reported by most other workers. It is particularly important that the incidence of vascular complications in this group was not different from that in the group as a whole.

The conclusions which can be drawn from the larger treated group are less clear-cut, for treatment may alter plasma renin levels in a variety of ways. It has been argued that treatment with hypotensive drugs which raise plasma renin levels may lead to an increased risk of vascular complications. Our data suggest that levels of plasma renin do not have prognostic significance in either treated or untreated patients.

It would be surprising if the level of plasma renin related to the incidence of vascular complications. Our results show that the incidence of both stroke and myocardial infarction was much commoner in men than in women in both series. In our larger series of patients 24 out of 59 men had vascular incidents, whereas only nine of the 57 women had them. There was, however, no sex difference in the renin levels. Moreover, if stroke and myocardial infarction shared a common risk factor of raised plasma renin it would have to be explained why drug treatment greatly reduces the incidence of stroke but not of myocardial infarction (Breckenridge *et al.*, 1970).

The possible relation between raised plasma renin levels and small blood vessel disease is less clear-cut. There is certainly evidence that high levels of plasma renin occur in malignant hypertension and in patients with fundal haemorrhages and exudates. It is not clear whether the high levels of plasma renin follow the arteriolar lesions in malignant hypertension or are a causative factor. The possibility remains that in this situation high levels of renin may aggravate arteriolar necrosis, even though there seems little evidence that it can be implicated in the pathogenesis of atheroma or of thrombotic vascular disease.

Requests for reprints should be addressed to Professor A. E. Doyle.

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