Renin in hypertension: how important as a risk factor?

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Summary: An analysis of the plasma renin levels in relation to the incidence of severe cardiovascular complications (coronary thrombosis, stroke, ruptured aortic aneurysm) was made in 325 patients with various types of hypertension. These patients had one to four measurements of plasma renin activity taken under standard conditions of sodium intake and posture in the period 1963-68. The follow-up was 5 to 10 years in the four groups of hypertensive patients (essential hypertension, malignant hypertension, hypertension secondary to renal parenchymatous disease and hypertension caused by, or associated with, renal artery obstruction). For all 325 patients, the incidence of such complications was 23.6, 20.4 and 44.7% in the low, normal and high renin groups. These findings are at variance with the claim that renin constitutes a serious risk factor in hypertensive patients, especially if it is isolated from other parameters such as the level of diastolic pressure, the adequacy of kidney function, the effectiveness of dietary and drug management of hypertension, and especially the presence or absence of atherosclerotic lesions of the large vessels at the time of the renin determination.

Résumé: *La rénine dans l'hypertension: son importance comme facteur de risque*

L'auteur a analysé le rapport existant entre les concentrations plasmatiques de rénine et la fréquence des complications cardiovasculaires sévères (thrombose coronaire, accident cardiovasculaire, anévrysme aortique déchiré) chez 325 malades souffrant de diverses formes d'hypertension. Chez ces malades, on avait procédé à au moins un et au maximum quatre dosages de la rénine plasmatique dans des conditions standards d'apport sodique et de position corporelle au cours de la période 1963-68. Chez les quatre groupes d'hypertendus (hypertension essentielle, hypertension maligne, hypertension secondaire à une néphrite parenchymateuse et hypertension causée par ou accompagnant une oblitération de l'artère rénale) les malades ont été suivis pendant une période de 5 à 10 ans. Chez les 325 malades, répartis en trois groupes au point de vue de la concentration de rénine (concentration faible, normale et élevée), la fréquence desdites complications a été respectivement 23.6, 20.4 et 44.7%. Ces constatations sont en désaccord avec la prétention que la rénine est un facteur de risque grave chez les hypertendus, surtout si on l'isole d'autres paramètres, comme le niveau de la tension diastolique, le caractère adéquat de la fonction rénale, l'efficacité du traitement diététique et médicamenteux de l'hypertension et enfin, la présence ou l'absence de lésions athéromateuses des gros vaisseaux au moment du dosage de la rénine.

In the issue of March 2, 1972 of the *New England Journal of Medicine* Brunner *et al* reported that, out of a total of 219 patients with essential hypertension seen five years after measurement of their plasma renin activity, those with low renin levels had not suffered myocardial infarction or stroke during this period, while the incidence was 11 and 14% respectively in the patients with normal or high renin levels. On the basis of these observations they suggested that "the renin mechanism may be implicated at least in the pathogenesis of these vascular complications of essential hypertension" and that "the plasma renin level may be a meaningful indicator for evaluating such risks".[1]

This report has major prognostic implications for hypertensive patients and for life insurance companies and has created a great deal of interest and controversy. In three recent issues of the *New England Journal of Medicine* three groups, Schalekamp and Birkenhäger[2] from Belgium, Amery, Stroobandt and Fagard[3] from the Netherlands and Mroczek, Finnerty and Catt,[4] have challenged the hypothesis of the authors that low renin protects patients with essential hypertension against strokes and myocardial infarctions.

In view of the interest and controversy created by this report, we wish to present findings from our Hypertension Clinic on this subject. A large number of patients have been studied for plasma renin activity by our group since Boucher *et al*[5] established the first accurate and specific method for measuring renin activity in 1963.

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Plasma renin activity was measured under standard conditions of sodium intake and posture in 325 patients with various types of hypertension, on one to four occasions during the period 1963 to 1968. The patients were divided into four subgroups: (a) 202 patients with essential hypertension, the diagnosis being made after exclusion of all known causes by means of a thorough clinical and biochemical (including plasma electrolytes) evaluation and renal function studies (including phenolsulfonphthalein excretion and creatinine clearance measurements and intravenous pyelography), all patients having normal renal arteriograms; (b) 8 patients with malignant hypertension characterized by papilledema, retinopathy and high diastolic pressure; (c) 53 patients with parenchymatous renal hypertension secondary to chronic glomerulonephritis, chronic pyelonephritis and polycystic kidney disease and (d) 62 patients with hypertension caused by, or associated with, renal artery stenosis, atherosclerotic in nature in almost all instances. The distribution of the patients of these four subgroups according to their plasma renin levels is analysed in Table I.

Patients were studied on the fourth day of a fixed sodium intake of either 135 or 10 mEq./day (potassium intake 90 mEq./day in both cases), in the recumbent position and after four hours of ambulation. The numbers of patients studied in each situation are set forth in Table II.

Boucher's method[5] was used for all renin activity determinations and results are expressed as nanograms of angiotensin I/litre of plasma/minute of incubation. In normal recumbent subjects on a sodium intake of 135 mEq./day the mean plasma level is 9.5 ng./l./min. with a range of 3 to 20. Low renin hypertensive patients were those with plasma renin activity levels below 3 and with absent or minimal response to the stimuli of upright posture and sodium restriction. Normal renin hypertensives were those with renin levels between 3 and 20 and with normal response to the same stimuli, and those with high renin were patients with levels greater than 20 ng./l./min.

Severe vascular complications are defined (irrespective of outcome, i.e. death or survival) as proved clinical and electrocardiographic myocardial infarction, cerebral strokes and ruptured aortic aneurysms.

Results

The overall results of the 5- to 10-year observation period in the total group of 325 hypertensive patients are shown in Table III. It can be clearly observed that the incidence of severe vascular complications in the low renin group is quite significant at 23.6%, although it is greater in the high renin group at 44.7%.

Table IV sets forth the clinical and biochemical data, the mean blood pressure and the relative incidence of the severe vascular complications in the 202 patients with essential hypertension. Again, it can be seen that the low renin, essential hypertension patients have a 24% incidence of severe vascular complications, significantly higher than in the normal renin group. The apparently high incidence of severe vascular complications in the high renin, essential hypertension group (66.7%) may be a result of the small number (6 only) of patients in this subgroup.

Similar data from the subgroup of eight patients with malignant hypertension are set forth in Table V. It is obvious that most of these patients were in severe renal failure with azotemia and elevated serum creatinine. With proper therapeutic management, the incidence of severe cardiac complications was low.

Table VI shows similar data from the subgroup of 53 patients with renal hypertension secondary to renal parenchymatous diseases. Several of these patients were in some degree of renal failure and the mean blood pressure was slightly higher in the high renin group than in the low and normal renin groups. The incidence of severe vascular complications is the same in the normal and high renin groups and still quite significant in the low renin group (17.6%).

The subgroup of patients with hypertension caused by, or associated with, renovascular stenosis, atherosclerotic in almost all patients, yields the most important and mean ingful data, underlining the greater significance of the presence of atherosclerotic lesions at the time of the renin determination than the renin value by itself. In this group of patients with well defined atherosclerotic lesions at the time of the renin determination, the incidence of severe vascular complications is about the same whether the patient had a low, normal or high renin determination (Table VII).

Discussion

Our results are in complete agreement with those reported by Amery, Stroobandt and Fagard,[3] Schalekamp and Birkenhäger,[2] Mroczek *et al*[4,6] and Kem *et al*,[7] and do not support the findings of Brunner *et al*.[1] The suggestion that the renin mechanism may be implicated in the pathogenesis of vascular lesions in essential hypertension

Table I—Plasma renin levels* in the four subgroups

No. of patients	Low (0-3)	Normal (3-20)	High (>20)	Total
Total	106	181	38	325
Essential HT	75	121	6	202
Malignant HT	2	4	2	8
Renal parenchymatous HT	17	26	10	53
HT associated with, or caused by, renal artery stenosis	12	30	20	62

*ng./l./min. (divided by 18 = ng./ml./hr.)

Table II—Plasma renin levels under varying conditions of sodium intake and posture

No. of patients	Low (0-3)*	Normal (3-20)*	High (>20)*	Total
Total	106	181	38	325
On 135 mEq. Na/day** Recumbent	103	169	36	308
After four hours ambulation	44	107	7	158
On 10 mEq. Na/day**	18	27	2	47

*ng/l./min.
**K intake constant at 90 mEq./day

Table III—Incidence of severe vascular complications in hypertensives*

No. of patients	Low (0-3)	Normal (3-20)	High (>20)	Total
Total	106	181	38	325
Severe vascular complications				
Myocardial infarction	11	15	12	38
Cerebral strokes	13	21	5	39
Ruptured aortic aneurysm	1	1	0	2
Total	25 (23.6%)	37 (20.4%)	17 (44.7%)	

*As a mixed population

has some experimental basis when pharmacological doses are used. But we believe that there is little factual evidence that renin in the physiological range is related to the severe complications of atherosclerosis as shown especially in our follow-up of patients with renal artery stenosis.

There are several objections to the claim that renin may be an important risk factor in severe cardiovascular complications:

1. Renin and aldosterone are significantly elevated in patients with nephrotic syndrome or cirrhosis of the liver. Nevertheless severe vascular complications in such patients do not occur or are extremely rare.
2. If high renin carried such a serious prognosis, it would be necessary to withhold or stop all antihypertensive drugs which stimulate renin release such as the thiazides and apresoline. The impressive results obtained by Freis and his collaborators[8-10] in the Veterans' Administration Cooperative Study in which hypertensive patients received, in addition to reserpine, hydrochlorothiazide and apresoline, two drugs which increase plasma renin activity, are at variance with the claim of Brunner *et al.*[1]
3. Should hypertensive patients with labile, mild or moderate hypertension be turned down by life insurance companies because of a single (or more) high plasma renin level(s)? In the present state of our knowledge and with the evidence at hand, it would be an unfortunate tragedy if this should occur.
4. A single plasma renin measurement done at one instant in the life of a hypertensive patient has very limited value, even if done under strictly controlled conditions of diet and posture. We have evidence that in some hypertensive patients plasma renin activity has repeatedly been undetectable (three hours' incubation) over several months or even years. On the other hand, there is also evidence that some hypertensive patients may have suppressed plasma renin activity on one occasion and normal activity or a normal response to the stimulus of posture or severe sodium restriction on another occasion.[11] Particularly, spironolactone administration can cause a "de-inhibition" of renin suppression and modify renin release.[12] This illustrates the fragility of claims based on one or two measurements of renin.
5. The adequate dietary and drug management of hypertensive cardiovascular disease to reduce the risk of severe cardiovascular complications is much more important, as shown by many, particularly by the

Table IV—Clinical and biochemical data of 202 patients with essential hypertension

	No. of patients	Mean age	Blood urea mg./100 ml.	Serum creatinine mg./100 ml.	Serum Na mEq./l.	Serum K mEq./l.	Mean BP mm. Hg	Severe vascular complications: Myocardial infarction	Severe vascular complications: Cerebral strokes	Severe vascular complications: Ruptured aortic aneurysm	Percent of patients
Low renin	75	47	36	0.9	141.0	4.1	177/110	8	9	1	24.0
Normal renin	121	42	35	1.0	142.5	4.2	177/112	6	11	1	14.9
High renin	6	42	33	0.9	141.0	3.9	180/115	3	1	0	66.7

Table V—Clinical and biochemical data of 8 patients with malignant hypertension

	No. of patients	Mean age	Blood urea mg./100 ml.	Serum creatinine mg./100 ml.	Serum Na mEq./l.	Serum K mEq./l.	Mean BP mm. Hg	Severe vascular complications: Myocardial infarction	Severe vascular complications: Cerebral strokes
Low renin	2	34	132	4.4	146.5	4.3	210/135	0	0
Normal renin	4	31	121	5.1	138.5	4.0	216/143	0	1
High renin	2	46	189	5.5	128.0	4.3	200/133	1	0

Table VI—Clinical and biochemical data of 53 patients with renal parenchymatous hypertension

	No. of patients	Mean age	Blood urea mg./100 ml.	Serum creatinine mg./100 ml.	Serum Na mEq./l.	Serum K mEq./l.	Mean BP mm. Hg	Severe vascular complications: Myocardial infarction	Severe vascular complications: Cerebral strokes	Percent of patients
Low renin	17	41	57	1.7	141.0	4.1	181/117	1	2	17.6
Normal renin	26	42	63	1.9	140.5	4.2	181/111	3	5	30.8
High renin	10	43	61	2.0	139.0	3.9	205/120	2	1	30.0

Table VII—Clinical and biochemical data of 62 patients with hypertension caused by, or associated with, atherosclerotic renal artery stenosis

	No. of patients	Mean age	Blood urea mg./100 ml.	Serum creatinine mg./100 ml.	Serum Na mEq./l.	Serum K mEq./l.	Mean BP mm. Hg	Severe vascular complications: Myocardial infarction	Severe vascular complications: Cerebral strokes	Percent of patients
Low renin	12	49	48	1.2	141	4.1	185/113	2	2	33.3
Normal renin	30	49	44	1.0	141	4.0	189/111	6	4	33.3
High renin	20	47	39	1.0	139	4.0	205/121	6	3	45.0

Veterans' Administration Cooperative Study,[8,9] than is reliance on a single plasma renin determination to predict the risk.

6. It is recognized by all workers in the field that the level of the diastolic pressure in untreated hypertensive patients is a much better predictor of severe complications than is a single low renin measurement. This is well illustrated by the data of Brunner *et al*[1] which show a mean diastolic pressure of 124 mm. Hg in the high renin hypertensive group in contrast to 104 mm. Hg in the low and normal renin groups.

It must also be stressed that approximately 25% of the 219 patients studied by Brunner *et al* had an "uncontrolled" sodium intake since they were studied in the outpatient clinic. These patients were "all instructed not to avoid sodium in the diet" and their "daily rates of sodium excretion ranged from 100 to 250 mEq./day".

Also, we cannot agree with the claim of Brunner *et al* in their answer to Amery, Stroobandt and Fagard[3] that: "Renin is physiologically suppressed to very low values when sodium intake exceeds 120 mEq./day". Our results do not support this finding,[11] nor do the data published by Laragh,[13] a member of the same group. Our findings of normal or low renin and of normal serum potassium levels in some patients with malignant hypertension are in agreement with previous findings from our group and those recently reported by Johnson *et al*.[14]

Conclusion

The data we have presented are at variance with the claim that renin constitutes a serious risk factor in patients with essential hypertension, especially if it is considered in isolation from other parameters, namely the level of diastolic pressure, the adequacy of kidney function, the effectiveness of dietary and drug management of hypertension, and especially the presence or absence of atherosclerotic lesions in the large vessels at the time of the renin determination.

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