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Plasma Epinephrine and Norepinephrine Concentrations in Primary and Secondary Human Hypertension

FALKO SKRABAL, M.D., JOSEF AUBÖCK, M.D.,
HEIDE HÖRTNAGL, M.D., AND THOMAS BRÜCKE, M.D.

SUMMARY Supine plasma concentrations of epinephrine and norepinephrine were measured by a radioenzymatic method in 69 patients with essential hypertension and were compared with the levels found in 40 patients with hypertension resulting from chronic parenchymatous renal disease and in 18 normotensive controls. Mean plasma levels of epinephrine and norepinephrine were not statistically different in primary and secondary hypertension and comparable to levels in normotensive controls. If the upper confidence limit is taken to be 0.4 ng/ml of plasma norepinephrine in renal hypertension, only three of 69 patients with essential hypertension (4%) had a slightly raised plasma norepinephrine and, with an upper confidence limit of 0.3 ng/ml in normal subjects, only four of 69 patients (6%) had a definitely raised plasma norepinephrine. Plasma norepinephrine was significantly higher in high-renin as compared to low-renin essential hypertension; it correlated neither with age nor blood pressure. Plasma epinephrine was suppressed in about 30% of the patients with primary and secondary hypertension and correlated significantly with heart rate and pulse pressure. On the basis of the present results, differences in the sympathetic tone in primary hypertension and secondary hypertension of renal origin are not obvious. Supine plasma catecholamine levels do not add any new evidence to the concept that increased activity of the sympathetic nervous system is involved in the pathogenesis of essential hypertension. In fact, plasma epinephrine is suppressed in a substantial number of patients with primary and secondary hypertension. Furthermore, since plasma renin correlated with plasma norepinephrine only in essential but not in renal hypertension, it appears that the sympathetic nervous system contributes to basal renin release only in primary hypertension. In secondary hypertension resulting from chronic renal disease, basal renin release is probably maintained by the renal baroreceptors of the diseased kidneys. (Hypertension 3: 373-379, 1981)

KEY WORDS • plasma epinephrine • plasma norepinephrine • sympathetic nervous system • plasma renin • essential hypertension • renal hypertension

THE final conclusion about the neurogenic origin of essential hypertension is still under debate. Conflicting results are still being reported: whether in essential hypertension plasma catecholamines are raised¹⁻⁹ or not,¹⁰⁻¹³ whether they correlate with plasma renin activity^{14, 15} or not,⁹ whether they correlate with blood pressure^{5, 9} or not,^{4, 6} and whether they increase with age^{10, 12} or not.^{4, 5} In all studies performed, patients with essential hypertension have been compared with normotensive controls, ignoring the possibility that the raised blood pressure per se could have an influence on the activity of the

sympathetic nervous system and on plasma catecholamines. A comparison of plasma levels of catecholamines in patients with essential hypertension and those with secondary hypertension of renal origin has to our knowledge not yet been performed. The purpose of the present investigation is to compare the plasma levels of epinephrine, norepinephrine, and renin in primary hypertension and secondary hypertension of renal origin.

Material and Methods

We investigated 69 patients (24 females) with essential hypertension, 40 patients (22 females) with hypertension associated with well-established chronic parenchymatous renal disease, and 19 normal control subjects (all male). In patients with essential hypertension, we used routine clinical procedures including urinalysis, rapid sequence urography, and determination of urinary catecholamines to exclude secondary forms of hypertension. The diagnoses in patients with renal hypertension were: chronic pyelo-

From the Universitätsklinik für Innere Medizin and The Institute of Pharmacology, University of Innsbruck, A-6020 Innsbruck, Austria.

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Present address for Dr. Hörtnagl: Institute of Biochemical Pharmacology, University of Vienna, Austria.

Address for reprints: Dr. Falko Skrabal, Univ.-Klinik f. Innere Medizin, A-6020 Innsbruck, Austria.

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nephritis (16), chronic glomerulonephritis (8), dysplastic kidneys (9), hydronephrosis (4), polycystic kidney disease (1), diabetic nephropathy (1), and analgesic nephropathy (1). Serum creatinine was normal in 28 patients and raised in 12 patients, ranging from 2 to 11 mg/dl. Age, blood pressure, and 24-hour urinary excretion of sodium and potassium for the day prior to the study are given in tables 1-3 for the hypertensive subjects and normal controls. All patients were investigated after being off all medication for at least 2 weeks. Most patients (essential as well as renal hypertensives) had had antihypertensive therapy previously; drugs included saluretics, methyldopa, reserpine, beta-blockers, and clonidine.

After the patients had observed an overnight fast and 90 minutes of supine bed rest, 5 ml of heparinized blood containing reduced glutathione in a final concentration of 5 mM was taken by venipuncture of a forearm vein for catecholamine measurement and 5 ml EDTA blood for determination of plasma renin activity (PRA). Blood was immediately chilled to 4°C in an ice bath and plasma separated in a cooled centrifuge within 30 minutes. The heparinized plasma was frozen at

-30°C until the samples were assayed for epinephrine and norepinephrine by a modification¹⁷ of the method of Passon and Peuler.¹⁸ Samples for PRA were incubated on the same day without prior freezing to avoid cryoactivation, and PRA was measured using the method of Boyd et al.¹⁹ Concentrations of 24-hour urinary sodium and potassium from the day before the study were determined. Group differences were assessed either by Student's *t* test when the values were normally distributed, or by the Wilcoxon test.

Results

Tables 1-3 show mean values \pm standard deviation (SD) of age, systolic, diastolic, and mean blood pressure, plasma norepinephrine and epinephrine, PRA, and 24-hour urinary sodium and potassium excretion in patients with essential and renal hypertension and in normal subjects. On the whole, plasma norepinephrine and epinephrine were statistically not different in primary and secondary hypertensives and in normal controls. Significantly higher plasma norepinephrine

TABLE 1. Age, Systolic (BP_s), Diastolic (BP_d), and Mean Blood Pressure (BP_m), Plasma Norepinephrine (NE), Epinephrine (E), and 24-Hour Urinary Sodium (24-Na) and Potassium (24-K) Excretion in Patients with Essential Hypertension (Mean \pm SD)

Renin	n	Age (yrs)	BP _s	BP _d	BP _m	NE (ng/ml)	E (ng/ml)	PRA (pg/ml/hr)	24-Na (mmole)	24-K (mmole)
high	10	34.6 \pm 12.7	160.5 \pm 21.9	104.0 \pm 17.1	128.9 \pm 18.4	0.26 \pm 0.13	0.040 \pm 0.032	785.5 \pm 183.4	198.3 \pm 83.0	75.6 \pm 26.8
normal	42	34.4 \pm 12.5	163.5 \pm 24.7	102.3 \pm 18.9	130.2 \pm 19.5	0.19 \pm 0.10	0.045 \pm 0.049	278.7 \pm 122.0	159.0 \pm 76.4	69.1 \pm 41.2
low	17	48.4 \pm 15.7	188.2 \pm 33.6	116.2 \pm 20.8	147.9 \pm 24.9	0.15 \pm 0.07	0.043 \pm 0.049	47.9 \pm 24.3	206.4 \pm 69.9	59.6 \pm 23.0
combined	69	37.9 \pm 14.5	169.1 \pm 28.8	105.9 \pm 19.8	134.3 \pm 21.9	0.19 \pm 0.10	0.044 \pm 0.047	295.3 \pm 253.7	176.4 \pm 72.2	67.7 \pm 31.6

TABLE 2. Age, Systolic (BP_s), Diastolic (BP_d), and Mean Blood Pressure (BP_m), Plasma Norepinephrine (NE), Epinephrine (E), and 24-Hour Urinary Sodium (24-Na) and Potassium (24-K) Excretion in Patients with Renal Hypertension (Mean \pm SD)

Serum creatinine	n	Age (yrs)	BP _s	BP _d	BP _m	NE (ng/ml)	E (ng/ml)	PRA (pg/ml/hr)	24-Na (mmole)	24-K (mmole)
normal	28	35.2 \pm 11.4	164.8 \pm 25.0	109.2 \pm 17.2	131.8 \pm 21.2	0.19 \pm 0.10	0.0252 \pm 0.023	557.4 \pm 360.7	172.0 \pm 69.3	52.8 \pm 19.0
raised	12	45.6 \pm 17.1	181.2 \pm 33.0	112.5 \pm 13.7	141.2 \pm 20.4	0.20 \pm 0.10	0.0325 \pm 0.043	557.5 \pm 368.3	190.6 \pm 73.5	57.4 \pm 22.0
combined	40	38.8 \pm 14.1	169.1 \pm 28.4	109.5 \pm 16.6	135.9 \pm 20.6	0.19 \pm 0.10	0.0274 \pm 0.030	548.9 \pm 361.4	179.8 \pm 66.7	54.4 \pm 19.7

TABLE 3. Age, Systolic (BP_s), Diastolic (BP_d), and Mean Blood Pressure (BP_m), Plasma Norepinephrine (NE), Epinephrine (E), and 24-Hour Urinary Sodium (24-Na) and Potassium (24-K) Excretion in Normotensive Controls (Mean \pm SD)

Normal (n)	Age (yrs)	BP _s	BP _d	BP _m	NE (ng/ml)	E (ng/ml)	PRA (pg/ml/hr)	24-Na (mmole)	24-K (mmole)
19	40.0 \pm 16.5	140.3 \pm 8.0	88.5 \pm 3.9	109.8 \pm 5.6	0.19 \pm 0.06	0.037 \pm 0.030	262.6 \pm 361.4	183.4 \pm 66.7	71.0 \pm 19.7

was seen in the high-renin as compared to the low-renin subgroup only in patients with essential hypertension ($p < 0.05$) (fig. 1). The significant correlation coefficients of plasma norepinephrine to other parameters are shown in table 4, and the correlations of plasma epinephrine to either norepinephrine or heart rate are shown in figures 2 and 3. Plasma norepinephrine correlated only with plasma epinephrine; it only correlated significantly with PRA when the correlation was corrected for age by partial correlation analysis. No correlation was found with age and with systolic, diastolic, or mean blood pressure.

Plasma epinephrine levels in hypertensive patients and normal controls are shown in tables 1-3 and figure

4. No differences in plasma epinephrine were found between patients with essential and renal hypertension (fig. 4) or in the three renin subgroups of patients with essential hypertension (table 1). The distribution of epinephrine concentrations in plasma varied in normal controls and hypertensive patients, the values in primary and secondary hypertension being positively skewed. Therefore, group differences had to be evaluated by the Wilcoxon test. Correlations of plasma epinephrine to other parameters are shown in table 4. Plasma epinephrine correlated positively with plasma norepinephrine, pulse rate, and pulse pressure in patients with essential hypertension; it correlated negatively with diastolic blood pressure.

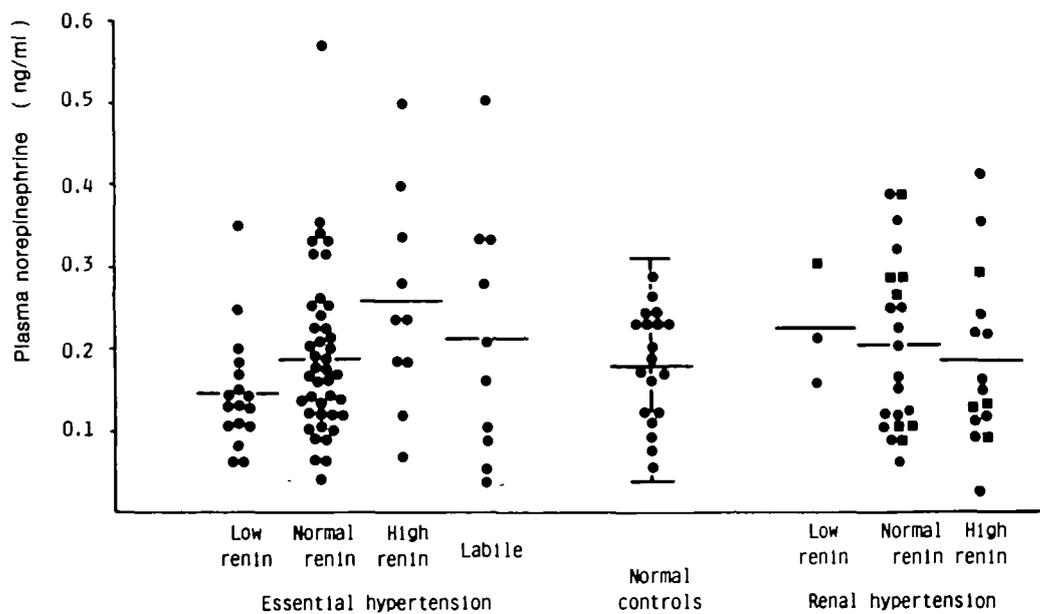


FIGURE 1. Plasma norepinephrine in patients with essential hypertension as compared with normal controls and patients with renal hypertension with normal (•) and raised (■) serum creatinine.

TABLE 4. Correlations between Age, Blood Pressure (BP), Heart Rate (HR), Pulse Pressure (PP), Plasma Renin Activity (PRA), Plasma Norepinephrine (NE), and Epinephrine (E) in Patients with Essential and Renal Hypertension and in Normal Controls (Only Significant Correlations Shown)

Patient group	Age vs PRA	Age vs NE	Age vs E	Age vs BP _s	Age vs BP _d	NE vs E	NE vs PRA	E vs PRA	E vs HR	E vs RR _d	E vs PP
Essential hypertension											
high renin	—	—	—	—	—	—	—	—	—	—	0.68 $p < 0.05$
normal renin	—	—	—	0.40 $p < 0.01$	0.53 $p < 0.001$	0.30 $p < 0.05$	—	—	0.44 $p < 0.01$	—	0.40 $p < 0.01$
low renin	—	—	—	0.62 $p < 0.01$	0.53 $p < 0.05$	0.54 $p < 0.05$	—	—	0.58 $p < 0.05$	—	—
combined	-0.35 $p < 0.01$	—	—	0.55 $p < 0.001$	0.53 $p < 0.001$	0.30 $p < 0.01$	0.42* $p < 0.01$	—	0.46 $p < 0.001$	-0.23 $p < 0.05$	—
Renal hypertension	—	—	—	—	—	—	—	—	—	—	—
Normal subjects						not done					

*Corrected for age by partial correlation analysis.

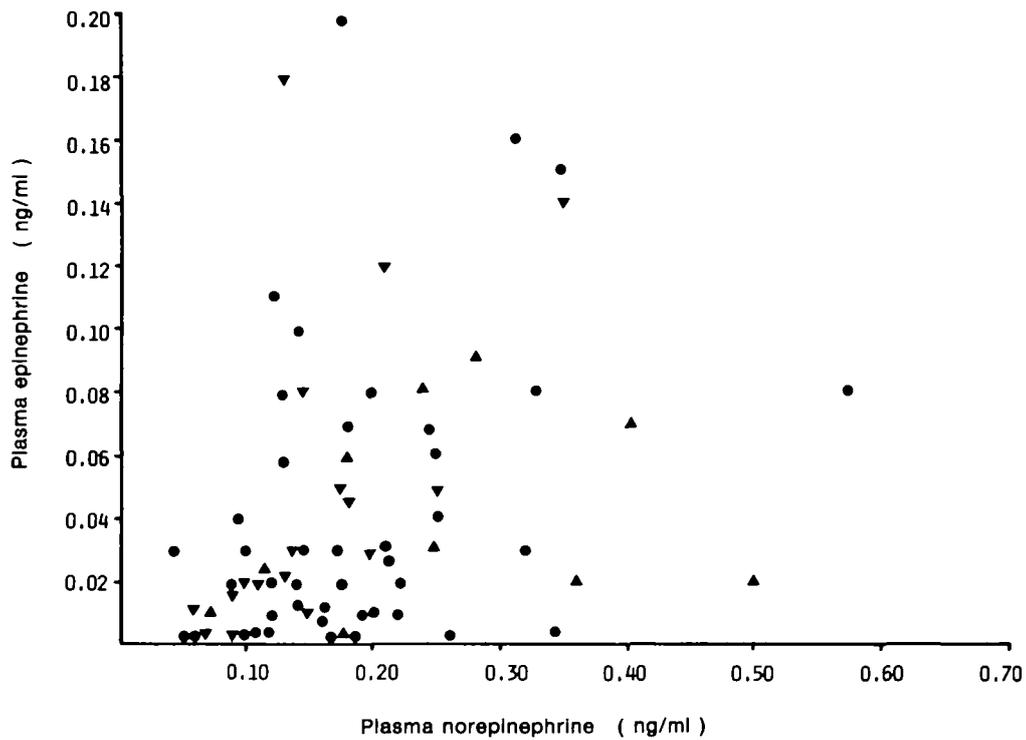


FIGURE 2. Correlation of plasma norepinephrine to plasma epinephrine in patients with essential hypertension and low (∇), normal (\bullet) and high (\blacktriangle) plasma renin activity. Only a weak correlation with a coefficient of $r = 0.30$, $p < 0.01$ was observed.

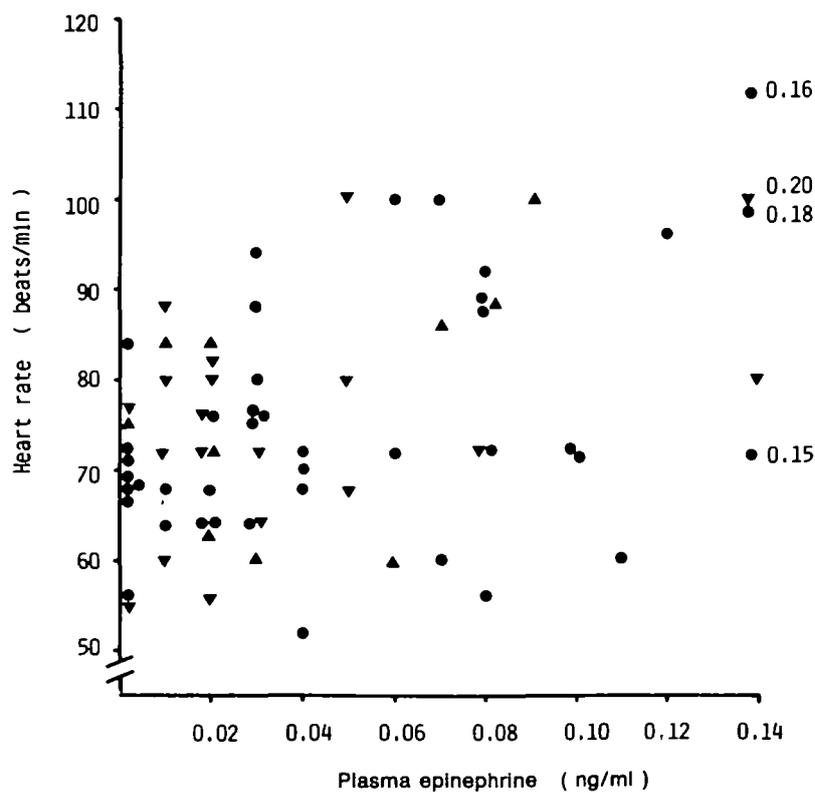


FIGURE 3. Correlation of plasma epinephrine to heart rate in patients with essential hypertension and low (∇), normal (\bullet), and high (\blacktriangle) plasma renin activity.

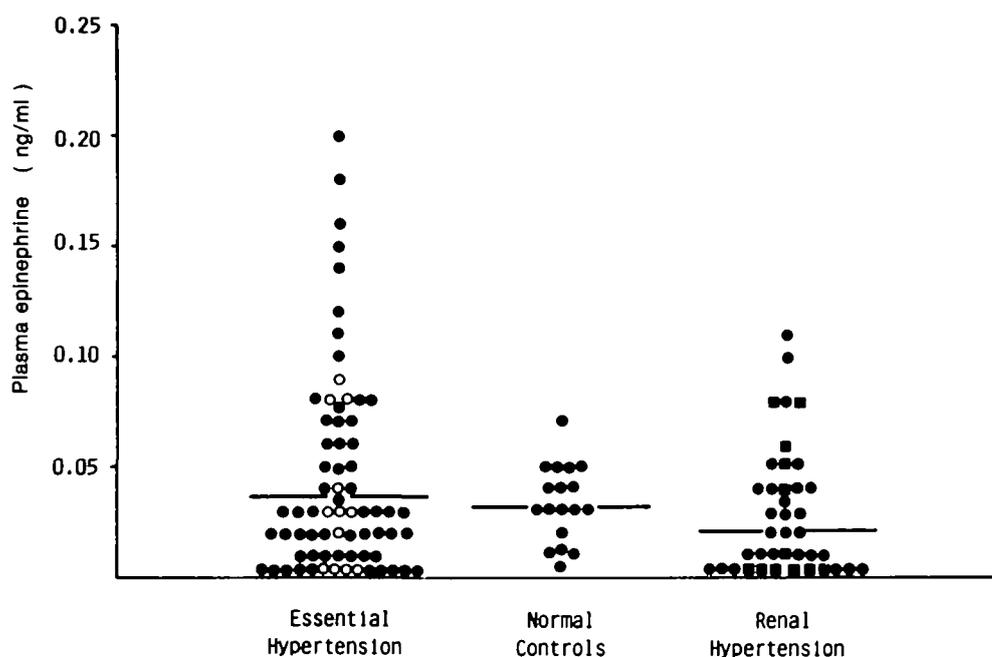


FIGURE 4. Plasma epinephrine in patients with labile (○) and stable (●) essential hypertension as compared with normal controls and patients with renal hypertension with normal (●) and raised (■) serum creatinine. The three renin subgroups are shown combined, since there was no difference between low-, normal-, and high-renin essential hypertension (see table 1).

Discussion

Our study does not reveal any major differences of plasma catecholamine concentrations in primary hypertension and secondary hypertension of renal origin. A group of patients with hypertension of known cause such as hypertension secondary to renal disease may be a better control group for assessing the relevance of plasma catecholamines in primary hypertension than normotensive controls, for two reasons: 1) alterations of plasma catecholamines in primary hypertension, if any, might not be the cause but the consequence of raised blood pressure; and 2) many patients with hypertension have had drugs in the past that are known to interfere with catecholamine synthesis or release. The drug-free interval before catecholamine determination in many previous studies (and in our present study) may have been much too short for any after-effects of antihypertensive therapy on plasma catecholamines to wear off. Therefore a comparison of primary and secondary hypertension patients with similar blood pressure values (tables 1 and 2), similar drug histories, and identical drug-free periods might be more relevant than the usual comparison with normal subjects who had never had antihypertensive therapy. One obvious question is: Do some of the 28 patients with secondary hypertension and normal serum creatinine in fact have primary hypertension? Although we have taken great care in patient selection, this problem is impossible to solve.

If we take the upper confidence limit of 0.4 ng/ml of plasma norepinephrine in renal hypertension (table 1), we find that only three of the 69 patients with essential hypertension (4%) had a plasma norepinephrine concentration slightly raised above that value (fig. 1). Even if we compare plasma catecholamines in essential hypertension with our small group of normal subjects, we find only four of the 69 patients (6%) had a definitely raised plasma norepinephrine. Therefore, our findings strongly support the results of several studies indicating that plasma catecholamine concentrations and catecholamine excretion in primary hypertension are not raised,^{10-13, 20-24} and we are thus unable to support the results of Engelman et al.⁷ and many other studies.^{1-9, 25-30, 34, 35}

With respect to renin subgroups of essential hypertension, we found that patients with high-renin hypertension have significantly higher plasma norepinephrine levels than those with low-renin hypertension. This result is in agreement with the findings of De Quattro et al.¹⁶ and, with respect to urinary catecholamines, confirms the results of Imura et al.³¹ and Horky et al.¹⁶ Our findings confirm that the sympathetic nervous tone is a determinant of renin release even under basal conditions.³² It remains an open question whether the better indicator of sympathetic nervous system tone is the renin released into the circulation predominantly under sympathetic control³² or the plasma norepinephrine spilled over into the circulation.

Unfortunately, we were unable to extend our study to include responses of plasma catecholamines to maneuvers that are known to influence the activity of the sympathetic nervous system. Nevertheless, we still believe that extended supine bed rest gives the best standardized conditions for comparison of different patient groups, since maneuvers that influence sympathetic nervous system tone, such as dietary sodium depletion, are likely to have different basic mechanisms in patients with normal renal function and in those with chronic parenchymatous renal disease.

No correlation between plasma norepinephrine and systolic, diastolic, or mean blood pressure was found, even when the correlation was corrected for age or PRA. This is in agreement with the results of Sever et al.,⁴ Esler et al.,⁶ Engelman et al.,⁷ but in contrast to the results of Louis et al.^{9, 25} and Brecht and Schoeppe.²⁹ Correlation between plasma norepinephrine and blood pressure cannot be expected, however, if we acknowledge that there is little dispute that patients with low-renin hypertension have higher blood pressure values (table 1) and lower plasma norepinephrine levels (fig. 1) than normal subjects or high-renin hypertensives.

Epinephrine levels in plasma in hypertensive patients have rarely been reported, and results are conflicting as to whether these levels are raised^{3, 36} or not.^{11, 13} Plasma epinephrine levels in our study were similar in all subgroups of patients with essential and renal hypertension (table 1) and also not higher in patients with labile hypertension as compared with stable essential hypertension (fig. 4). It is noteworthy that about 30% of the patients with primary and secondary hypertension had suppressed plasma epinephrine levels, leading to a positively skewed frequency distribution (fig. 2). It appears possible that in a significant number of hypertensive patients the hypertensive process itself might lead to a suppression of epinephrine release. Values of plasma epinephrine and norepinephrine found by us in renal hypertension are probably not affected by the reduced kidney function, since plasma levels were similar in patients with and without raised serum creatinine. Furthermore, the accuracy of the epinephrine levels in our study is emphasized by their positive correlation to heart rate (fig. 4) and pulse pressure. Such correlations would be expected from the action of epinephrine on heart and blood vessels.

Furthermore, it is noteworthy (table 2) that the PRA in the renal hypertensives is similar in the normal serum-creatinine group and the high serum-creatinine group. This suggests that, in this study, progression of renal disease does not affect PRA.

Although in our study plasma norepinephrine was comparable in primary hypertension and secondary hypertension of renal origin, mean PRA was twice as high in the latter group. This confirms our previous observation³² that the PRA in renal hypertension, although not absolutely elevated, may be inappropriately high for any given sympathetic tone. In contrast to essential hypertension, where (even basal) renin secretion is primarily controlled by sympathetic tone,³⁷

in secondary hypertension of renal origin renin secretion appears to be independent of the sympathetic nervous system³² and maintained by the renal baroreceptors of the diseased underperfused kidney. Evidence for this is also the exclusive unilateral renin secretion in unilateral renovascular disease after nitroprusside-induced normotension.³⁷

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