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Research Article

A study was made of the possible mechanism(s) underlying minoxidil-induced increase in plasma renin activity (PRA). 10 patients with essential hypertension were treated with minoxidil and subsequently with a combination of minoxidil plus propranolol. Minoxidil lowered mean arterial pressure 31.6 plus or minus 3.3 mm Hg, mean plus or minus SEM. There was an associated increase in both PRA, 6.26 plus or minus 2.43 NG/ML/H, and heart rate, 21.4 plus or minus 2.7 beats/min. The changes in PRA and heart rate were positively correlated, r, 0.79. Addition of propranolol reduced mean arterial pressure by a further 10.1 plus or minus 1.5 mm Hg and returned heart rate to control levels. Propranolol reduced PRA significantly but not to control levels. Control PRA positively correlated with PRA on minoxidil, r, 0.97, and with PRA on minoxidil plus propranolol, r, 0.98. We conclude that control PRA is a major determinant of change in PRA with minoxidil. Minoxidil increased PRA by at least two mechanisms: (a) an adrenergic mechanism closely related to change in heart rate and blocked by propranolol, and (b) a mechanism(s) not sensitive to propranolol and possibly related to decrease in renal perfusion pressure.

Control Plasma Renin Activity and Changes in Sympathetic Tone as Determinants of Minoxidil-Induced Increase in Plasma Renin Activity

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Abstract A study was made of the possible mechanism(s) underlying minoxidil-induced increase in plasma renin activity (PRA). 10 patients with essential hypertension were treated with minoxidil and subsequently with a combination of minoxidil plus propranolol. Minoxidil lowered mean arterial pressure 31.6±3.3 mm Hg, mean ±SEM. There was an associated increase in both PRA, 6.26±2.43 ng/ml/h, and heart rate, 21.4±2.7 beats/min. The changes in PRA and heart rate were positively correlated, *r*, 0.79. Addition of propranolol reduced mean arterial pressure by a further 10.1±1.5 mm Hg and returned heart rate to control levels. Propranolol reduced PRA significantly but not to control levels. Control PRA positively correlated with PRA on minoxidil, *r*, 0.97, and with PRA on minoxidil plus propranolol, *r*, 0.98. We conclude that control PRA is a major determinant of change in PRA with minoxidil. Minoxidil increased PRA by at least two mechanisms: (*a*) an adrenergic mechanism closely related to change in heart rate and blocked by propranolol, and (*b*) a mechanism(s) not sensitive to propranolol and possibly related to decrease in renal perfusion pressure.

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INTRODUCTION

Blood pressure-lowering agents have variable effects on plasma renin activity (PRA).[1] Whereas the adrenergic-blocking drugs, methyldopa (1) and propranolol (2) reduce PRA, vasodilator antihypertensives such as diazoxide (3), hydralazine (4), and sodium nitroprusside (5) increase PRA in hypertensive patients. The new potent antihypertensive vasodilator, minoxidil, has been shown to increase PRA in the rat (6) and in patients with hypertension (7, 8). Minoxidil-induced increase in PRA may be attributable to any one of three known pharmacological effects of the drug: decrease in arterial pressure, reflex increase in sympathetic tone (7), or decrease in sodium excretion rate (8, 9). The present study was undertaken to assess the relative roles of these three variables in the genesis of minoxidil-induced increase in PRA in patients with essential hypertension.

Hospitalized patients were treated initially with minoxidil and changes in PRA, blood pressure, heart rate (an index of sympathetic activity), and urinary sodium excretion were measured. The effect of beta adrenergic blockade on these parameters was examined by addition of propranolol to this regimen.

PATIENTS AND METHODS

10 patients with essential hypertension resistant to conventional antihypertensive treatment were admitted to the Clinical Research Unit of Emory University Hospital for study. Signed informed consent was obtained in all cases. PRA, blood pressure, heart rate, and sodium excretion rate were measured under control conditions, during minoxidil ther-

[1] *Abbreviation used in this paper:* PRA, plasma renin activity.

TABLE I

The Clinical Status of Patients before Minoxidil Therapy

Patient	Age	Sex	Blood pressure*	Serum creatinine	Chest X ray	EKG‡	Retinal change (KWB)§
			mm Hg	*mg/100 ml*			
1	41	F	161/114	0.9	Cardiomegaly	LVH	II
2	47	M	176/120	1.2	Normal	LVH	II
3	38	F	150/116	1.2	Normal	Normal	II
4	37	F	214/141	0.8	Cardiomegaly	LVH	III
5	28	F	187/136	0.9	Normal	Normal	II
6	49	M	260/144	1.8	Cardiomegaly	LVH + S	II
7	41	M	128/99	1.4	Normal	Normal	I
8	38	M	159/109	0.9	Normal	LVH	I
9	39	F	183/121	1.0	Cardiomegaly	LVH	II
10	65	F	185/117	0.9	Normal	Normal	II

* Mean of eight supine systolic and diastolic readings taken every 3 h on control day.

‡ LVH indicates left ventricular hypertrophy and S strain pattern.

§ Keith-Wagener-Barker classification of hypertensive retinopathy.

apy, and on the combination of minoxidil and propranolol. As all patients had severe ambient hypertension, it was decided on ethical grounds that antihypertensive therapy could not be stopped for a prolonged period before admission. Therefore, patients were maintained on hydralazine, propranolol, and a thiazide diuretic until 48 h before admission. The clinical status of these patients after admission is summarized in Table I. All patients were black. Pretreatment blood pressure ranged from 128/99 to 260/144 mm Hg. Serum creatinine varied from 0.9 to 1.8 mg/100 ml. Six patients had evidence of left ventricular hypertrophy by electrocardiogram and in one of these, evidence of left ventricular strain was present. Chest X ray evidence of mild cardiomegaly was found in four patients. In no case was there radiological or clinical evidence of congestive heart failure. On admission, patients were placed on a diet containing 100 meq sodium/day. Supine blood pressure (mercury sphygmomanometer) and pulse rate were measured in duplicate every 3 h. When no significant difference was found between mean 24-h blood pressures over 2 successive days, a suitable base-line state was assumed and the control measurements were made.

Minoxidil was administered on a cumulative basis, with a dosage interval of 6 h. The initial dose of minoxidil was 5 mg. In the absence of a blood pressure response within 6 h, a further 5 mg was given. At each subsequent 6-hourly interval, the cumulative dose to that point was administered up to a maximum of 20 mg at a single dose. When a fall in blood pressure was recorded, patients were titrated with minoxidil so as to produce a major reduction in blood pressure. Such responses were obtained in all patients within 42 h of starting therapy, total loading dose varying from 20 to 100 mg. Maintenance therapy was then instituted and "minoxidil values" for the various parameters were measured. Patients were then given a 10-mg test dose of propranolol, and subsequently regular propranolol dosing began with 20 mg, every 6 h. At the end of each 24-h period, the dose of propranolol was doubled for a maximum of 4 days (160 mg, 6 hourly), or until incremental dosing was terminated due to a slowing of pulse rate. Maximal doses of propranolol used ranged from 40 to 160 mg, every 6 h. All parameters were measured at each propranolol dose level. For purposes of analysis, mean arterial pressure (diastolic + 1/3 pulse pressure) and pulse rate for 8:00 a.m., 11:00 a.m., and 2:00 p.m. for each study day were averaged. On these days, blood samples for PRA were drawn in the standing position at 12:00 noon after 1 h of ambulation and 4 h after the previous dose of minoxidil or minoxidil plus propranolol. PRA was measured by the radioimmunoassay of angiotensin I using a technique similar to that described by Haber, Koerner, Page, Kliman, and Purnode (10). Plasma was collected in chilled Vacutainer tubes[2] containing EDTA, centrifuged in the cold, and the plasma was stored at −20°C until the time of assay. After addition of neomycin, dimercaprol, and 8-hydroxyquinoline, and adjustment of pH to 7.4±0.05 with 1.5 N HCl, incubation for generation of angiotensin I was carried out at 37°C for 3 h. Each sample was assayed in duplicate. Results are expressed in nanograms per milliliter per hour. To minimize interassay variation, all samples for each patient were analyzed together. The coefficient of variation by this method is 8% ($n = 14$).

Differences between means were assessed using the Student's t test for paired observations. Regression analysis was by the least squares method.

RESULTS

Individual values are given in Table II. Minoxidil caused marked changes in mean arterial pressure, heart rate, and PRA. The mean arterial pressure fell from 140.1±5.1 (mean ±SEM) to 108.5±3.0 mm Hg ($P < 0.001$). This fall in blood pressure was accompanied by an average increase in the heart rate of 21.4±2.7 beats/min (76.4±3.2–97.8±4.7; $P < 0.001$), and by a substantial increase in PRA (1.03±0.26–7.29±2.68 ng/ml/h; $P < 0.05$). As shown in Fig. 1, a positive correlation was found between the minoxidil-induced changes in heart rate and PRA (r, 0.79; $P < 0.005$).

[2] Becton, Dickinson & Co., Rutherford, N. J.

TABLE II

The Effect of Minoxidil and Minoxidil with Propranolol on PRA, Mean Arterial Pressure, Heart Rate, and Urinary Sodium Excretion

	Mean arterial pressure			Heart rate			PRA			Urinary sodium excretion		
Patient	C*	M	M + P	C	M	M + P	C	M	M + P	C	M	M + P
		mm Hg			*min*			*ng/ml/h*			*meq/24 h*	
1	117	94	85	76	87	60	0.32	0.39	0.13	93	91	150
2	144	105	89	80	95	75	0.51	2.18	1.22	85	28	14
3	129	103	102	81	119	78	1.39	13.27	3.70	129	36	28
4	167	123	112	93	112	88	0.75	4.40	0.96	44	30	24
5	146	112	97	90	124	90	3.1	29.20	9.28	71	7	21
6	163	123	115	60	81	76	0.63	4.10	2.72	68	44	37
7	129	104	97	75	91	66	1.52	6.51	4.44	103	145	131
8	126	114	107	70	92	81	1.09	7.0	3.10	81	170	99
9	145	102	87	67	90	62	0.46	2.22	0.44	42	68	85
10	135	105	93	72	87	58	0.52	3.66	1.53	65	36	32
Mean ±SEM	140.1±5.1	108.5±3.0	98.4±3.3	76.4±3.2	97.8±4.7	73.4±3.6	1.03±0.26	7.29±2.68	2.75±0.85	78.1±8.4	65.5±1.71	62.1±15.8
P‡		<0.001	<0.001		<0.001	<0.001		<0.05	<0.05		<0.05	<0.05

* C, control; M, minoxidil; M + P, minoxidil plus propranolol.

‡ *P* values for minoxidil are against control, those for minoxidil plus propranolol are against minoxidil alone.

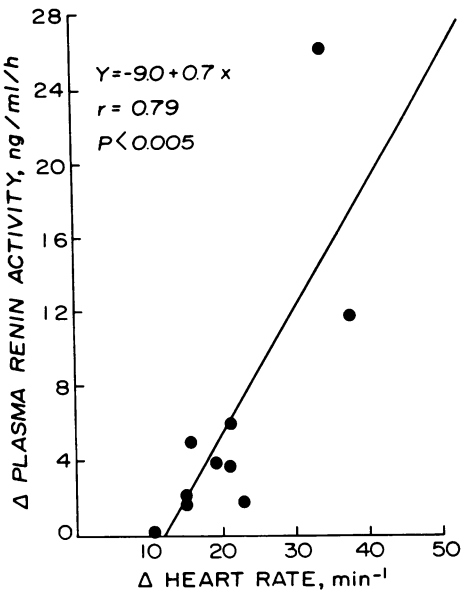

FIGURE 1 Correlation between minoxidil-induced changes in heart rate and PRA.

Addition of propranolol produced an average decrement in mean arterial pressure of 10.1±1.5 mm Hg ($P < 0.001$) at the highest dose level. Heart rate was reduced to a value (73.4±3.6), not significantly different from control. PRA fell to 2.75±0.85 ng/ml/h; a level significantly greater ($P < 0.05$) than the control of 1.03±0.26 ng/ml/h. Propranolol-induced changes in heart rate and PRA were not significantly correlated. Whereas minoxidil reduced sodium excretion in seven of the patients, there were substantial increases in the remaining three, so that no statistically significant trend emerged. The magnitude of changes in sodium excretion rate and blood pressure were not significantly correlated with changes in PRA on minoxidil alone or on the drug combination.

Positive correlations emerged between control PRA on the one hand, and PRA on minoxidil alone (r, 0.97, $P < 0.001$) and on minoxidil plus the highest dose of propranolol on the other (r, 0.98, $P < 0.001$—Fig. 2). By analysis of covariance, the slopes of these two regression lines were found to be significantly different ($P < 0.001$).

DISCUSSION

The present study shows that the control level of PRA is a major determinant of the plasma renin response to the vasodilator minoxidil as indicated by the strong positive correlation between control PRA and PRA on the drug. The slope of the regression line, 9.8, indicates that the "gain" in this system is considerable. It follows that patients whose PRA is high before minoxidil treatment will respond to the drug with larger increases in PRA than will those with lower pretreatment values. After addition of propranolol to minoxidil therapy, PRA also correlated positively with control PRA. The regression line on the combination had a slope of 3.2, i.e., the PRA on the combination would be expected to be 3.2 times greater than any given control value.

It is well established that renal nerve stimulation and administration of norepinephrine or epinephrine systemically or into the renal artery of experimental animals (11–13) stimulate renin release. Similarly, in man a number of procedures that increase sympathetic nervous activity are associated with increased PRA. Gordon, Küchel, Liddle, and Island (14) demonstrated that exposure to cold and upright posture resulted in increases in urinary catecholamines and PRA. Further, Kotchen et al. (15) found paralleled increases in PRA and urinary catecholamines in response to graded exercise. Recently, Esler and Nestel (16) showed that changes in PRA and urinary norepinephrine in response to head-up tilting positively correlated.

Various vasodilator antihypertensives have been shown to cause reflex increase in sympathetic tone as reflected by increases in heart rate (5, 7, 17) and blood (18) or urinary catecholamines (9). In the present study, all patients showed an increase in heart rate on minoxidil therapy which was reduced to control values by propranolol. A positive correlation was found between changes in heart rate and PRA with minoxidil administration. This finding is in agreement with that

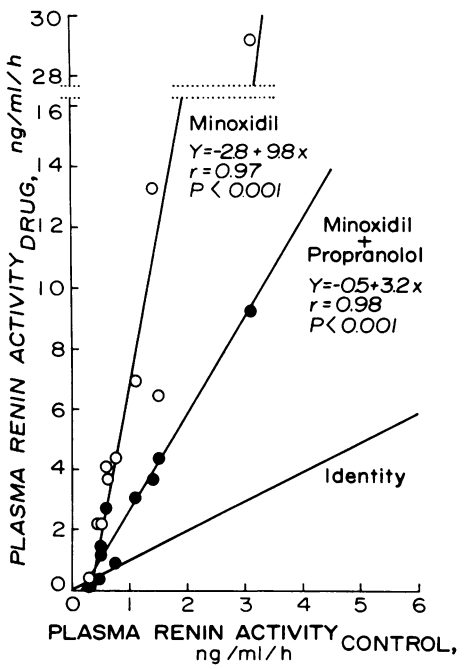

FIGURE 2 Relationship of control PRA to PRA on minoxidil and on minoxidil plus propranolol.

of Ueda, Kaneko, Takeda, Ikeda, and Yagi (4) who showed that changes in heart rate and PRA induced by another vasodilator, hydralazine, positively correlated. They postulated an adrenergic mechanism for plasma renin release in response to vasodilation. In this regard, it is also of interest to note that Küchel, Fishman, Liddler, and Michelakis (3) found that the PRA response to diazoxide tended to follow the heart rate changes. They found that for comparable reduction in blood pressure, patients who showed an increase in PRA also had an increase in heart rate, whereas those in whom small changes in heart rate occurred had little if any changes in PRA status. In the present study, the implication of the sympathetic nervous system is further strengthened by the finding that control PRA positively correlated with PRA on minoxidil plus propranolol, reduction in slope of the regression line from the minoxidil slope being ascribable to the action of propranolol and presumably beta blockade.

The failure of PRA to return to control values (Fig. 2) with propranolol suggests that another mechanism(s) is involved in minoxidil-induced increase in PRA. As reflected by the slopes of the regression lines relating control PRA to drug PRA (Fig. 2), the minoxidil values exceed control by a factor of 9.8, whereas with addition of propranolol therapy, there is still a threefold excess relative to control. It is likely that adequate doses of propranolol were given to produce beta blockade because heart rate returned to control values. Also, we considered it highly probable that the maximum effective renin-lowering dose of propranolol was used as we have shown in a parallel study (19) that the plasma levels of propranolol achieved at the highest dose levels were all greater than 70 ng/ml, a level above which further decrements in PRA are not abolished by propranolol. In hydralazine-treated rats, Pettinger, Campbell, and Keeton (6) found that propranolol reduced PRA by only 50–80%. Lowering of blood pressure may be important in this context as Robie, Malveaux, and McNay (20) have shown in the dog that the increase in PRA in response to lowering of renal perfusion pressure by aortic constriction was only partially blocked by propranolol.

Sodium balance is known to be an important factor in controlling PRA in patients with essential hypertension (21). In the present study, although urinary sodium excretion rate tended to fall on minoxidil and on addition of propranolol, the differences from control were not statistically significant. Further, we have not been able to correlate alterations in sodium excretion rate to changes in PRA. We suggest, therefore, that it is unlikely that sodium balance has played an important role in this study. Our finding of incomplete antagonism of minoxidil-induced increase in PRA by propranolol is not in agreement with that of one group, Winer, Chokshi, Yoon, and Freedman (22), who showed in an acute study in man that the increase in PRA caused by diazoxide was completely abolished by propranolol. In this case, however, normal volunteers were used and the magnitude of the fall in blood pressure, and by inference, the stimulus to renin secretion, was less than occurred in our study.

We conclude that control PRA is a major determinant of minoxidil-induced change in PRA, and that sympathetic tone has a modulating function. The failure of propranolol in high doses to completely suppress the plasma renin response indicates the presence of a second mechanism(s) possibly related to a decrease in renal perfusion pressure.

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