Pathophysiologic and pharmacokinetic determinants of the antihypertensive response to propranolol

The tendency for patients with essential hypertension to differ markedly in antihypertensive response to propranolol could arise from pathophysiologic or pharmacokinetic differences between them. This possibility was investigated in 23 men with mild to moderately severe essential hypertension. At each of three propranolol doses, 40 mg, 80 mg, and 320 mg daily, approximately a 20-fold range in steady-state plasma propranolol concentrations was observed. Clinical response however was unrelated to plasma propranolol:oral dose ratio, since patients with higher plasma levels were less sensitive to the existing plasma drug concentration. When falls in blood pressure and plasma propranolol concentration were compared overall, a biphasic dose-response relationship was noted, with a first component at plasma propranolol concentrations of 3 to 30 ng/ml and a second at concentrations above 30 ng/ml. Only patients with increased sympathetic nervous system activity and high plasma renin activity (PRA) had substantial falls in pressure at propranolol levels of 3 to 30 ng/ml. Cardiac beta adrenergic receptor blockade, not suppression of PRA, seemed to be the antihypertenisve mechanism. This relation of pretreatment sympathetic nervous activity and PRA to antihypertensive response existed only at lower plasma propranolol concentrations. With a propranolol dose of 320 mg daily, both plasma norepinephrine concentration and PRA were unrelated to the clinical response.

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Patients with essential hypertension show widely differing sensitivity to the blood pressure–lowering effect of beta adrenoceptor blocking drugs.[24] Attempts to explain this phenomenon have focused on presumed differences in the pathophysiology of the essential hypertension. Early reports emphasized a high cardiac output,[10] increased plasma renin activity,[1] and enhanced sympathetic nervous system responsiveness[6] as predictors of a good antihypertensive response to beta adrenoceptor blockers and reduction in cardiac output,

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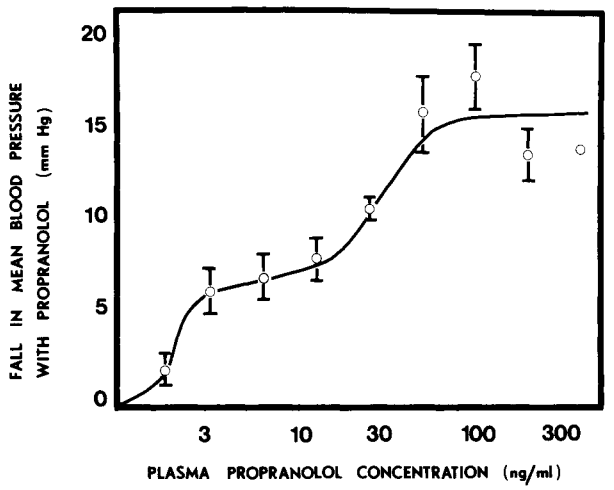

Fig. 1. Relation of fall in blood pressure to plasma propranolol concentration. Mean values ± standard errors are plotted for the logarithmic plasma propranolol intervals < 2 ng/ml, 2 to 4, 4 to 8, 8 to 16, . . . 256 to 512 ng/ml. Each point, except for the highest propranolol value, is based on a minimum of five observations.

plasma renin activity, and sympathetic nervous activity as blood pressure–lowering mechanisms. Subsequent studies by other workers have often failed to confirm the earlier findings,[5, 18, 22] which generates widespread confusion as to the mechanism by which beta adrenoceptor blocking drugs reduce blood pressure and the degree of predictability of the response.

Frequently in such studies observations on plasma drug concentrations have not been reported. With propranolol, patients achieve widely differing plasma concentrations on a given dose,[23] thus pharmacokinetic factors are potentially an important source of variability in the blood pressure response. In our study we evaluated the relative importance of pathophysiologic factors and differences in plasma propranolol concentration as determinants of the magnitude of the antihypertensive response to propranolol in patients with essential hypertension. Of the possible pathophysiologic determinants, abnormal plasma renin status and increased sympathetic nervous system activity were thought to be most relevant and were selected for investigation.

Methods

The study was performed in 23 men, aged 18 to 58 yr, with untreated mild to moderately severe essential hypertension. Pretreatment blood pressure was 155 to 185 mm Hg systolic, 95 to 125 mm Hg diastolic, or both. No patient had grade III or grade IV hypertensive retinopathy or a serum creatinine above 1.6 mg/100 ml. Secondary hypertension was adequately excluded by clinical testing which included an intravenous pyelogram and measurement of urinary aldosterone excretion. Prior to the commencement of the drug trial, patients were admitted to hospital for investigation of the pathophysiology of essential hypertension.

Tests were performed in a metabolic ward on the patients in sodium balance after a minimum of 5 days on a daily sodium intake of 160 mEq. After the patients had been standing for 1 hr, blood was drawn for estimation of plasma renin activity (PRA) by radioimmunoassay.[11] Plasma renin activity in relation to urinary sodium excretion was referred to the limits of normality for the PRA–dietary sodium relationship[1] established in 41 age-matched normal male volunteers. Plasma renin activity was elevated in 7 patients, normal in 10, and low in 6. In patients with low PRA, plasma renin subsequently remained suppressed after 6 days of sodium deprivation (10 mEq sodium daily). This plasma renin distribution was a consequence of selective recruitment for the study, based on earlier clinical renin typing, such as to give approxi-

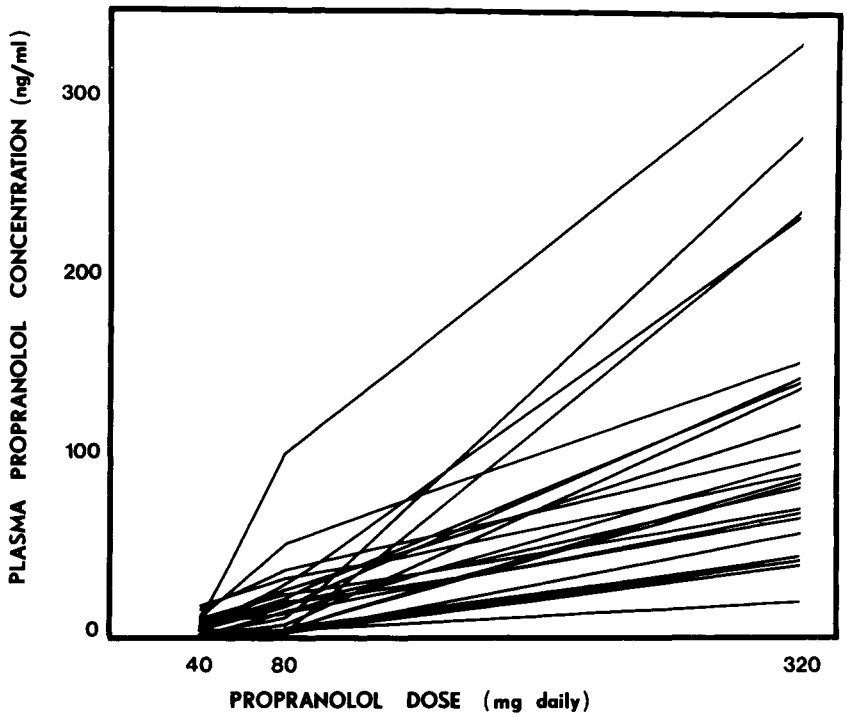

Fig. 2. Relation of plasma propranolol concentration to oral dose of drug.

mately equal numbers of patients in each renin subgroup.

On a second day, after a minimum of 1 hr of supine rest, blood was drawn via an indwelling intravenous catheter for estimation of plasma norepinephrine concentration. The sample was assayed "blind" by one of us (V. DeQ), without knowledge of the diagnosis, with the use of the sensitive fluorimetric method of Renzini and associates.[19] Hemodynamic measurements were performed at rest in all patients. Attention was directed specifically at hemodynamic indices related to sympathetic nervous system activity. After antecubital brachial artery puncture for arterial dye sampling and transvenous catheterization of the right atrium for dye delivery, cardiac output was determined by dye dilution with the use of indocyanine green. Heart rate was read from the electrocardiogram. Stroke volume was calculated from cardiac output and heart rate. Cardiac systolic time intervals were derived from the electrocardiograph, the phonocardiograph, and the external carotid arterial pressure tracings.[12] These were expressed as systolic time indices by adjusting for the influence of heart rate.[12] Mean left ventricular ejection rate was calculated from stroke volume index and left ventricular ejection time. Plasma norepinephrine concentration and hemodynamics at rest were also measured under identical conditions of sodium balance in 11 male normotensive subjects 18 to 45 yr of age. Results obtained were used as norms for comparison with the values in hypertensive patients.

The drug trial part of the study was performed after completion of physiologic testing. The following treatment regimen was instituted after a minimum of 4 wk with no antihypertensive medication: placebo for 2 wk and propranolol, 10 mg 4 times daily for 4 wk, 20 mg 4 times daily for 4 wk, and 80 mg 4 times daily for 4 wk. The trial was single blind. Patients attended the clinic between 8 and 10 A.M. after 2 wk on placebo and at the end of each 4-wk dosage period. Blood pressure and pulse rate were recorded with the patient supine (mean of three observations) after 3 min of rest. Blood was drawn 1 to 3 hr after the morning dose for estimation of plasma propranolol concentration with the use of a fluorimetric method[20] (performed by Ayerst Laboratories). After 1 hr

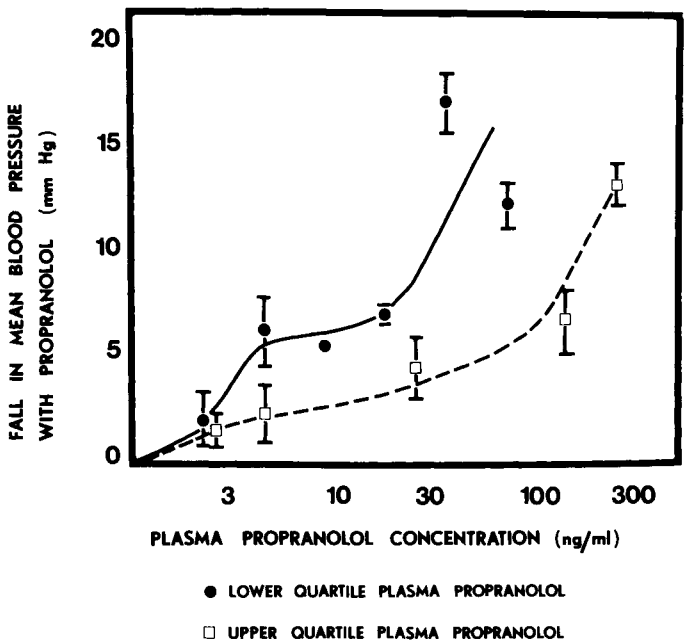

Fig. 3. Influence of differences in pharmacokinetics on sensitivity to the antihypertensive effect of propranolol. Patients falling in the upper and lower quartile for plasma propranolol:oral dose ratio are plotted separately. Each point is based on a minimum of three observations.

Table I. *Influence of differences in pharmacokinetics on the antihypertensive response to propranolol*

	Propranolol, 40 mg daily		*Propranolol, 80 mg daily*		*Propranolol, 320 mg daily*	
Parameter	*Plasma propranolol concentration (ng/ml)*	*Change in mean BP (%)*	*Plasma propranolol concentration (ng/ml)*	*Change in mean BP (%)*	*Plasma propranolol concentration (ng/ml)*	*Change in mean BP (%)*
Patient plasma Propranolol/dose status						
Lower quartile (n = 6)	1 ± 3	−2.3 ± 5.1	7 ± 13	−7.1 ± 7.4	47 ± 29	−14.1 ± 5.4
Upper quartile (n = 6)	4 ± 2	−2.2 ± 1.9	36 ± 24*	−4.0 ± 3.6	232 ± 57†	−11.3 ± 5.8

Mean values and standard deviations are listed. The significance of any difference between the 2 groups is indicated.

*$p < 0.05$.

†$p < 0.01$, Student's t test.

standing, venous blood was drawn for estimation of PRA.

Results

The relation between plasma propranolol concentration and fall in blood pressure for all patients combined, which appears to be biphasic, is shown in Fig. 1, with an early antihypertensive response, almost complete at a plasma propranolol concentration of 10 ng/ml, and a later component at plasma propranolol concentration above 30 ng/ml. In these patients with mild to moderately severe hypertension the blood pressure response seemed to plateau at plasma propranolol concentrations above 100 ng/ml.

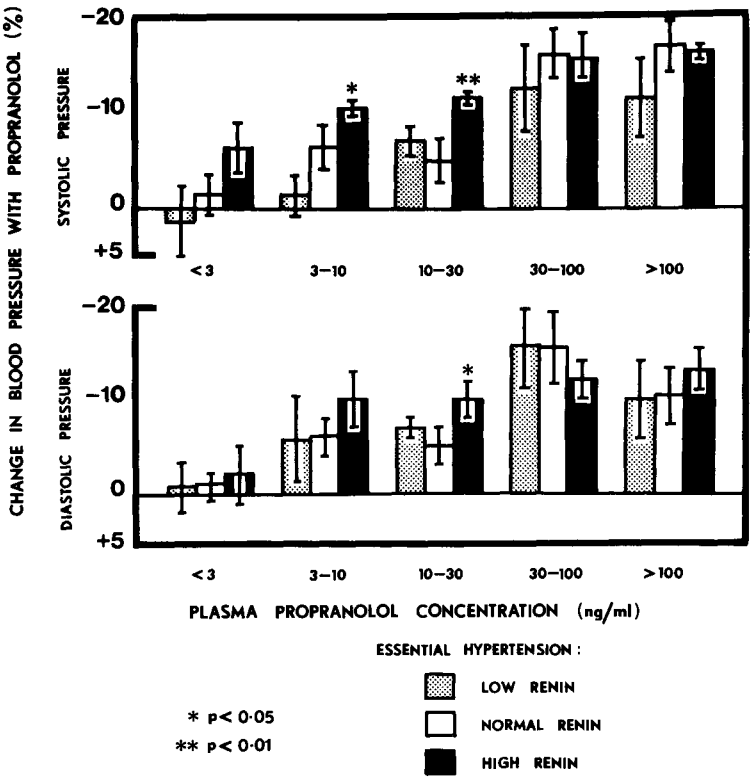

Fig. 4. Fall in blood pressure (%) expressed in relation to plasma renin status. The significance of any differences in blood pressure fall between patients with normal PRA and those with high or low plasma renin is indicated (Student's t test).

As expected[23] at a given oral dose large differences between subjects in plasma propranolol concentration were noted (Fig. 2). Since plasma propranolol concentration and fall in blood pressure were related overall, it was relevant to investigate whether patients with the lowest plasma propranolol levels at a given dose had the poor therapeutic responses. Differences between patients in the plasma propranolol level achieved by oral dosing, however, was found not to be a determinant of antihypertensive response. When patients in the upper and lower quartile for plasma propranolol:oral dose ratio were compared, the fall in blood pressure at each propranolol dose in the 2 groups was similar (Table I). Thus when blood pressure fall and plasma propranolol concentration are compared, patients with the lowest plasma propranolol:oral dose ratio appear to have greater sensitivity to the existing plasma drug levels (Fig. 3).

The relation of plasma renin status to antihypertensive response is shown in Fig. 4.* At low doses of the drug only patients with elevated PRA had greater blood pressure decrease with propranolol than those with normal or low plasma renin. At plasma propranolol concentrations of 3 to 30 ng/ml, the fall in blood pressure in the high-renin hypertensive patients was approximately double that in the other 2 renin subgroups (Fig. 4), but at plasma propranolol concentrations above 30 ng/ml renin status did not correlate with antihypertensive effect of the drug.

The dose-response relationships for lowering of PRA, heart rate at rest, and blood pressure are compared in Fig. 5. The early component of the antihypertensive effect of propranolol, at

*The 4 patients with plasma propranolol concentration above 200 ng/ml (on 320 mg propranolol daily; Fig. 2) were excluded from this analysis to minimize distortion arising from differences in pharmacokinetics, since dose-response relationships in such patients fall on a different curve than those in most subjects.[23] Of these 4, 1 had high PRA while PRA was normal in 3. Plasma renin status was unrelated to plasma propranolol:oral dose ratio.

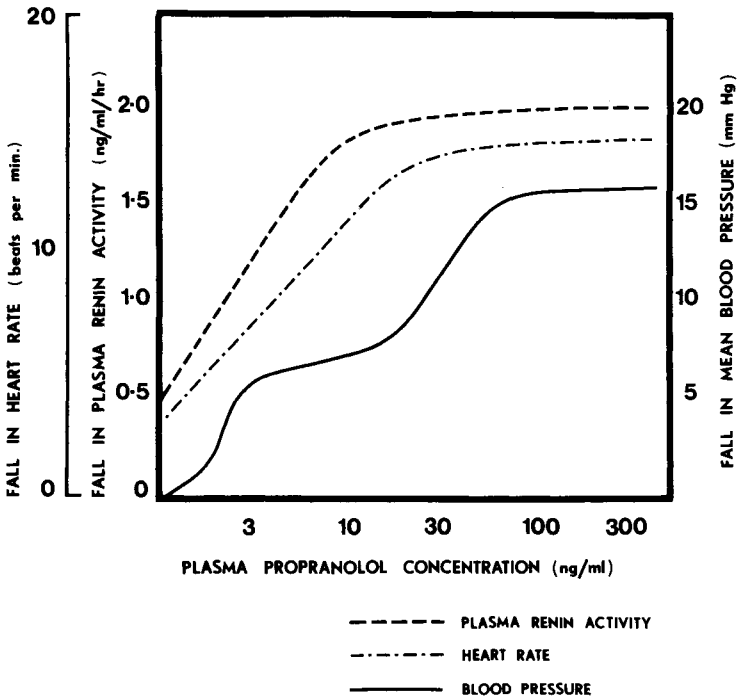

Fig. 5. Relation between plasma propranolol concentration and reduction in blood pressure, plasma renin activity, and supine heart rate.

plasma concentrations of 3 to 30 ng/ml, coincided with maximum suppression of PRA and heart rate. The late component of the blood pressure fall occurred at a plasma concentration well in excess of that necessary to suppress PRA and heart rate maximally.

Since the early component of the antihypertensive response was accentuated in patients with elevated PRA and occurred at a plasma propranolol concentration causing maximal suppression of plasma renin, it was of interest to see whether changes in blood pressure and PRA correlated at plasma propranolol concentrations of 3 to 30 ng/ml. There was a correlation, but of low order only ($r = 0.39$, $p < 0.05$). It appears that renin suppression, as an antihypertensive mechanism, cannot explain the relationship of renin status to blood pressure decrease at low plasma propranolol levels.

An alternative explanation of the greater pressure decrease in high-renin patients was sought in a possible relation of high PRA to sympathetic nervous overactivity.[3, 7, 21] Compared with normal subjects and hypertensive patients with normal or low PRA, the high-renin hypertensive patients were characterized as a group by features of sympathetic nervous system overactivity such as elevated plasma norepinephrine concentration, higher cardiac output and heart rate, shortened cardiac preejection period index, and increased mean left ventricular ejection rate (Table II). When the 7 patients with elevated plasma norepinephrine concentration (above 210 ng/L) were compared with those with normal plasma norepinephrine, an enhanced antihypertensive effect of propranolol was noted in the former which was most prominent with systolic pressure and again only at a plasma propranolol concentration of 3 to 30 ng/ml (Fig. 6).

Discussion

When the blood pressure decrease with propranolol was related to plasma concentration of the drug, the dose-response relationship appeared to be biphasic. Approximately 30% of the maximum blood pressure fall occurred at a plasma propranolol concentration below 20 ng/ml. A second component of the antihypertensive response was noted at plasma proprano-

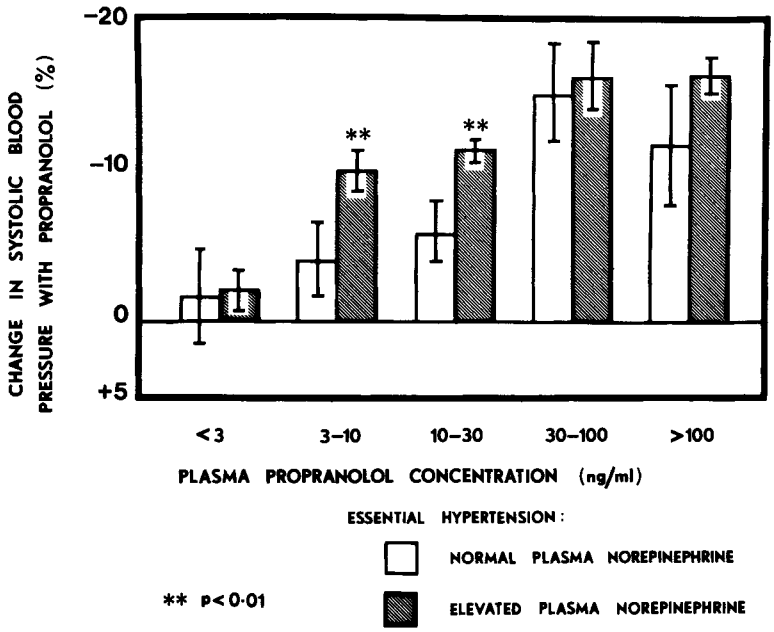

Fig. 6. Fall in systolic blood pressure (%) expressed in relation to pretreatment plasma norepinephrine concentration. The fall in pressure was greater in patients with elevated plasma norepinephrine concentration at plasma propranolol levels of 3 to 30 ng/ml.

Table II. *Indices of sympathetic nervous system activity in patients with high-renin essential hypertension*

			Cardiac hemodynamics at rest				
					Systolic time indices		
Subjects	*Plasma renin activity, standing (ng/ml/hr)*	*Plasma norepinephrine concentration (ng/L)*	*Cardiac index (L/min/m²)*	*Heart rate/ min*	*PEPI (msec)*	*LVETI (msec)*	*Mean left ventricular ejection rate (ml/sec)*
Normal subjects	2.10 ± 0.52	138 ± 36	2.66 ± 0.32	60 ± 7	130 ± 8	405 ± 16	150 ± 19
Essential hypertension subjects							
High-renin	4.82 ± 0.55*	261 ± 47*	3.28 ± 0.57†	69 ± 8†	119 ± 7†	405 ± 16	170 ± 14†
Normal-renin	2.40 ± 0.61	161 ± 58	2.37 ± 0.33	60 ± 8	130 ± 6	394 ± 21	139 ± 29
Low-renin	0.96 ± 0.27	101 ± 54	2.30 ± 0.51	55 ± 7	141 ± 7†	396 ± 9	141 ± 45

PEPI: pre-ejection period index; LVETI: left ventricular ejection time index. Mean values and standard deviations are listed. The significance of the differences between values for the hypertension renin subgroups and the normal subjects is indicated.

*$p < 0.01$, Student's t test.

†$p < 0.05$.

lol concentrations above 30 ng/ml, with an apparent plateau in the blood pressure response at drug concentrations above 100 ng/ml. Our findings are in general agreement with the concept of a biphasic dose-response relationship for the antihypertensive effect of propranolol, such as was recently proposed by Hollifield and associates.[14] Although a peak blood pressure fall seemed to be achieved at a plasma propranolol concentration of 100 ng/ml, the clinical question of whether further useful therapeutic effect can be achieved in unresponsive severely hypertensive patients by higher doses of the drug was not elucidated,[24] because the present study was confined to patients with mild to moderately severe disease only and the maximum daily propranolol dose given was 320 mg.

When plasma propranolol concentration was

measured in these patients and related to oral dose, the expected[23] wide spread was noted. Since there was a significant relationship between plasma propranolol concentration and blood pressure fall overall, it was pertinent to determine whether patients with the lowest plasma drug level had the poorest therapeutic response. This was found not to be the case. At a given dose of propranolol, the fall in blood pressure was not smaller in patients with lower plasma concentrations.

This anomalous finding of an adequate antihypertensive response coincident with a low plasma propranolol concentration seemed to be due to the fact that sensitivity to propranolol was related to pharmacokinetic characteristics. Such a relationship has been noted previously—subjects with the lowest plasma propranolol level showing the greater sensitivity.[23] Possible mechanisms advanced to explain this observation include more active first-pass hepatic biotransformation in patients with low plasma propranolol concentrations with production of an active metabolite, increased volume of distribution of the drug associated with greater tissue binding and beta receptor avidity and resultant low plasma levels of drug, and diminished plasma protein binding causing proportionally more drug to be present in plasma in the free state with a reduction in total plasma propranolol concentration.[20, 23] Whatever the mechanism, it seems that any pharmacokinetic differences between patients which cause plasma propranolol levels to differ widely are not responsible for differences in clinical responsiveness to propranolol in essential hypertension.

When possible pathophysiologic predictors of the response to propranolol were sought, it was found that the blood pressure decrease was greatest in patients with high PRA, but only at low plasma propranolol concentrations (3 to 30 ng/ml). At plasma levels of 30 to 100 ng/ml and above, the magnitude of the blood pressure decrement in high-renin hypertensive patients did not differ from that in patients with normal and low PRA. Since this low-dose component of the antihypertensive response to propranolol is accentuated in patients with elevated PRA and coincides with maximal suppression of plasma renin, it would appear to support the view that the blood pressure decrease with the drug in essential hypertension is a consequence, at least in part, of lowering of PRA.[1, 14] However, when changes in blood pressure and PRA were compared, the order of correlation was low which suggests that renin suppression was not a major antihypertensive mechanism even at low plasma propranolol concentrations. At drug concentrations above 30 ng/ml, blood pressure decrements and PRA were totally unrelated.

Recent studies in patients with mild high-renin essential hypertension strongly suggest that in this condition the blood pressure elevation is not renin-dependent,[5, 21] which is in contrast with the situation in severe and accelerated essential hypertension in which PRA values are higher, with sufficient elevation of plasma angiotensin levels to raise blood pressure by direct arteriolar constriction.[2, 3]

In mild high-renin essential hypertension the elevation of PRA is viewed as secondary to a generalized increase in sympathetic nervous system activity in what appears to be a neurogenic form of hypertension.[3, 4, 21] In our study patients with high PRA had mild hypertension, 3 of 7 having isolated systolic hypertension accompanied by features of sympathetic nervous system overactivity. Plasma norepinephrine concentration was elevated in high-renin patients and the hemodynamic findings of a higher cardiac output and heart rate, shortened cardiac pre-ejection period index, and increased mean left ventricular ejection rate suggested the presence of sympathetic cardiac stimulation. It may be that patients with increased sympathetic nervous cardiovascular tone experienced the greatest fall in blood pressure with low doses of propranolol. In our study, fall in blood pressure at low plasma propranolol levels was greatest in patients with an elevated pretreatment plasma norepinephrine concentration. There are earlier reports also of increased sensitivity to low doses of other beta adrenoceptor antagonists (practolol, acebutolol) in patients with essential hypertension with increased sympathetic nervous system activity.[6, 9] It is likely that any relation there may be between PRA and respon-

siveness to beta adrenergic blocking drugs is incidental to the role of the sympathetic nervous system in determining renin status.[4, 8, 21]

The antihypertensive action of propranolol in essential hypertension appears to involve two mechanisms[14]—a relatively minor mechanism at plasma drug levels of 3 to 30 ng/ml and a more important action at concentrations in excess of 30 ng/ml. The low-dose antihypertensive action was accentuated in patients with features of sympathetic nervous overactivity and high PRA in whom it was responsible for more than 50% of the antihypertensive action of the drug. The antihypertensive mechanism does not appear to be suppression of plasma renin, although this occurs concurrently. A second action of propranolol, occurring at similar plasma concentrations, is blockade of cardiac beta adrenoceptors. It seems possible that in the patients with sympathetic nervous overactivity and high plasma renin there is also an important cardiac component which is antagonized at low plasma propranolol concentrations. Cardiac output and left ventricular ejection rates were highest in these patients. An early report by Frohlich and associates[10] described a relationship between pretreatment cardiac output and the antihypertensive response to propranolol, but it was not confirmed in most subsequent studies.[22] This disagreement may have arisen because the relation of cardiac suppression to antihypertensive effect depends on patient selection, since it occurs only in patients with pronounced sympathetic cardiac stimulation and is dose-related, demonstrable only at propranolol doses of approximately 40 to 80 mg daily.

In the majority of patients the antihypertensive effect of propranolol was minimal at plasma propranolol concentrations under 30 ng/ml and appeared only at higher plasma drug concentrations. Our study tells nothing of the mechanism of this blood pressure fall, other than that it seems to be independent of lowering of PRA and occurs at plasma propranolol concentrations in excess of those needed to induce near maximal plasma renin suppression.[16] It is not clear whether the results obtained bear on the possible significance of a second major antihypertensive mechanism of beta adrenoceptor blocking drugs—suppression of sympathetic nervous system function.[6, 15] They do not, however, appear to support this view, since the antihypertensive response to propranolol, at the highest dose, was not related to pretreatment plasma norepinephrine concentration.

With the use of pathophysiologic indices, prediction of the blood pressure decrease with propranolol was possible only at low doses of the drug. Since normalization of blood pressure in essential hypertension can be achieved in most patients at higher doses,[24] possible clinical benefits arising from the use of plasma renin or indices of sympathetic nervous function as aids to the individualization of therapy appear to be negligible. Clinical rather than pathophysiologic criteria probably offer more appropriate guidelines for the selection of propranolol as the antihypertensive drug of choice in some patients with essential hypertension.[13, 25]

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