Baroreflex sensitivity in hypertension during beta-adrenergic blockade

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SUMMARY Baroreceptor function was measured in 18 patients with essential hypertension by plotting the change in pulse interval against a phenylephrine-induced transient rise in systolic blood pressure. The influence of propranolol (160 mg daily for at least 4 weeks) on this function and on heart rate after maximal exercise was studied and correlated with the plasma propranolol level. In 13 out of the 18 patients only baroreflex resetting occurred with no change in sensitivity during propranolol administration. A definite correlation was found between the degree of beta-adrenergic blockade, expressed as the reduction in maximal exercise heart rate and the change in mean arterial pressure. No relation could be shown between plasma propranolol steady state levels and these changes. The fall in blood pressure during beta-adrenergic blockade with a low dosage of propranolol apparently does not depend on changed baroreflex sensitivity, but on the intrinsic action of this drug on beta-receptors.

Beta-adrenergic blocking agents lower blood pressure effectively, but their mode of action remains obscure. The antihypertensive effect has variously been ascribed to a reduction in cardiac output (Frohlich *et al.*, 1968) or renin activity (Bühler *et al.*, 1972), but the relative importance of these changes has been disputed. Theories based on a central mechanism of action remain controversial (Offerhaus and van Zwieten, 1974; Meyers *et al.*, 1975), while Prichard proposed that a gradual conditioning of the baroreceptors by the damping of pressor responses to regulate the blood pressure at a lower level might be the most likely explanation (Prichard and Gillam, 1966).

We therefore studied the baroreflex sensitivity in hypertensive patients before and during treatment with a beta-adrenergic blocking drug (propranolol). Such sensitivity can be measured repeatedly by plotting the rise in blood pressure after a bolus injection of phenylephrine against the concomitant decrease in heart rate (Bristow *et al.*, 1969; Smyth *et al.*, 1969). Reflex changes were correlated with the degree of beta-adrenergic blockade, determined by the heart rate reduction during exercise and the plasma levels of propranolol.

Patients and methods

Baroreflex sensitivity was measured before and after

4 to 6 weeks of treatment with propranolol 80 mg orally twice daily in 18 outpatients who gave informed consent. All had essential hypertension (diastolic pressure between 100 and 130 mmHg). Their ages were 25 to 69 years, mean 43. All other medication was stopped two weeks before the first measurement and patients were advised to moderate their dietary sodium intake.

Intra-arterial blood pressure and electrocardiograms were recorded simultaneously on a multi-channel ink-jet writer at a paper speed of 50 mm/s.

Between 3 and 5 bolus injections of phenylephrine, 200 µg, were given through an intravenous cannula in an antecubital vein. The interval between the injections always exceeded 5 minutes. During the rapid rise in blood pressure after injection, baroreflex sensitivity was calculated by plotting the RR interval against the systolic pressure of the preceding beat. Measurements were made from the moment arterial pressure began to rise acutely until it reached its peak, and the linear correlation between these points was then calculated using the method of least squares. Reflex sensitivity was expressed as the slope of the regression line, and the result was included only if the P value was less than 0.05 and the correlation coefficient was greater than 0.60. Occasionally these conditions were not met.

Baroreceptor function can be modified in two ways. When the slope of the relation between arterial pressure and pulse interval remains unaltered, the regression lines before and during

Baroreflex during propranolol

treatment are parallel, indicating that baroreflex sensitivity is unchanged. The shift observed is called resetting. On the other hand, a change in the slope of the regression line during treatment is indicative of an alteration in the sensitivity of the reflex arc. A combination of resetting and a change in sensitivity is also possible. For practical reasons in our experiments resetting was calculated as the percentage change in the systolic arterial pressure at an RR interval of 1000 ms.

All patients performed a multistage maximal exercise treadmill test according to the Bruce protocol (Bruce *et al.*, 1963) before and during treatment. The degree of beta-adrenergic blockade was calculated as the percentage reduction in heart rate at maximal exercise during treatment with propranolol.

After 4 to 6 weeks of treatment plasma propranolol levels were measured in 16 patients in the fasting state and 2, 3, 4, 5, and 6 hours after administration of propranolol 80 mg orally. The mean steady state concentration was calculated from the area under the curve, divided by the dosage interval; the plasma propranolol concentration was determined by a modified fluorimetric method (Offerhaus and van der Vecht, 1976).

Statistical analysis was performed using the *t* test for unpaired data, with Bessel correction for small numbers.

Results

As expected, both mean arterial pressure and heart rate at rest and during exercise decreased after 4 to 6 weeks of propranolol, 160 mg daily (Table 1). Baroreflex sensitivity did not change significantly in the group as a whole, though in 4 patients there was a significant increase above control values

Table 1 Effects of propranolol on haemodynamics (mean $\pm$ SEM) in 18 patients

	Before treatment	Propranolol 160 mg/day	Significance of change
Mean arterial pressure (mmHg)	123 $\pm$ 4	111 $\pm$ 3	$P < 0.05$
Resting heart rate (b/min)	72 $\pm$ 2	57 $\pm$ 2	$P < 0.001$
Maximal heart rate during exercise (b/min)	162 $\pm$ 4	126 $\pm$ 4	$P < 0.001$
Baroreceptor reflex sensitivity (ms/mmHg)	8.53 $\pm$ 1.18	11.17 $\pm$ 2.06	NS
Systolic arterial pressure at RR interval of 1000 ms (mmHg)	206 $\pm$ 10	149 $\pm$ 7	$P < 0.001$
Phenylephrine induced rise in systolic arterial pressure (mmHg)	40 $\pm$ 3	51 $\pm$ 3	$P < 0.05$

Fig. 1 Baroreceptor-reflex sensitivity before and during propranolol therapy. Four patients show increased sensitivity (Δ), 13 no significant change ($\bullet$), and 1 a decrease in sensitivity ($\blacksquare$). The open circles represent the mean values for all patients.

(group B) (Fig. 1). In 13 patients (group A) there was only resetting of the baroreceptors, since propranolol lowered heart rate and blood pressure equally. One patient showed a decrease in baroreceptor sensitivity. The 4 patients with increased sensitivity also showed baroreceptor resetting (Fig. 2). When resetting was plotted against the reduction in maximal heart rate or mean arterial pressure, two linear relations were obtained (Fig. 3), showing the relative contributions of changes in heart rate and blood pressure to such resetting. There was no significant difference between groups A and B with regard to age, initial mean arterial pressure, pretreatment baroreflex sensitivity, heart rate, and blood pressure reduction during propranolol treatment, or in the mean steady state concentration of plasma propranolol (64 ± 8 versus 84 ± 19 ng/ml, NS). However, in group A the transient rise in blood pressure after phenylephrine was augmented during propranolol treatment, but this phenomenon was not seen in the 4 patients with both resetting and increased sensitivity (Table 2).

In all patients an inverse correlation was found,

Fig. 2 Influence of propranolol on baroreceptor reflex function. The slope of the lines represents the means of baroreceptor reflex sensitivities before (open symbols) and during (closed symbols) propranolol treatment. In group A ($\circ$) the slopes are not significantly different and the lines are parallel (resetting). In group B ($\triangle$) there is a significant ($P < 0.05$) difference between the slopes (resetting and change in sensitivity).

Fig. 3 Relation between resetting versus beta-blocking and antihypersensitive properties of propranolol. In all 18 patients a correlation was found between the degree of resetting versus the percentage reduction in maximal heart rate during exercise (closed symbols) and the change in mean arterial pressure (open symbols). The form of the symbols refers to Fig. 1.

Table 2 Response to alpha-adrenergic stimulation in group A and B before and during propranolol treatment (mean $\pm$ SEM)

	Group A n = 13	Group B n = 4	
Phenylephrine induced rise in systolic arterial pressure before treatment (mmHg)	39 $\pm$ 2	42 $\pm$ 13	NS
Phenylephrine induced rise in systolic arterial pressure during propranolol 160 mg daily (mmHg)	55 $\pm$ 3	33 $\pm$ 6	P < 0.01
	P < 0.001	NS	

both before and during propranolol treatment, between baroreflex sensitivity and the rise in systolic arterial pressure after phenylephrine ($P < 0.01$).

Plotting the change in mean arterial pressure during propranolol treatment against the heart rate reduction during maximal exercise yielded a definite linear relation (Fig. 4). No correlation was found between the propranolol mean steady state concentration and the antihypertensive effect or the reduction in heart rate at rest, or during maximal exercise.

Discussion

The influence of propranolol on baroreceptor function has previously been studied by Pickering *et al.* (1972), who found an increase in baroreflex sensitivity after intravenous propranolol in 4 of 5 healthy volunteers. We found no change in the majority of our hypertensive patients during chronic oral treatment with propranolol, using their method of determining baroreflex sensitivity. This finding confirms the results of Simon *et al.* (1977) who were also unable to find increased sensitivity in their hypertensive patients after propranolol intravenously. The difference between our results and those of Pickering *et al.* (1972) may be attributable to the low pretreatment sensitivity values in our group showing only resetting (group A)—about one-third of those in the healthy volunteers given propranolol intravenously—and to the fact that such values decrease with age and the severity of hypertension. In 3 of our 4 patients who responded with increased sensitivity, the initial value lay far above the mean (Fig. 1).

The propranolol-induced excessive rise in blood pressure after phenylephrine in those patients showing no change in sensitivity may possibly have been the result of unopposed peripheral alpha-adrenergic activity. The fact that this rise was absent

Fig. 4 Correlation between the decrease in blood pressure and the reduction in maximal exercise heart rate during treatment with propranolol.

in the 4 patients with increased sensitivity on propranolol indicates that a sensitive baroreflex system, functioning normally, protects against an excessive blood pressure response provoked by alpha-adrenergic stimulation, for example by phenylephrine or the cold pressor test (Guazzi *et al.*, 1976).

Although some investigators (Coltart and Shand, 1970; Pine *et al.*, 1975) have reported a linear relation between the degree of beta-adrenergic blockade and the logarithm of the plasma propranolol level, no such relation was found in our study between mean steady state propranolol and its effect on maximal exercise heart rate. This discrepancy might be explained by their method of quantifying beta-blockade in a limited number of healthy volunteers on various dosage schedules or, alternatively, by variations in the metabolic clearance or plasma protein binding of the drug.

Functional beta-adrenergic blockade with a standard propranolol regimen was found to be closely related to its antihypertensive effect and a similar observation was made in a study of hypertensive patients treated with five different beta-blocking agents (Davidson *et al.*, 1976). In doses that produced similar reductions in exercise tachycardia, all drugs had identical blood pressure lowering activity which was more pronounced on systolic than diastolic pressure and was greatest during exercise.

We, therefore, conclude that the antihypertensive effect of beta-adrenergic blockade is not explained by changes in baroreflex sensitivity; resetting is the major change in function during administration of low dosages of propranolol. The intrinsic action of this drug on the beta-receptors explains adequately the observed fall in blood pressure.

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