The Paradox of Beta-Adrenergic Blockade in Hypertension

By Edward D. Frohlich, M.D., Robert C. Tarazi, M.D., Harriet P. Dustan, M.D., and Irvine H. Page, M.D.

SUMMARY

The effects of long-term treatment with propranolol, a beta-adrenergic blocking drug, were determined in 19 hypertensive patients (five with renal arterial disease, two with renal parenchymal disease, and 12 with essential hypertension) whose vascular disease was of mild to moderate severity. The drug reduced arterial pressure in 16 patients during 32 weeks of treatment (average); daily dose was 180 mg (average). No side effects required discontinuation of treatment. Orthostatic hypotension did not occur, an unusual finding for an antihypertensive drug which acts to inhibit autonomic neural function. In seven patients, hemodynamic studies, performed during treatment (after 10 months, average), confirmed reduction of arterial pressure and heart rate, and demonstrated associated diminution of cardiac output and increased peripheral resistance.

Additional Indexing Words:
Propranolol    Essential hypertension    Renovascular hypertension
Hemodynamics    Renal parenchymal disease    Cardiac output
Drug treatment of hypertension

Because hypertension has long been ascribed to increased peripheral resistance, its treatment has been primarily directed toward blood pressure reduction by decreasing vascular resistance. Beta-adrenergic receptor stimulation results in peripheral vasodilatation, and at first thought inhibition of beta receptors in the treatment of hypertension seems paradoxical. However, beta-adrenergic inhibition also reduces cardiac output, another hemodynamic variable directly affecting arterial pressure. Perhaps the effectiveness of beta-adrenergic receptor blocking drugs in treatment of diastolic hypertension may be related to this effect, but hemodynamic studies during long-term treatment have not yet been reported.

The present report concerns the clinical and hemodynamic effects of prolonged treatment of diastolic hypertension with propranolol, a new beta-adrenergic blocking drug.

Methods

Nineteen patients, who have been part of a long-term follow-up study of hypertensive patients, were treated with propranolol after a 1 to 3-month period during which time they received no therapy at all, a placebo, or both sequentially. A summary of the clinical information concerning these patients is presented in table 1. Of the 19 patients, five had renal arterial lesions, two renal parenchymal disease, and 12 essential hypertension; all had renal arteriography performed to define arterial disease. There were 10 men and nine women, whose average age was 41 years, with a range of 24 to 55 years. All had hypertension of mild to moderate severity, as graded by the criteria of Corcoran and associates.

All patients took their own blood pressures at home twice daily; weekly supine and standing blood pressure averages were tabulated during the control and treatment periods. For ease of handling data, however, pretreatment pressures are defined as the average for the one complete month immediately before propranolol was begun, and treatment pressures are defined as the
average pressures for the most recent treatment month.

Patients were seen periodically in the office by the same physician, during which time blood pressures and heart rate were measured and information concerning symptoms and side effects were recorded. Measurement of hematological (hematocrit, hemoglobin, white blood cell count), hepatic (serum glutamic oxalacetic transaminase, alkaline phosphatase), and renal (blood urea) functions were performed at monthly intervals at the beginning of the investigation; more recently, these determinations were made at bimonthly intervals.

Treatment was always begun after at least a 1-month control period; initially 10 to 20 mg four times daily was prescribed. Dosage was progressively increased to as much as 120 mg four times daily. At no time during treatment were other antihypertensive medications or diuretics included. Therapy was continued for an average of 32 weeks (range, 2 to 88 weeks); the average total daily dosage was 180 mg.

Hemodynamic studies were performed on seven patients before and during treatment. Each study was conducted in a manner similar to that described previously.2, 8 In brief, catheters were inserted centrally through a brachial artery and a contralateral antecubital vein for recording pressures, injecting indocyanine-green dye, and obtaining indicator-dilution curves for determination of cardiac output. After obtaining base-line studies in the supine position, isoproterenol was infused intravenously at increasing rates (1, 2, and 3 µg/min). These studies constitute the "before treatment" measurements. After oral propranolol treatment for some time and after significant reduction of arterial pressure, some patients were rehospitalized for investigation of the hemodynamic mechanisms underlying the reduction in their arterial pressure. Inhibition of beta-adrenergic activity was confirmed by failure of isoproterenol to increase heart rate at the previously infused rates. Cardiac output was calculated using the Stewart-Hamilton method10, 11 and is expressed as cardiac index (ml/min/m²). Total peripheral resistance is expressed as mm Hg/ml/min as the quotient of mean arterial pressure divided by cardiac output. Left ventricular ejection rate is expressed as ml/sec/m² by dividing stroke index by left ventricular ejection time.

Results

Hypotensive Effects

Arterial pressure was reduced in 16 of the 19 patients studied. For the entire group,
pretreatment supine and standing home pressures fell from 156/97 and 161/106 mm Hg to 140/86 and 145/99 mm Hg, respectively, after an average of 32 weeks. Of the three patients who failed to respond to treatment, one (no. 19) was the first treated and propranolol was, perhaps, withdrawn prematurely; patient 12 is still taking propranolol, but in conjunction with hydrochlorothiazide, and his arterial pressures have been reduced (table 2).

Of the 16 patients who responded to propranolol, systolic and diastolic pressures were equally reduced in the supine or sitting and standing positions, whether the home or office pressure data are compared (table 3).
Table 4
Hemodynamic Changes Following 10 Months (Average) Propranolol Treatment (Range, 4 to 18 Months) in Seven Hypertensive Patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Arterial pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Cardiac output (ml/min)</th>
<th>Cardiac index (ml/min/m²)</th>
<th>Stroke index (ml/beat/m²)</th>
<th>Total peripheral resistance (mm Hg/ml/min)</th>
<th>Ejection time (corrected) (msec)</th>
<th>Mean rate left ventricle ejection (ml/sec/m²)</th>
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<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Mean</td>
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<td>76</td>
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<td>2593</td>
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<td>6915</td>
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<td><strong>88</strong></td>
<td><strong>6130</strong></td>
<td><strong>3459</strong></td>
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<td><strong>65</strong></td>
<td><strong>4615</strong></td>
<td><strong>2581</strong></td>
<td><strong>40</strong></td>
<td><strong>.026</strong></td>
<td><strong>319</strong></td>
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<td>0.01</td>
<td>0.005</td>
<td>0.005</td>
<td>0.001</td>
<td>ns</td>
<td>.10</td>
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se = Standard error; ns = not significant.
Thus, at the office, as well as at home, arterial pressure was significantly reduced in over 80% of patients selected for treatment. The reduction of supine and standing pressures during treatment was proportionate, thereby preserving the pretreatment response of systolic, diastolic, and mean arterial pressures to the upright position; orthostatic hypotension was never observed with propranolol therapy. Thus far, no evidence of drug tolerance has developed. Sitting heart rate (obtained in the office) was reduced in all 19 patients receiving propranolol from an average of 84 to 66 beats/min.

**Side Effects**

Major side effects were not observed with treatment. One patient (no. 3) complained of minor wheezing during the second week of treatment, and since she had a history of asthmatic bronchitis as a child, treatment was discontinued because beta-adrenergic blocking drugs are contraindicated in patients having asthmatic bronchitis.12 Three patients noted somnolence and some lethargy, and one patient complained of weakness; but these symptoms disappeared with modification of the dosage schedule, and treatment was not discontinued. One patient (no. 6), who had suffered from depression prior to treatment with propranolol, had treatment discontinued after 8 months in anticipation of antidepressant therapy, but it was our belief, as well as that of the patient and consulting psychiatrist, that propranolol was unrelated. Although arterial pressure had increased following withdrawal of the drug, the depression persisted. One patient noted constipation and another, flatulence. Eleven patients noted a feeling of well-being, diminished anxiety, and volunteered that they were more able to cope with their daily problems.

**Laboratory Studies**

Measurements of hematological, hepatic, and renal function were performed at monthly intervals, and no significant changes were observed during the treatment period. Consequently, more recently, we have only re-evaluated these tests at bimonthly intervals.

**Hemodynamic Studies**

Hemodynamic functions were measured before and during propranolol therapy in seven patients, and their results are presented in table 4. The second hemodynamic study was performed 10 months (average) after propranolol was begun (range, 4 to 15 months), and at times when home treatment blood pressure was significantly lower than pretreatment pressures. Associated with the reduction in arterial pressures (systolic, diastolic, and mean) in all seven patients was a significant decrease in cardiac output (6,130 to 4,615 ml/min; P < 0.005). The reduction in output is explained solely by decreased heart rate from 88 to 65 beats/min (P < 0.005), since stroke volume remained unchanged. Despite the lack of change in stroke index, left ventricular ejection rate was significantly reduced (146 to 129 ml/sec/m²; P < 0.025) because of prolongation of left ventricular ejection time (uncorrected for heart rate). When ejection time was corrected for heart rate, however, there was no significant difference before and during drug treatment. Total peripheral resistance increased in five and decreased in two patients (in one, only minimally). Thus, arterial pressure was reduced in all seven hypertensive patients, primarily by a reduction in cardiac output, and in five the pressure fall was accompanied by increased total peripheral resistance. Isoproterenol was infused intravenously in all patients at the conclusion of the hemodynamic studies, and the drug failed to increase heart rate even at infusion rates as high as 3 µg/min.

**Discussion**

The results of this study show that in some hypertensive patients beta-adrenergic blocking therapy, with propranolol, is effective in reducing arterial pressure with little or no side effects and no orthostatic hypotension. These findings seem paradoxical for two reasons. First, the drug fails to reduce arterial pressure immediately following its intravenous administration but only reduces cardiac output and heart rate.2 Secondly,
arterial pressure is reduced with prolonged treatment in hypertensive patients by a mechanism which does not decrease total peripheral resistance.

The mechanism by which arterial pressure is lowered must be attributed to prolonged reduction of cardiac output. Output has remained reduced by approximately 25% of pretreatment levels after 10 months' (average) therapy, and in some patients this has been maintained for as long as 15 months. That this reduction is related to persistent beta-adrenergic inhibition is shown by the failure of isoproterenol to increase heart rate. This indicates that with prolonged inhibition of beta-adrenergic activity there is no physiological "tolerance" of the heart. We have previously shown that output was reduced by 20% following intravenous administration of propranolol.

These studies also confirm our previous observation that output is lowered in patients with hypertension by reduction in heart rate, and further suggest that by prolonged inhibition of beta-adrenergic activity, arterial pressure may be reduced. It seems unlikely that only patients with elevated cardiac output respond to beta-adrenergic inhibition since several patients who responded to propranolol had normal or low-normal cardiac output prior to therapy.

Reduction in cardiac output and left ventricular ejection rate does not represent latent cardiac failure because of the slowing of heart rate, marked symptomatic improvement, absence of shortness of breath, unchanged cardiac silhouette without pulmonary congestion, and in one patient, actual reduction of cardiopulmonary volume. That arterial pressure reduction is not attributable to a non-specific tranquilizing effect was demonstrated to us by the persistent reduction in pressure at more stressful times in some patients, and when one patient was severely depressed.

The hemodynamic findings suggest to us a new approach whereby arterial pressure may be reduced in hypertension. It seems likely that with persistent reduction of cardiac output there is a decrease in arterial pressure without concomitant systemic vasodilation. Since peripheral resistance increases and remains increased with reduction of arterial pressure, the mechanism cannot be explained solely by resetting of baroreceptors, as has been previously suggested by Prichard and Gillam. For the same reasoning, it does not seem likely that pressure is reduced by an arterial myogenic response, such as that described by Bayliss. Perhaps a clearer understanding of the pressure-flow-autoregulation relationship in hypertension may shed some light on the mechanism of blood pressure reduction by prolonged reduction of cardiac output.

Acknowledgment

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References


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Early Clinical Impressions Concerning Angina (Parry-1799)

Benefits of Exercise

But though organic diseases of the heart may be produced by violent exertions, it has been thought that they are counteracted by moderate bodily exercise. Thus Senac observes, that they are rarely to be met with in foot-soldiers. It is probable, however, that these men combine with their uniform exercise more strict temperance as to food and drink, than most other persons who live by bodily labour; to which it must be added, that the Syncope Anginosa is commonly the fate of men advanced in years, while soldiers rarely continue their occupation much beyond the middle period of life. Notwithstanding the objections which may be adduced against this argument of Senac, it appears to me that the principle is well founded and that nothing guards more certainly against irregular action of the heart than uniform and gentle bodily exertion.—CALEB HILLIER PARRY: An Inquiry into the Symptoms and Causes of the Syncope Anginosa, Commonly Called Angina Pectoris. London, Cadell and Davies, 1799, p. 148.
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