Antihypertensive Therapy with Prazosin in Patients with Left Ventricular Dysfunction*

Improvement in Cardiac Performance and Exercise Tolerance

Barry M. Massie, M.D.,† and Samuel Chan, M.D.

Although the relationship between blood pressure and cardiac performance has been widely recognized, there are few published clinical observations concerning the effect of blood pressure control on cardiac function. We evaluated the effect of prazosin, an antihypertensive agent which also improves hemodynamic measurements in normotensive patients with heart failure, in 16 patients with moderate hypertension and reduced ejection fractions. Therapy with digoxin and diuretics was continued throughout the study, but other antihypertensive agents were withdrawn at least one week prior to the initiation of the study. Measurements of ejection fraction, cardiothoracic ratio and the duration of maximal treadmill exercise were made before and after two months of antihypertensive therapy with prazosin. On prazosin, blood pressure fell from a mean of 169/103 to 141/84. Excellent control was achieved in 13/16 patients and significant reductions were noted in the remaining three. Concomitantly, ejection fraction rose from .38 ± .02 (SEM) to .43 ± .03 (P<.02), cardiothoracic ratio decreased from .55 ± .02 to .53 ± .02 (P<.05) and exercise capacity increased from 9.2 ± 0.9 to 11.9 ± 1.1 minutes (P<.005). Prazosin was well tolerated except in one patient who experienced worsening angina. These findings emphasize the importance of rigorous blood pressure control in hypertensive patients with left ventricular dysfunction and indicate that prazosin is effective in this setting.

For many years, clinicians and investigators have recognized that hypertension may lead to heart failure, either as the primary etiology or as an exacerbating factor in patients with other cardiac diseases. More recently, the dynamic interrelationship between blood pressure and left ventricular function has been appreciated. Thus, a rise in arterial pressure resulting from increased peripheral vascular resistance may be sufficient to produce clinical deterioration in patients with previously compensated left ventricular dysfunction. Conversely, a reduction in impedance to left ventricular ejection, which may be accomplished by treating hypertension or lowering peripheral vascular resistance in normotensive patients, may improve performance.

Despite this knowledge, clinical observations concerning the response to antihypertensive therapy in patients with elevated blood pressure and impaired left ventricular function are limited. We undertook the present study to determine the effect of antihypertensive therapy with prazosin on cardiac function and exercise tolerance in patients with left ventricular dysfunction. We employed prazosin because this agent has also shown some promise in the treatment of heart failure in normotensive subjects and therefore is potentially a particularly appropriate medication for use in this setting.

METHODS

Patients

Sixteen male patients with both moderate hypertension (defined by sitting diastolic blood pressure above 95 mmHg while continuing on diuretic therapy), and left ventricular dysfunction, as evidenced by an ejection fraction below 50 percent, were studied. Their mean age was 63 years, with a range of 55-83. All were previously diagnosed as having hypertension and had been receiving antihypertensive therapy for a mean of 11 years (range 6 months to 35 years). Patients with myocardial infarction within the previous three months, severe angina pectoris, renal insufficiency with elevated serum creatinine, or other significant medical illnesses were excluded.

Thirteen of the 16 patients had clinical and historical evidence of congestive heart failure, while the remaining three had only radiographic signs of left ventricular enlargement or failure and a reduced ejection fraction (<50 percent). In addition to hypertension, 14 patients had atherosclerotic heart disease diagnosed by clinical or electrocardiographic evidence of prior infarction, angina pectoris, or both. Twelve patients were receiving digoxin chronically and all were maintained on diuretics (six on hydrochlorothiazide, 50 or 100 mg daily; four on metolazone, 5 mg daily, and six on furosemide, 80 to 160 mg daily).
were discontinued for a washout period of 7 to 14 days. Patients meeting the entry blood pressure criteria on three determinations then underwent complete clinical and laboratory evaluation. Baseline measurement of cardiothoracic ratio, ejection fraction and exercise tolerance by the techniques described below were performed at the end of the washout phase. Then, prazosin, 1 mg bid, was initiated and the dosage increased progressively to 2 mg bid, 4 mg bid, 5-8 mg bid, 10 mg bid, and 10 mg tid at weekly intervals until the sitting diastolic pressure was lowered to 85 mm Hg or below, or until the sitting diastolic pressure was reduced by at least 15 mm Hg and the maximum tolerated dosage of prazosin was administered. Prazosin dosage was determined solely by these blood pressure criteria.

Once the therapeutic dosage was established, patients were seen at monthly intervals for two months. The dose of prazosin was not changed during this maintenance phase. Then, at the end of the two-month maintenance phase, a complete clinical laboratory evaluation was again performed and the measurements of cardiothoracic ratio, ejection fraction and exercise tolerance were repeated.

**Efficacy Parameters**

The effect of antihypertensive therapy with prazosin on cardiac function was evaluated by comparing the pre-treatment and post-treatment measurements of ejection fraction, cardiothoracic ratio and exercise tolerance. Ejection fraction was determined using a co-axial scintillation probe, according to previously published methods, using 2mCi 99m technetium pertechnetate as the radioactive tracer. Cardiothoracic ratio was measured by the standard technique. Exercise tolerance was assessed by the duration of treadmill exercise on a gradually progressive protocol (the Naughton protocol, modified so that the workload was increased every three minutes instead of every two). The exercise tests were discontinued when the patients experienced limiting dyspnea or fatigue. The patients were questioned concern-

**Study Design**

All antihypertensive medications, except for diuretics,

**Table 1—Patient Characteristics and Effects of Prazosin Therapy**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Clinical</th>
<th>Heart Rate Pre-Prazosin</th>
<th>Heart Rate on Prazosin</th>
<th>BP Pre-Prazosin</th>
<th>BP on Prazosin</th>
<th>EF Pre-Prazosin</th>
<th>EF on Prazosin</th>
<th>C-T Ratio Pre</th>
<th>C-T Ratio Prazosin</th>
<th>Ex Time Pre (min)</th>
<th>Ex Time Prazosin (min)</th>
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*Measurements on prazosin are those obtained after 2 months of maintenance therapy.
*Patient maintained on propranolol plus prazosin; results not included in calculations of mean changes.
*Patient suffered myocardial infarction after 6 weeks; results not included in calculations of mean changes.
Met = metolazone; Fur = furosemide; Hcts = hydrochlorothiazide

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ing changes in symptoms, and all side effects, adverse reactions, and laboratory abnormalities were noted.

The data were analyzed for statistical significance using the Student t test for paired samples.

**Results**

**Blood Pressure Control**

The mean daily dose of prazosin administered was 9 mg (standard deviation 7 mg, range 2-30 mg). The effect of prazosin therapy on the mean blood pressures of the group is shown in Figure 1 and the changes in individual patients are listed in Table 1. Excellent blood pressure control, as defined by a reduction of the sitting diastolic pressure to 85 mm Hg or below at the end of the titration phase and a diastolic pressure of 90 mm Hg, or below during the two monthly maintenance phase visits, was obtained in 11 patients. Significant improvement in blood pressure was noted in the remaining five patients. Patient 11 was controlled at the end of titration and at two months, but had blood pressure of 142/94 mm Hg at the one month visit. Patients 10 and 13 were also controlled at the end of titration, but had diastolic pressures between 90 and 95 mm Hg during maintenance therapy. The remaining two subjects (numbers 7 and 14) had more than 15 mm Hg reductions in their diastolic pressures, but nonetheless remained moderately hypertensive on the maximum tolerated dosage of prazosin (30 mg and 20 mg daily, respectively).

Heart rate was generally unaffected by prazosin therapy, varying only between 82 ± 9, 83 ± 9, 81 ± 7 and 80 ± 10 at the pre-treatment, end-titration, one month and two month visits. Only one patient, number 11, showed a clinically significant rise, from 84 to 101 during titration, and this increase was sustained throughout the study.

Side effects which could be attributed to prazosin were noted in four patients. Two experienced intermittent headaches shortly after taking prazosin, but these were controlled with mild analgesics and tended to abate with time. Two other patients, including patient 11 who displayed a consistent rise in heart rate during treatment, experienced frequent episodes of palpitations and dizziness after taking prazosin. While both of the latter completed the protocol successfully, one was the only subject who chose not to continue prazosin thereafter.

One patient (number 3) with only laboratory evidence of left ventricular dysfunction and who had been taking propranolol 40 mg qid and hydralazine experienced worsening of his previously mild, stable angina pectoris during the first week of prazosin. His chest pain subsided when propranolol was re instituted in addition to the prazosin.

Although he successfully completed the protocol on this combination, his data have been excluded from subsequent analysis. Another patient (number 9) suffered an acute myocardial infarction during the second month of maintenance therapy. This event did not appear to be related to prazosin, since this patient had three previous infarctions and had been doing well up until the acute event. Both his blood pressure and pulse rate were in the desired range, and the infarction began during the night, approximately six hours after the previous prazosin dose. He was dropped from the protocol and did not undergo the efficacy measurements on prazosin. Neither of these patients with ischemic complications was noted to have increase in heart rate during the study.

**Effect of Antihypertensive Therapy on Cardiac Function**

The changes in ejection fraction, cardiothoracic ratio and exercise tolerance are given in Table 1 and are illustrated in Figures 2-4. The ejection fraction rose from .38 ± .09 (SD) to .43 ± .12 (P < .02). This parameter increased in nine patients, fell slightly in three, and was unchanged in two. The cardiothoracic ratio decreased slightly, but significantly, from .55 ± .06 to .53 ± .06 (P < .05). It fell in eight subjects by as much as .11, was unchanged in two, and rose slightly in four.

![Figure 2. The changes in ejection fraction after two months of treatment with prazosin are shown. The mean ejection fraction rose from .38 ± .09 to .43 ± .12.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21262/)
The duration of treadmill exercise increased in all 14 patients, from 9.4 ± 3.4 to 11.9 ± 4.5 min (P<.005). Of the 13 patients with symptomatic heart failure, nine considered themselves improved and four felt unchanged. There was no discernible relationship between the actual dosage of prazosin and the amount of blood pressure reduction or in the changes in the three efficacy parameters (correlation coefficients by linear regression analysis ranging from 0.11 to 0.26).

**Discussion**

**Background**

Chronic hypertension plays an important etiologic role in many patients with congestive heart failure. Hypertension alone, with resulting chronic pressure-loading of the left ventricle, is an important cause of heart failure. In addition, hypertension may produce or exacerbate left ventricular failure in patients with associated ischemic, valvular or cardiomyopathic heart disease. In the Framingham study, the onset of heart failure was preceded by hypertension in 75 percent of patients, and heart failure was six times as frequent in hypertensive patients as in the normotensive population. Control of hypertension significantly reduces the risk of subsequently developing heart failure.

Conversely, treatment of hypertension in patients with chronic heart failure should result in improved left ventricular function. Experimental studies have shown that a decrease in afterload leads to greater shortening in isolated muscle preparations and to increased left ventricular ejection in intact heart preparations. While in intact animals and man, arterial pressure is not the sole determinant of left ventricular afterload, lowering of blood pressure from hypertensive to normal levels should have a similar beneficial effect. Previous studies have, in fact, noted hemodynamic and clinical improvement with antihypertensive therapy in patients with elevated blood pressure and congestive heart failure, although they have not included objective measurements of cardiac performance during longterm treatment. However, a number of reports have noted the appearance of worsening congestive heart failure in patients treated with sympatholytic agents, such as reserpine, guanethidine and methyl-
dopa. This may reflect the increased dependence of patients with congestive heart failure on compensatory mechanisms mediated by the autonomic nervous system. The potentially deleterious effects of adrenergic blocking agents in this setting are apparent.

More recently, many workers have found that the same rationale for afterload reduction applies to the...
treatment of heart failure in patients without hypertension. Thus, a number of drugs which dilate the arteriolar resistance vessels and thereby reduce left ventricular afterload have been shown to produce hemodynamic and clinical improvement in these patients. Two of these, hydralazine and prazosin, are effective and commonly employed antihypertensive agents. In the present study, we administered prazosin in doses chosen solely to achieve blood pressure control in a group of hypertensive subjects with documented left ventricular dysfunction.

**Findings of the Present Study**

Our findings indicate that prazosin is a highly effective antihypertensive agent in patients with cardiac dysfunction. Satisfactory blood pressure control was achieved and maintained in most patients, often with quite low doses of medication, and significant lowering of arterial pressure occurred in the remaining subjects. With this therapy, most patients experienced symptomatic improvement and an increase in exercise tolerance. Without a control group, these changes must be interpreted with caution. In particular, the increase in exercise time may have, in part, reflected a "learning" effect with successive tests, although the baseline measurements were taken from the second of two consecutive tests in approximately half of the patients. The increase in ejection fraction and reduction in cardiothoracic ratio provide further objective evidence for the beneficial effects of antihypertension therapy with prazosin in this patient group. It should be noted that although several groups have reported tachyphylaxis to the hemodynamic effects of prazosin in normotensive patients with heart failure, we did not observe any consistent decline in its antihypertensive activity and the measurements of cardiac function were performed after two months of continuous treatment.

Our data do not permit us to determine whether the improvement in cardiac performance and exercise tolerance were primarily a result of the lower arterial pressure or whether they might also result in part from the vasodilating action of prazosin which has been shown to be beneficial in normotensive patients with congestive heart failure. However, the changes in the ejection fraction did not correlate with the dose of prazosin and appear to be more closely related to the magnitude of blood pressure reduction. It should be noted that the dosage of prazosin used in many patients was considerably lower than that generally employed for the treatment of heart failure in nonhypertensive subjects. Therefore, administration of higher doses of prazosin than those required for blood pressure control may have produced greater improvement in cardiac function. Further studies with other antihypertensive medications, particularly with the sympatholytic agents, would help clarify to what extent blood pressure reduction alone was responsible for the beneficial changes which occurred.

Prazosin therapy was generally well tolerated in this group. However, one patient developed worsening angina pectoris during the first week of treatment. The phenomenon has been reported previously. Our patient's situation was somewhat complicated by the withdrawal of propranolol seven days earlier, which may itself have led to an increase in ischemia. It is also noteworthy that this individual did not have clinical or symptomatic heart failure, despite his moderately reduced ejection fraction. Vasodilator drugs are more likely to produce reflex tachycardia in such patients than in those with elevated left ventricular filling pressures and more advanced left ventricular dysfunction.

**Clinical Implications**

Our findings demonstrate the beneficial effects of controlling hypertension in patients with chronic left ventricular failure and provide further clinical corroboration for our theoretical understanding of the interaction between blood pressure and cardiac performance. While we did not determine whether prazosin offers any advantage over other antihypertensive agents in this setting, our experience suggests that this drug is both safe and effective. Furthermore, the use of vasodilators such as prazosin or hydralazine, which have demonstrable beneficial effects in normotensive subjects with congestive heart failure, to treat these hypertensive patients has both theoretical and practical appeal.

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