Role of the Renin-Angiotensin System in the Development of Hemodynamic and Clinical Tolerance to Long-Term Prazosin Therapy in Patients With Severe Chronic Heart Failure

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Right heart catheterization was performed before and during long-term therapy with prazosin in 27 patients with severe chronic heart failure who underwent serial hemodynamic studies during 3 to 12 weeks of treatment with the drug. Doses of digoxin and furosemide remained constant during the trial; in addition, 11 of the 27 patients were assigned to concomitant therapy with spironolactone, while the remaining 16 patients did not receive the aldosterone antagonist.

First doses of prazosin produced marked increases in cardiac index and marked decreases in mean arterial pressure, left ventricular filling pressure and systemic vascular resistance in both groups of patients (all p < 0.01), but these effects became rapidly attenuated (p < 0.01) in both groups after 48 hours and remained attenuated during long-term therapy. After 3 to 12 weeks, values for cardiac index returned to pretreatment levels and did not decrease when the drug was withdrawn; values for mean arterial pressure, left ventricular filling pressure and systemic vascular resistance remained significantly decreased (although attenuated) after 3 to 12 weeks (p < 0.01) and increased to pretreatment values when the drug was withdrawn. The magnitude and time course of these responses were not altered by concomitant therapy with spironolactone. Complete loss of hemodynamic efficacy (prazosin tolerance) was noted in 14 (58%) of the 24 patients who underwent long-term hemodynamic study and was not accompanied by long-term changes in plasma renin activity or body weight.

These data indicate that prazosin produces long-term hemodynamic and clinical benefits in only 30 to 40% of patients with severe chronic heart failure and do not support a role for the renin-angiotensin system in the development of tolerance to alpha-adrenergic blockade. This low response rate explains why most randomized double-blind trials of prazosin in heart failure have not been able to demonstrate a significant difference between patients treated with placebo and those receiving active drug.

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Although the sympathetic nervous system plays an important role in the pathogenesis of the marked systemic vasoconstriction that characterizes patients with congestive heart failure, the usefulness of alpha-adrenergic blockade with prazosin in the long-term management of these individuals remains controversial. Despite the dramatic enhancement of left ventricular performance that follows the administration of first doses of the drug (1), prolonged treatment with prazosin produces inconsistent long-term clinical benefits. Only one of the five randomized double-blind placebo-controlled trials (2–6) that have been conducted to evaluate the drug’s efficacy has shown a significant improvement in symptoms and exercise capacity after 1 to 12 months of treatment with prazosin compared with treatment with placebo. However, the mechanisms underlying the occurrence of drug failure during long-term alpha-adrenergic blockade remain incompletely elucidated, because in none of these controlled trials were serial hemodynamic and hormonal measurements performed.

Previous uncontrolled hemodynamic studies (7–11) have suggested that the principal cause of treatment failure during long-term prazosin therapy is the development of hemodynamic and clinical tolerance to the pharmacologic actions of the drug. Despite dramatic responses to initial doses of prazosin, repeated administration of the drug for 2 to 4 days is accompanied by a rapid loss of its hemodynamic effects (7–9). Whether such short-term attenuation persists during long-term treatment, however, and is responsible for the lack of sustained clinical efficacy in controlled clinical trials...
remains unknown; the two reports (12,13) that have specifically examined this question disagree strongly in their findings. Furthermore, none of the studies that have evaluated the hemodynamic efficacy of long-term prazosin therapy (2,6,11-20) has simultaneously allowed for the occurrence of circulatory changes related to intravascular instrumentation (21), kept diuretic drug dose constant and included a withdrawal phase at the end of treatment; therefore, these studies could not distinguish between hemodynamic benefits related to prazosin from those attributable to protocol design. Few of these studies attempted to elucidate the mechanisms underlying the development of tolerance by measuring serial alterations in circulating hormones and, more important, by antagonizing the effects of these hormones in an effort to prevent the development of tolerance. Finally, all previous long-term hemodynamic studies (2,6,11-20) treated only small numbers of patients and, thus, were limited in their ability to reach statistically justifiable conclusions.

To address these issues, we performed sequential hemodynamic and hormonal measurements during treatment with prazosin and after the withdrawal of long-term therapy with the drug in a large series of patients with severe chronic heart failure, in whom digitalis and diuretic drugs remained constant and in whom spironolactone was utilized to evaluate the contribution of the renin-angiotensin system to the development of tolerance to long-term alpha-adrenergic blockade.

Methods

Study patients. Our study group comprised 27 consecutive patients with severe chronic heart failure who received treatment with oral prazosin. There were 17 men and 10 women, aged 44 to 81 years (mean 64). The cause of heart failure was ischemic heart disease in 13 patients, primary dilated cardiomyopathy in 13 patients and persistent left ventricular dysfunction after mitral valve replacement in 1 patient; all patients had a left ventricular ejection fraction less than 30% by radionuclide ventriculography. All patients had symptoms at rest or on minimal exertion, but were studied during a period of clinical stability; none had experienced an acute myocardial infarction or an acute exacerbation of congestive heart failure within 4 weeks.

All patients were fed a 2 g sodium diet and received constant doses of digoxin and furosemide for at least 2 weeks before the trial. Seven to 14 days before the study, patients were hospitalized and immediately assigned to one of two treatment groups: the first 16 patients received no diuretic drugs other than furosemide for the treatment of heart failure, whereas the last 11 patients were treated with the aldosterone antagonist spironolactone, 150 mg orally daily, in addition to furosemide before and throughout the study. No patient in either group had received spironolactone within the previous 2 months. All patients entered the trial after body weight and renal function remained unchanged for 3 days on stable doses of digoxin and diuretic drugs.

Hemodynamic measurements. At the end of the stabilization period and after written, informed consent was obtained, right heart catheterization and arterial cannulation were performed for the measurement of intracardiac and systemic pressures, respectively. Patients were permitted to rest overnight before control hemodynamic determinations were made prior to the administration of prazosin, and all measurements were performed with the patient in a postprandial state. These guidelines were followed to minimize the occurrence of spontaneous hemodynamic changes that follow cardiac catheterization and meals in patients with congestive heart failure, which might mimic a vasodilator response (21). The performance of these invasive procedures and hemodynamic measurements has been described in detail previously (21). Left ventricular filling pressure was measured as the pulmonary artery wedge pressure or as the pulmonary arterial diastolic pressure after its identity with wedge pressure was established. Cardiac output was determined by the thermodilution technique using iced injectate.

Drug administration. On the day after intravascular instrumentation, after all medications (including digoxin and diuretic drugs) had been withheld, the following variables were measured repeatedly for at least 2 hours (with a variation of < 10%) to ensure stability of the pretreatment hemodynamic state before the administration of prazosin: mean arterial pressure, heart rate, left ventricular filling pressure, mean right atrial pressure and cardiac output. Each patient then received an initial dose of prazosin, 5 mg orally, followed by 5 mg of the drug every 8 hours. All hemodynamic variables were measured before and every 30 minutes for 3 hours after the first dose of prazosin on day 1, the fourth dose of prazosin on day 2 and the seventh dose of prazosin on day 3, after which hemodynamic monitoring was discontinued. During this 48 hour period, patients continued to receive digoxin and diuretic drugs in unchanged doses, but these drugs were administered in the evening after completion of each day’s hemodynamic measurements, so as not to interfere with assessment of the effects of prazosin.

Long-term therapy with prazosin. 5 mg three times daily, was then continued for 3 to 12 weeks (mean 6.2), during which time patients were fed a 2 g sodium diet and received the same doses of digoxin and diuretic drugs that they had been taking before the trial; no other vasodilator drugs were added. At the end of the treatment period, patients were readmitted to the hospital for 5 to 10 days to duplicate the conditions at the start of the study, after which right heart catheterization and arterial cannulation were performed for a second time during uninterrupted prazosin therapy using procedures identical to the first catheterization. The next morning, all hemodynamic variables were measured before
and every 30 minutes for 3 hours after the patient's usual dose of prazosin (5 mg). Prazosin therapy was then abruptly withdrawn, and while digoxin and diuretic drugs were continued, all hemodynamic variables were reassessed every 12 to 24 hours for the next 48 hours.

**Hormonal and clinical determinations.** Blood samples were collected in each patient for determination of plasma renin activity (by radioimmunoassay) before the first dose of prazosin, 90 minutes after the first dose (on day 1), after the seventh dose (on day 3), after the dose evaluated after 3 to 12 weeks of treatment, and 48 hours after withdrawal of the drug. All samples were taken at the same time of day, with patients maintaining a 2-g sodium diet, 12 to 24 hours after the last dose of diuretic drug and after at least 4 hours in the supine position.

*The clinical status of each patient* was evaluated during a control period of 3 days before institution of prazosin therapy and after 3 to 12 weeks of treatment with the drug. Changes in the severity of dyspnea and fatigue at rest, in exercise tolerance and in body weight were noted. Because all patients had symptoms at rest or on minimal exertion, formal exercise testing was not performed.

**Data analysis.** Mean systemic pressure was determined by electronic filtration. Derived hemodynamic variables were calculated as follows: cardiac index = cardiac output/body surface area (liters/min per m²) and systemic vascular resistance = 80 × (MAP - MRAP)/cardiac output (dynes cm⁻⁵), where MAP = mean arterial pressure and MRAP = mean right atrial pressure.

*The responses to short- and long-term prazosin therapy were compared at five points: *before prazosin, after the initial 5 mg dose of the drug, after 48 hours of therapy, during long-term drug administration (after 3 to 12 weeks) and 48 hours after drug withdrawal. At each point during therapy, hemodynamic variables were measured 90 ± 30 minutes after the administration of prazosin, at the time of its peak effect on left ventricular filling pressure and systemic vascular resistance. Changes in each hemodynamic variable and in plasma renin activity were compared at each of the five reference points by a repeated measures analysis of variance procedure in which Duncan's multiple range test was used to differentiate among significant responses. Qualitative and quantitative differences between subgroups of patients were evaluated by the *t* test for independent variables and the chi-square statistic using Yates' correction for continuity, respectively. Group data are expressed as mean ± SEM.

**Definitions.** The following hemodynamic definitions were used throughout the study. An initial response to the drug was defined as a 5 mm Hg or greater decrease in left ventricular filling pressure and systemic vascular resistance at peak effect compared with pre-prazosin values. In patients who demonstrated initial responses to the drug, we considered early hemodynamic attenuation to have occurred when at least 50% of the initial decrease in left ventricular filling pressure and systemic vascular resistance was lost after 48 hours. A triphasic response was identified when attenuated responses were observed after 48 hours, but spontaneous restoration of drug effect was noted during long-term treatment, such that the responses observed after 3 to 12 weeks were similar to those observed after the first dose of the drug. Tolerance was defined when the hemodynamic variables measured after 3 to 12 weeks of therapy had returned to pretreatment values. These definitions are similar to those used in previous hemodynamic studies (22).

**Results**

Of the 27 patients who entered the trial, no patient discontinued therapy because of adverse reactions, but 3 patients died (1 who was pretreated with spironolactone and 2 who were not). Each of the remaining 24 patients completed the study and underwent all hemodynamic, biochemical and clinical evaluations.

**Overall short- and long-term hemodynamic responses.** First doses of prazosin produced marked increases in cardiac index (*p < 0.01*), but repeated administration of the same dose of the drug resulted in a rapid and complete loss of its initial effect on this variable (*p < 0.01*) after 48 hours. Values for cardiac index returned to pretreatment levels during long-term therapy with prazosin and did not decrease when the drug was withdrawn (Fig. 1).

**Figure 1.** Values for cardiac index (CI), mean arterial pressure (MAP), heart rate (HR), left ventricular filling pressure (LVFP), mean right atrial pressure (MRAP), systemic vascular resistance (SVR) before prazosin (C), after the first dose of the drug (D₁), after 48 hours of therapy (D₂), during long-term treatment (3 to 12 weeks, LT) and 48 hours after drug withdrawal (W). *Symbols* indicate significance of differences from control values; *p* values at the top of each panel indicate significance of differences between D₁ and LT. Data are shown as mean ± SEM.
First doses of prazosin produced marked decreases in mean arterial pressure, left ventricular filling pressure, mean right atrial pressure and systemic vascular resistance (p < 0.01); the magnitude of these effects became partially but significantly (p < 0.01) attenuated after 48 hours and remained partially attenuated to a similar degree after 3 to 12 weeks. Compared with pretreatment values, the decreases in mean arterial pressure, left ventricular filling pressure, mean right atrial pressure and systemic vascular resistance during long-term prazosin therapy were modest but significant (p < 0.01); all four variables returned to control values when prazosin was withdrawn. No significant changes in heart rate were noted at any time during the study. The hemodynamic state 48 hours after the withdrawal of long-term prazosin therapy was similar to that seen before the first dose of the drug.

**Individual hemodynamic patterns of response.** All 27 patients responded hemodynamically to the first dose of prazosin with a decrease in left ventricular filling pressure of at least 5 mm Hg or a decrease in systemic vascular resistance of at least 20%. After 48 hours of prazosin therapy, however, 16 of the 27 patients showed a loss of at least 50% of the decrease in systemic vascular resistance and in left ventricular filling pressure seen with first doses of the drug (early attenuation), whereas 11 patients showed persistent effects on one or both of these variables. Of the 16 patients who showed early hemodynamic attenuation, 3 died during the study and 10 showed persistent loss of efficacy after 3 to 12 weeks of therapy (long-term tolerance); only 3 patients showed spontaneous restoration of effect during prolonged treatment after the occurrence of an early attenuated response (triphasic response) (12,22). Long-term tolerance developed in 14 (58%) of the 24 patients who completed the trial, 4 of whom did not show early hemodynamic attenuation but demonstrated loss of efficacy only after 3 to 12 weeks of treatment.

Overall, 10 (37%) of 27 patients improved hemodynamically during long-term prazosin therapy; withdrawal of the drug at the end of the study for 48 hours resulted in significant hemodynamic deterioration in 9 of these 10 responders but in only 1 of the 14 nonresponders who were still alive. The 10 responders and 17 nonresponders did not differ with respect to pretreatment hemodynamic and clinical variables.

**Overall hormonal and clinical responses.** Plasma renin activity increased significantly after the first dose and after 48 hours of prazosin, but decreased to control values after 3 to 12 weeks of treatment and did not decrease when the drug was withdrawn (Fig. 2). Weight did not change during the course of therapy (68.8 ± 2.8 to 68.6 ± 2.8 kg); although it increased by more than 2 kg in four patients, it decreased by more than 2 kg in five patients. Hemodynamic responders and nonresponders did not differ with respect to changes in plasma renin activity or in body weight during long-term treatment; there was no relation between changes in plasma renin activity or in body weight and changes in any hemodynamic variable.

Nine (33%) of 27 patients improved clinically during long-term prazosin therapy, 8 of whom responded hemodynamically after 3 to 12 weeks of treatment. Therapy was complicated by transient dizziness after the first dose of prazosin in one patient and by edema formation in three patients, each of whom gained more than 2 kg during the trial.

**Effect of spironolactone on clinical and hemodynamic responses.** The 11 patients who received spironolactone did not differ from the 16 patients who did not with respect to pretreatment clinical, hemodynamic or hormonal variables (Table 1). Both groups of patients showed similar and marked increases in cardiac index with first doses of prazosin; cardiac index returned to control values after 48 hours in both groups and showed little further change during long-term treatment and after withdrawal of the drug (Fig. 3). Both groups of patients showed similar and marked decreases in left ventricular filling pressure, mean right atrial pressure, mean arterial pressure and systemic vascular resistance with initial administration of prazosin, which became partially attenuated after 48 hours and after 3 to 12 weeks of therapy; these variables returned to pretreatment values in both groups when prazosin was withdrawn (Fig. 4 to 6). Neither group showed significant changes in heart rate during the trial. There was no significant difference between the two groups in the magnitude of drug-induced changes in any hemodynamic variable at any time during the study. Individually, long-term tolerance developed in 6 (60%) of the 10 patients pretreated with spironolactone who completed the trial and in 8 (57%) of the 14 patients who received only digoxin and diuretic drugs in addition to prazosin for 3 to 12 weeks.

Three (27%) of the 11 patients pretreated with spirono-
Table 1. Pretreatment Hemodynamic and Clinical Characteristics of Patients Who Received Concomitant Therapy With Spironolactone and Those Who Did Not

<table>
<thead>
<tr>
<th></th>
<th>With Spironolactone (n = 11)</th>
<th>Without Spironolactone (n = 16)</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63.5 ± 2.4</td>
<td>64.8 ± 3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>7/4</td>
<td>10/6</td>
<td>NS</td>
</tr>
<tr>
<td>Cause of heart failure</td>
<td>ICM (7), PDC (4)</td>
<td>ICM (6), PDC (9), MVR (1)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.7 ± 4.3</td>
<td>67.2 ± 3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml per h)</td>
<td>5.7 ± 2.0</td>
<td>6.1 ± 3.7</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index (liters/min per m²)</td>
<td>1.71 ± 0.16</td>
<td>1.93 ± 0.13</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>80.7 ± 2.7</td>
<td>84.7 ± 3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular filling pressure (mm Hg)</td>
<td>26.3 ± 2.0</td>
<td>26.8 ± 1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>11.5 ± 2.5</td>
<td>11.7 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>83.8 ± 3.4</td>
<td>89.9 ± 4.7</td>
<td>NS</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne·cm⁻²)</td>
<td>1.956 ± 171</td>
<td>1.864 ± 130</td>
<td>NS</td>
</tr>
</tbody>
</table>

F = female, ICM = ischemic cardiomyopathy; M = male. MVR = mitral valve replacement for valvular heart disease, PDC = primary dilated cardiomyopathy. Number of patients with each diagnosis is designated in parentheses. The p values in last column designate significance of differences between the two groups, where NS = not significant.

lactone and 6 (38%) of the 16 patients who did not receive the aldosterone antagonist improved clinically during long-term prazosin therapy. Neither group showed significant changes in weight (67.0 ± 4.7 to 65.8 ± 5.0 kg in patients who received spironolactone; 70.2 ± 3.5 to 70.6 ± 3.3 kg in patients who did not). Plasma renin activity increased significantly after first doses of prazosin in both groups (4.0 ± 1.1 to 7.7 ± 2.5 ng/ml per h in patients who received spironolactone; 2.4 ± 1.0 to 5.9 ± 2.1 ng/ml per h in patients who did not; both p < 0.05), but this did not persist in either group during long-term treatment (3.9 ± 1.2 and 2.3 ± 0.9 ng/ml per h, respectively). None of

Figure 3. Values for cardiac index before, during treatment with and after the withdrawal of prazosin in patients grouped according to concomitant therapy with spironolactone. The p values indicate significance of differences between D₁ and D₃ in each group. Format and abbreviations as in Figure 1.

Figure 4. Values for left ventricular filling pressure before, during treatment with and after the withdrawal of prazosin in patients grouped according to concomitant therapy with spironolactone. The p values indicate significance of differences between D₁ and D₃ in each group. Format and abbreviations as in Figure 1.
the observed differences in the clinical or hormonal responses to prazosin in the two groups was significantly different.

Discussion

Our findings indicate that despite marked hemodynamic responses to first doses of the drug, the long-term administration of prazosin produces only modest hemodynamic and clinical improvement in patients with congestive heart failure. Only 30 to 40% of our patients showed notable amelioration of symptoms after 3 to 12 weeks of treatment, and their clinical state deteriorated significantly when the drug was withdrawn. In contrast, in most of our patients, amelioration of symptoms after 3 to 12 weeks of treatment, according to concomitant therapy with spironolactone. The p values indicate significance of differences between D3 and D1 in each group. Format and abbreviations as in Figure 1.

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Comparison of present results with previous hemodynamic studies. Previous reports by ourselves (7) and other investigators (8, 9) suggested several years ago that the initial beneficial hemodynamic effects of prazosin in patients with heart failure became rapidly attenuated after several days of treatment; however, the importance of these observations remained unclear, because most of the early uncontrolled clinical experience with the drug was highly favorable (1, 23), and long-term hemodynamic studies generally showed sustained beneficial effects (12, 15–17). In an attempt to reconcile these differences, Awan et al. (12) suggested that the short-term hemodynamic attenuation that we and others observed after 2 to 4 days was a transient phenomenon and that long-term treatment (for 4 weeks) resulted in the spontaneous restoration of the effect of the drug. Such an explanation received widespread acceptance as long as prazosin was considered to be useful, but this hypothesis proved difficult to support when double-blind randomized clinical trials (2, 4–6) failed to show significant differences between patients treated with prazosin and those treated with placebo for 1 to 12 months. The results of the present study are in direct conflict with those of Awan et al. (12, 23), who believed that the loss of efficacy observed during short-term prazosin therapy was a transient reversible event. The early hemodynamic attenuation that we noted in our patients with heart failure generally persisted during long-term treatment with the drug; only 10 to 15% of patients showed spontaneous restoration of responsiveness during the course of therapy with prazosin, a frequency similar to that seen with other vasodilator drugs (22). Long-term tolerance developed in nearly 60% of our patients and was the principal reason for drug failure. Given a placebo response rate in patients with heart failure of nearly 20 to 25% (25, 26), the low frequency (30 to 40%) of long-term hemodynamic benefits with prazosin in our study explains why most randomized double-blind trials have not demonstrated a sig-
significant difference between placebo-treated and actively treated patients (2–6).

We believe that differences in study design explain why our findings concerning the long-term efficacy of prazosin in heart failure differ from those of previous reports. Many early studies utilized exercise duration, echocardiography and radionuclide ventriculography to document clinical benefits (1,23,27), but exercise tolerance commonly improves after placebo therapy (25,26,28) and noninvasive measures of cardiac performance correlate poorly with invasively derived hemodynamic variables (29,30). In several hemodynamic studies (6,11,14–16,18,19) doses of diuretic drugs were generally increased during treatment with prazosin to prevent fluid retention, and this practice may have contributed to the long-term hemodynamic benefits noted in these reports (18,31); we kept doses of digoxin and diuretic drugs constant. Previous investigators administered prazosin within hours after right heart catheterization at a time when patients with heart failure are in a transiently vasoconstricted state, the dissipation of which closely mimics a vasodilator drug response (21). Similar degrees of systemic vasoconstriction may not be provoked during a second catheterization procedure (32) and, hence, hemodynamic data obtained at that time will usually show values for ventricular filling pressures and systemic vascular resistance that are lower than those measured before initiation of treatment. Such hemodynamic responses will be interpreted as a favorable effect of therapy even if the drug is exerting no beneficial actions; the contribution of treatment to the hemodynamic changes observed at the time of the second catheterization can only be assessed if the drug is withdrawn at the completion of the trial, a procedure that generally was omitted in previous reports (2,6,12–15,17–20). We did not perform hemodynamic measurements until 24 hours after right heart catheterization to minimize instrumentation-related artifacts and confirmed the magnitude of drug effect after 3 to 12 weeks by drug withdrawal. It is of interest, therefore, that the only previous study that took similar precautions in study design noted short- and long-term hemodynamic responses to prazosin similar to those seen in our patients (13), and previous studies that evaluated the effects of prazosin withdrawal observed clinical response rates similar to ours (16,33).

Long-term tolerance to prazosin did not develop in all of our patients with congestive heart failure, and it did not develop similarly with respect to all hemodynamic variables. With first doses of prazosin, 21 of 27 patients showed an increase in cardiac index of at least 20%, and all 27 patients showed a decrease in left ventricular filling pressure of at least 5 mm Hg. During long-term treatment, however, only 3 patients showed sustained increases in cardiac index, but 10 patients showed sustained decreases in left ventricular filling pressure. Accordingly, prazosin produced no long-term increases in cardiac index in our group as a whole, but did produce modest but significant long-term decreases in right and left ventricular filling pressures. These findings suggest that pharmacologic tolerance developed preferentially to the arterial dilating actions of prazosin; similar findings have been reported by other investigators (8,15,16,18,34) during short- and long-term therapy with the drug. In addition, once pharmacologic tolerance is established, the withdrawal of prazosin restores responsiveness to the drug more rapidly and completely in the venous than in the arterial circulation (10). These observations may result from differences between systemic arteries and veins in the distribution and kinetics of alpha-adrenergic receptor subpopulations (35,36).

Role of renin-angiotensin system in the development of prazosin tolerance. Other studies (3,11,23,24) have suggested that activation of the renin-angiotensin system is the principal mechanism responsible for the development of tolerance to long-term prazosin therapy in patients with congestive heart failure. Such activation may be a direct result of antagonism of the intrarenal alpha-adrenergic receptors that inhibit renin release (37,38) or an indirect result of a prazosin-induced redistribution of blood flow away from the kidneys (39,40). Regardless of its mechanism, the resultant increase in circulating angiotensin II serves to limit the acute hypotensive actions of prazosin and may thereby lead to rapid attenuation of the short-term effects of alpha-blockade (41,42). Should such hormonal activation persist during prolonged therapy, similar antagonism of the long-term vasodilating effects of prazosin might be expected to occur. Furthermore, sodium retention secondary to angiotensin-mediated hyperaldosteronism may not only increase ventricular filling pressures by expanding intravascular volume but may also decrease the responsiveness of the peripheral vasculature to alpha-adrenergic blockade (10,11). Each of these mechanisms, alone or in combination, could be responsible for long-term hemodynamic and clinical tolerance to prazosin. Unfortunately, there has been little consistent support for these concepts. Although increases in plasma renin activity (3) or in plasma aldosterone (11) have been noted by some investigators during long-term prazosin therapy in patients with heart failure, they have not been observed by others (4,13,43); the sustained increases in plasma renin activity reported in a single study (3) were small in magnitude and may have resulted from increments in the dose of concomitantly administered diuretic drugs and not from an effect of the drug. Furthermore, although sodium retention and weight gain frequently develop during long-term treatment with prazosin (3,5,6,12,15,19,24,40,43), they may not be related to activation of the renin-angiotensin system (43–46) and may also occur during treatment with placebo (6,46); more important, attenuation of the hemodynamic responses to alpha-adrenergic blockade is seen in the absence of changes in plasma volume and body weight.
(7,13,20,34). Finally, although concomitant treatment with spironolactone has been claimed to prevent sodium retention and avert the development of long-term tolerance to prazosin, there is only anecdotal support for this approach.

Our findings do not support a major role for the renin-angiotensin system in the development of long-term hemodynamic and clinical tolerance to prazosin in heart failure. Although plasma renin activity increased significantly after first doses of the drug, long-term treatment was accompanied by a return of values for plasma renin activity to the pretreatment state. Because renin stimulation by prazosin is probably mediated by blockade of alpha-adrenergic receptors similar to those that mediate systemic vasoconstriction (37,38), attenuation of the hormonal effects of the drug developed parallel to the development of tolerance to its hemodynamic actions; similar findings have been reported by other investigators (34). Furthermore, it is unlikely that intravascular volume expansion occurred during the course of our trial and served to attenuate hemodynamic responsiveness, because weight did not increase significantly during long-term prazosin therapy in our patients, and ventricular filling pressures after the withdrawal of prazosin were not greater than were those seen before initiation of treatment with the drug. Finally, the hemodynamic responses to short- and long-term prazosin therapy were unaffected by concomitant treatment with spironolactone; aldosterone antagonism did not prevent the occurrence of hemodynamic and clinical tolerance in our patients or in the experience of others (13). The benefits previously reported from adjunctive therapy with spironolactone probably resulted from its independent diuretic actions and not from a synergistic effect with prazosin. Further studies are necessary, however, to determine whether circulating levels of angiotensin II may directly oppose the actions of prazosin (42); such an effect would be resistant to spironolactone and would require long-term converting enzyme inhibition to restore responsiveness to alpha-adrenergic blockade.

Alternative mechanisms for the development of tolerance to prazosin. Other mechanisms have been proposed to explain the development of tolerance to prazosin in patients with chronic heart failure, but these have also been difficult to support. Although some reports (16,17) have suggested that progression of the underlying heart disease may closely mimic tolerance, our observations on withdrawal of the drug indicate that progression did not occur and could not account for the return of hemodynamic variables to pretreatment values during long-term therapy. Other investigators (8,46,47) have postulated that impaired absorption or enhanced metabolic inactivation of prazosin during long-term treatment may account for loss of efficacy, but plasma levels of the drug after the development of tolerance are higher than after the administration of first doses. Still others have proposed that the large doses of prazosin utilized in the treatment of heart failure exert blocking effects on both alpha-1- and alpha-2-adrenergic receptors (48,49); blockade of alpha-2-receptors (normally inhibitory to peripheral norepinephrine release) results in a marked elevation of plasma levels of catecholamines (11,14,34,43,48), which may lead to the development of pharmacologic tolerance by overwhelming the postsynaptic adrenergic blockade induced by the drug (43,44,46). We did not measure plasma norepinephrine in our patients, but the lack of long-term hemodynamic and clinical efficacy in previous studies (4,46) could not be explained by changes in circulating levels of catecholamines.

The physiologic and pharmacologic mechanisms underlying the development of tolerance of long-term alpha-adrenergic blockade remain unknown. Tolerance may involve an alteration in the number or affinity, or both, of postsynaptic alpha-adrenergic receptors (46,47,50), but direct measurement of radioligand binding sites has revealed no change in alpha-receptor density and affinity during experimentally induced tolerance to prazosin in the rabbit (46). Alternatively, alpha-adrenergic responsiveness in vascular tissue may be regulated in both animals and in humans at a postreceptor site (46,50), which may undergo significant modification during sustained alpha-blockade and may account for the loss of efficacy during long-term prazosin therapy.

Precautions and limitations. Our findings need to be interpreted cautiously. We did not evaluate a control group of patients (not treated with prazosin) in the present study to ensure that the hemodynamic changes that we observed were the result of drug therapy. Utilizing an identical protocol design, however, we (32) and other investigators (2,6,51,52) have not observed hemodynamic changes in the absence of effective treatment in other studies; furthermore, the hemodynamic state after the withdrawal of prazosin during long-term therapy in our patients was similar to that seen before initiation of treatment with the drug. Our primary objectives were to investigate the fate of the hemodynamic attenuation seen early during treatment with prazosin and to determine whether spironolactone can prevent the development of long-term tolerance to the drug; the control groups we utilized were suitable to address these questions.

Another limitation of the present study is that we evaluated the short- and long-term hemodynamic effects of prazosin only at rest and not during exercise. Rubin et al. (53) first suggested in a short-term hemodynamic study that attenuation of the effects of prazosin may occur only at rest and not during exertion; similar results were noted by Goldman et al. (27) during long-term treatment with the drug. Both groups of investigators postulated that, in view of the alpha-adrenergic blocking properties of prazosin, the drug's effects may be apparent only during states of high sympathetic activity (such as physical effort); others (54,55), however, have been unable to support this hypothesis. Indeed, the marked increase in plasma catecholamines that accom-
The effects of prazosin might be expected to be less apparent during effort. Regardless of the validity of these concepts, pancy exertion would be expected to overwhelm any competitive drug-induced alpha-adrenergic blockade; hence, the effects of long-term treatment with prazosin have noted repons during exercise that have closely paralleled those seen at rest (2,6,14,15,20,56); when tolerance developed to the hemodynamic effects of the drug at rest, it was also evident during exertion (2,20,56). Hence, randomized double-blind trials (2,4,6,56) have failed to show significant differences in the long-term hemodynamic response to exercise between patients treated with prazosin and those treated with placebo; therefore, exercise capacity did not improve during prazosin therapy in these studies. Consequently, we do not believe that our findings would be altered significantly had we conducted hemodynamic measurements during exercise as well as at rest.

**Conclusions.** Our findings indicate that the marked hemodynamic attenuation seen early in the course of therapy with prazosin in patients with severe chronic heart failure generally persists during long-term treatment with the drug and is the principal cause of drug failure. Such long-term tolerance was not accompanied by changes in plasma renin activity or in body weight and could not be prevented by concomitant treatment with aldosterone antagonists; hence, these observations do not support a role for the renin-angiotensin system in the development of pharmacologic tolerance to long-term alpha-adrenergic blockade. Our finding that only 30 to 40% of patients with heart failure treated with prazosin show notable long-term hemodynamic benefits explains why most randomized double-blind clinical trials (4–8) have failed to show significant differences between placebo-treated and actively treated patients.

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**References**


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