Hemodynamic patterns of response during long-term captopril therapy for severe chronic heart failure

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ABSTRACT To determine the relationship between the early and late hemodynamic effects of captopril in patients with severe heart failure, we performed serial right heart catheterizations in 51 such patients who were treated with the drug for 2 to 8 weeks. Four hemodynamic patterns of response were observed. Nine patients had minimal responses initially (type I); six failed to improve during long-term treatment, but three showed delayed hemodynamic benefits. Twenty-eight patients had initial beneficial drug effects that were sustained after 48 hr and after 2 to 8 weeks (type II). In seven patients, first doses of captopril produced marked beneficial responses, but these became rapidly attenuated after 48 hr; nevertheless, continued therapy for 2 to 8 weeks was accompanied by spontaneous restoration of the hemodynamic effects of first doses of the drug, i.e., triphasic response (type III). In the remaining seven patients, attenuation of initial response was not reversed by prolonged captopril therapy; hemodynamic variables after 2 to 8 weeks had returned to their pretreatment values, i.e., drug tolerance (type IV). Plasma renin activity was lower in patients with minimal responses (0.6 ± 0.2 ng/ml/hr) and was higher in patients with triphasic responses (9.4 ± 2.5 ng/ml/hr) than in patients with types II and IV response patterns (4.4 ± 0.7 and 2.8 ± 0.5 ng/ml/hr, respectively; both p < .05). Although first-dose effects of captopril are frequently sustained, the occurrence of delayed, attenuated, and triphasic responses indicates that a complex and variable relationship may exist between the early and late hemodynamic effects of vasodilator drugs in patients with severe heart failure.


INVASIVE hemodynamic testing is frequently performed to assess the short-term effects of vasodilator drugs in patients with severe chronic heart failure, but the degree to which these short-term responses reflect the long-term hemodynamic effects of these agents has not been established. Although the immediate responses to treatment may be sustained, recent investigations suggest that the early and late hemodynamic effects of vasodilator therapy may also be dissimilar. Some patients fail to benefit despite initial favorable hemodynamic responses because of the development of drug tolerance; on the other hand, some patients may improve during long-term treatment despite minimal or attenuated effects early in the course of therapy.

The precise relationship between the immediate and sustained hemodynamic effects of treatment has yet to be defined for any vasodilator drug. Delineation of such a relationship cannot be based on clinical criteria alone, since clinical responses may not accurately reflect changes in left ventricular performance. Patients with severe heart failure may show no improvement despite persistent pharmacologic effects; conversely, clinical benefits may accompany placebo treatment. Elucidation of the relationship between the effects of short- and long-term therapy therefore requires invasive hemodynamic evaluation during both phases of treatment. Such testing, however, has been previously performed in only small numbers of patients or in highly selected individuals reevaluated because of an observed difference between the long-term responses and the benefits anticipated on the basis of short-term hemodynamic studies. No previous work has correlated the short- and long-term effects of vasodilator therapy in a large series of patients with heart failure who were invasively reevaluated independently of their clinical response.

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The purpose of the present investigation is to define the hemodynamic patterns of response to short- and long-term vasodilator therapy with the oral angiotensin-converting enzyme inhibitor, captopril, in patients with severe heart failure. We compared the initial effects of captopril during cardiac catheterization with the responses seen after 48 hr and after 2 to 8 weeks of therapy in 51 patients. Our results indicate that a complex relationship exists between the early and late effects of vasodilator therapy in patients with severe chronic heart failure.

Methods

Patients. We studied 60 consecutive patients with severe chronic heart failure refractory to conventional therapy with digitalis and diuretics who were referred for vasodilator therapy. Each patient received captopril during invasive hemodynamic testing and was asked to undergo repeat cardiac catheterization 2 to 8 weeks later. Nine patients were excluded from analysis: four died, two refused repeat evaluation, and three had an alteration in their medical regimen that made impossible the independent evaluation of the response to captopril. The remaining 51 patients formed the study population.

There were 38 men and 13 women ranging in age from 29 to 83 years (mean 65). The cause of heart failure was ischemic cardiomyopathy in 31 patients, primary myocardial disease in 17 patients, and persistent severe left ventricular dysfunction after mitral valve replacement in three patients. Normal sinus rhythm was present in 37 patients, atrial fibrillation in 10, and a ventricular pacemaker rhythm in four. All patients were in New York Heart Association functional class IV; however, all studies were performed during a period of clinical stability. No patient had had a myocardial infarction within 4 weeks or an episode of acute heart failure within 10 days.

Prestudy stabilization. Before entry into the study, all patients were hospitalized and placed at bed rest for 5 to 7 days, during which doses of digoxin and diuretics remained constant. Forty patients had received no maintenance treatment with any vasodilator drugs within the previous 2 weeks. In the other 11 patients, captopril was administered after the development of tolerance to other vasodilator agents (hydralazine in five and prazosin in six); in these patients, both hydralazine and prazosin were discontinued at least 48 hr before the initiation of therapy with captopril.

Hemodynamic measurements. All medications, including digoxin and furosemide, were withheld on the morning of the initial captopril evaluation. After written informed consent was obtained, right heart catheterization was performed with a triple-lumen flow-directed catheter for measurement of right atrial, pulmonary arterial, and pulmonary capillary wedge pressures. Arterial cannulas were inserted into the radial artery of all patients for measurement of systemic pressures. Measurements were made with reference level at the midaxillary line with the patient supine. Left ventricular filling pressure was measured as the mean pulmonary capillary wedge pressure or as the pulmonary arterial diastolic pressure after its identity with wedge pressure was established. Thermodilution cardiac outputs were determined in triplicate by a bedside cardiac output computer with the use of iced injectant. Heart rates were derived from a continuously recorded electrocardiogram.

After insertion of the intravascular catheters, each patient was permitted to rest for a minimum of 3 hr. All measurements were obtained in the postabsorptive state; patients were permitted only liquids during periods of hemodynamic assessment.

Drug administration. After each patient had rested, the following hemodynamic variables were determined repeatedly for at least 2 hr (with a variation of less than 10%) to ensure the stability of the baseline hemodynamic state before administration of captopril: mean arterial pressure, heart rate, left ventricular filling pressure, mean right atrial pressure, and cardiac output. Each patient then received 25 mg of captopril, and all hemodynamic variables were redetermined every 30 min for 3 hr. Since the magnitude of the response to captopril is not dose dependent,1, 6 the second dose of the drug was determined by each patient’s renal function. This dose was 100 or 150 mg orally in the 40 patients with a serum creatinine level less than 2.2 mg/dl and 25 or 50 mg orally in the 11 patients with a serum creatinine level greater than 2.2 mg/dl; these doses of captopril were then administered every 8 hr. Repeat hemodynamic measurements were made before and every 30 min for 3 hr after the fourth dose of captopril on day 2 and after the seventh dose of the drug on day 3; hemodynamic monitoring was then discontinued.

The hemodynamic responses to captopril were reevaluated 2 to 8 weeks later. During this time, captopril was administered under close observation; continuous hospitalization was maintained in 39 patients, whereas the other 12 patients were sent home briefly but were rehospitalized for 5 to 7 days before the second invasive procedure. Patients were fed 2 g sodium diets, and the doses of digitalis and diuretics that each patient had been taking before entry into the study remained unaltered. The doses of captopril also remained constant and ranged from 75 to 450 mg daily (mean 265); no other vasodilator drugs were added. After 2 to 8 weeks (mean 25 days), the morning doses of digoxin and diuretics were again withheld and right heart catheterization and arterial cannulation were again performed under conditions identical to those of the first study. To ensure evaluation of uninterrupted captopril therapy, these invasive hemodynamic procedures preceded the timing of the next dose of captopril by at least 6 hr; this permitted time for rest and for establishment of a stable control hemodynamic state before the next scheduled administration of the drug. Captopril was then administered in the usual dose as during the preceding 2 to 8 weeks; hemodynamic determinations were performed every 30 min for 3 hr.

Because endogenous prostaglandins may mediate in part the response to captopril,14 no patient received prostaglandin synthetase inhibitors in the 5 days before or during the 2 to 8 weeks of continuous captopril therapy.

Humoral and clinical determinations. In 45 of the 51 patients, blood samples were collected for determination of plasma renin activity (by radioimmunoassay)15 before the first dose of captopril and 90 min after the first dose (on day 1), the seventh dose (on day 3), and the dose evaluated after 2 to 8 weeks of treatment. All samples were drawn at a similar time of day, on a constant 2 g sodium diet, 24 to 30 hr after the last dose of diuretic, after a minimum of 12 hr in the supine position. Serum sodium concentration was determined in all patients on the morning before the first dose of captopril.

The clinical status of each patient was evaluated during a control period of 3 days before institution of therapy with captopril and after 2 to 8 weeks of treatment with the drug. Changes in symptoms 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 and pulmonary artery pressures were determined by electronic filtration. Derived hemodynamic variables were calculated as follows: cardiac index (CI) = CO/body surface area (l/min/m²) stroke volume index (SVI) = CI/HR (ml/beat/m²)
systemic vascular resistance (SVR) = 80 × (MAP – MRAP)/CO (dyn-sec-cm⁻²)
where CO denotes cardiac output, HR heart rate, MAP mean arterial pressure, MRAP mean right atrial pressure, and LVFP left ventricular filling pressure.

The responses to short- and long-term captopril therapy were compared at four points: before therapy, after initial doses of the drug, after 48 hr of therapy, and during long-term administration (2 to 8 weeks). At each point all hemodynamic variables were measured at the peak effect of captopril on left ventricular filling pressure and systemic vascular resistance (0.5 to 2.0 hr after oral administration). Changes in each hemodynamic variable and in plasma renin activity were compared at each of the four reference points by a repeated-measures two-way analysis of variance procedure in which Duncan's multiple range test was used to differentiate among significant responses.¹⁶

The following hemodynamic definitions were used through the study: An initial response to the drug was defined as a 5 mm Hg or greater decrease in left ventricular filling pressure or a 20% or greater decrease in systemic vascular resistance at peak effect compared with precapitrol values. These criteria were similar to those used in previous hemodynamic studies¹⁷,¹⁸ and were based on the spontaneous changes observed over 3 hr in a control group of 16 patients: change in left ventricular filling pressure, +0.2 ± 2.4 mm Hg, and change in systemic vascular resistance, −1.0 ± 8.6% (mean ± SD). In patients who had initial effects, early hemodynamic attenuation was defined when at least 50% of the initial decrease in left ventricular filling pressure or systemic vascular resistance was lost after 48 hr. A triphasic response was identified when attenuated responses were observed after 48 hr, but the effects seen after 2 to 8 weeks were similar to those observed after first doses of the drug. Tolerance was defined when hemodynamic variables after 2 to 8 weeks of therapy had returned to their pretreatment values. These definitions were similar to those used in previous evaluations of vasodilator drugs in hypertension and heart failure.⁵,¹⁹

Patients were then divided into four groups on the basis of their early and late hemodynamic responses to captopril. The hypotheses that these four groups did not differ before treatment in terms of standard hemodynamic variables, plasma renin activity, and serum sodium concentration were tested by one-way analysis of variance. Changes in weight within each group were analyzed by the t-test for paired data. Group data are expressed as mean ± SEM.

**Results**

Overall hemodynamic and clinical responses. First doses of captopril produced significant increases in cardiac index and stroke volume index and decreases in mean arterial pressure, left ventricular filling pressure, mean right atrial pressure, heart rate, and systemic vascular resistance (all p < .001), which were sustained during long-term therapy (table 1). The increases in cardiac index and decreases in mean arterial pressure and systemic vascular resistance after 48 hr and after 2 to 8 weeks were slightly but significantly (p < .05) less marked than those seen with first doses of the drug; however, the increases in stroke volume index and decreases in left ventricular filling pressure, mean right atrial pressure, and heart rate remained unattenuated.

Of the total of 51 patients, 29 improved clinically over the next 2 to 8 weeks. Body weight in 31 patients remained within 2 kg of their control weight; 16 patients lost more than 2 kg, and weight increased by more than 2 kg in four.

**Individual hemodynamic response patterns.** Four response patterns were observed during the course of captopril therapy in the 51 patients evaluated.

**Minimal response** (type I). Nine patients had minimal hemodynamic responses to first doses (25 mg) of captopril; left ventricular filling pressure decreased less than 5 mm Hg without notable changes in stroke volume index, mean right atrial pressure, or heart rate. Repeated doses of captopril (25 to 150 mg) also produced fewer hemodynamic changes despite the administration of up to six times the initial dose; continued therapy during the next 48 hr with up to 450 mg daily failed to enhance the magnitude of these effects. After 2 to 8 weeks of treatment there was no overall improvement in stroke volume index or left ventricular filling pressures; the small decrease in mean arterial pressure and systemic vascular resistance seen after first doses of the drug persisted unchanged (figure 1).

Individually, six of the nine patients failed to show notable hemodynamic effects from long-term captopril therapy, and none improved clinically (type IA response). The remaining three patients, however, experienced a 1 to 3 kg weight loss during 2 to 4 weeks of treatment and showed substantial increases in cardiac

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<th>TABLE 1</th>
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<td>Short- and long-term hemodynamic effects of captopril in all 51 patients with severe heart failure</td>
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C = control; D₁ = first dose of captopril on day 1; D₃ = seventh dose of captopril on day 3; LT = long-term therapy (2 to 8 weeks); LVFP = left ventricular filling pressure.

Statistical comparisons: *p < .001 vs control; †p < .05, D₁ vs D₃ and LT vs D₁.
index (mean +0.45 l/min/m²) and decreases in left ventricular filling pressure (mean -13.0 mm Hg) at the time of repeat invasive testing (even though no response had been seen during initiation of captopril therapy); all three patients showed notable clinical improvement (type IB response).

Continuous response (type II). Twenty-eight patients had marked increases in cardiac index and stroke volume index and decreases in left ventricular filling pressure, mean arterial pressure, mean right atrial pressure, heart rate, and systemic vascular resistance with first doses of captopril; these changes were sustained without attenuation after 48 hr and after 2 to 8 weeks of continuous therapy (figure 2).

Twenty of these 28 patients showed symptomatic improvement; there was no significant change in weight in the patients in this group.

Triphasic response (type III). In seven patients we noted marked increases in stroke volume index and decreases in left ventricular filling pressure, mean arterial pressure, mean right atrial pressure, heart rate, and systemic vascular resistance with first doses of captopril, which were similar in magnitude to the effects seen in patients who had type II responses. However, the magnitude of these responses became rapidly and progressively less marked with repeated dose administration, so that after 48 hr only mild decreases in mean arterial pressure and systemic vascular resistance were seen. The initial improvements in stroke volume index and right and left ventricular filling pressure were no
longer present, being completely lost in four patients and partially attenuated in the other three. Despite this early attenuation, repeat assessment after 2 to 8 weeks of continuous captopril therapy (in unchanged dosage) showed a spontaneous return to the hemodynamic effects seen with first doses of the drug (figure 3).

Six of the seven patients showed sustained clinical improvement. Body weight decreased significantly (67.1 ± 6.9 to 63.8 ± 6.8 kg; p < .001); six patients lost more than 2 kg during the 2 to 8 weeks of captopril therapy.

Tolerance (type IV). In seven patients we noted marked increases in stroke volume index and decreases in left ventricular filling pressures, mean arterial pressure, and systemic vascular resistance with first doses of captopril, which were similar in magnitude to the effects seen with first doses of the drug in patients who had types II and III responses. However, these responses were not sustained, and these hemodynamic variables returned to their pretreatment values after 2 to 8 weeks of therapy (figure 4). At this time there was no acute hemodynamic response to captopril, and tolerance was not reversed by the administration of double doses of the drug (200 mg); hemodynamic deterioration did not occur when captopril was withdrawn for 24 hr. None of these patients improved clinically, and body weight did not change significantly.

Of the seven patients who manifested tolerance, five

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**FIGURE 3.** Hemodynamic values for patients demonstrating triphasic responses to captopril (type III response). For explanation of format, abbreviations, and symbols, see legend to figure 1.

**FIGURE 4.** Hemodynamic values for patients demonstrating long-term tolerance to captopril (type IV response). For explanation of format, abbreviations, and symbols, see legend to figure 1.
FIGURE 5. Patterns of plasma renin activity in patients with various hemodynamic patterns of response (types I to IV). Designated at the top are the number of patients in each group who had plasma renin determinations. Asterisks indicate significance from control (p < .05). For explanation of abbreviations, see legend to figure 1.

showed a marked attenuation of effect early during treatment (i.e., after 24 to 48 hr) in a fashion similar to that seen in patients with type III responses. However, continued therapy with captopril failed to spontaneously restore first-dose effects; rather, a further loss of response was observed after 2 to 8 weeks. The other two patients had no evidence for attenuation after 48 hr and developed tolerance only during long-term therapy. One of these two patients was the only individual who gained more than 3 kg of weight during treatment with captopril (6 kg); after repeated doses of intravenous furosemide induced a diuresis of 3.8 kg during the next 36 hr, responsiveness to captopril was restored, and values at peak drug effect were similar to those seen after the first dose of the drug. The other six patients showed no change in weight and did not receive diuretics in an attempt to reverse tolerance; two of these patients failed to respond to another angiotensin converting enzyme inhibitor, enalapril (MK-421),20 given as 5, 10, and 20 mg doses orally 24 hr after confirmation of tolerance to captopril.

Relationship of hemodynamic response pattern to plasma renin activity. All patients who showed minimal responses to initial doses of captopril (type I) had values for plasma renin activity less than 2.0 ng/ml/hr; the mean value of plasma renin activity in patients in this group (0.6 ± 0.2 ng/ml/hr) was significantly lower than that in patients who demonstrated marked responses to first doses of the drug (types II to IV), p < .05 (figure 5). Furthermore, these patients showed little change in plasma renin activity after short- or long-term captopril administration. After 2 to 8 weeks the plasma renin activity remained less than 2 ng/ml/hr in six patients, none of whom improved hemodynamically or clinically (type IA response). The other three patients, however, had an abrupt increase in plasma renin activity to levels of 5.4 to 36.0 ng/ml/hr (mean 17.2 ng/ml/hr) after 2 to 8 weeks of captopril; these were the only three patients in this group who showed hemodynamic and clinical improvement (type IB response).

Although all three groups of patients who responded to the initial administration of captopril had higher plasma renin activities than did type I patients, patients who had a triphasic response (type III) had a higher plasma renin activity (9.4 ± 2.5 ng/ml/hr) than did the other two groups of initial responders (types II and IV, 4.4 ± 0.7 and 2.8 ± 0.5 ng/ml/hr, respectively), both p < .05 (figure 5). Of the six patients with a plasma renin activity greater than 10 ng/ml/hr, a triphasic pattern of response (type III) was observed in three of them. In further contrast to the pattern seen in type I patients, patients who had types II, III, and IV responses showed marked increases in plasma renin activity after first doses of captopril. These values decreased significantly toward pretreatment values during long-term therapy (p < .01) in patients with types II and III responses but not in patients with type IV responses (figure 5).

Patients who demonstrated tolerance to captopril (type IV) had sustained elevations of plasma renin activity despite the loss of hemodynamic effects. At the time of long-term evaluation, the administration of double doses of captopril (200 mg) produced further increases in plasma renin activity in the two patients in whom this was measured; plasma renin activity decreased toward control values after captopril was withdrawn. One of the two patients who received enalapril showed an increase in plasma renin activity (from 5.0 to 23.2 ng/ml/hr) 4 hr after its administration. None of these humoral responses were accompanied by hemodynamic effects.

Although a plasma renin activity less than 2 ng/ml/hr was observed in all eight patients with minimal responses who had plasma renin activity determinations, an additional nine patients had plasma renin activities less than 2 ng/ml/hr but responded to first doses of captopril; sustained hemodynamic effects (type II responses) were seen in eight of them. Howev-
er, these responders had a marked increase in plasma renin activity after first doses of captopril (1.1 to 10.9 ng/ml/hr; p < .05), as did nearly all patients who responded to the drug, whereas plasma renin activity in the eight patients with minimal responses (type I) did not rise significantly after captopril (0.7 to 2.4 ng/ml/hr; p > .10).

The pretreatment serum sodium concentration was significantly higher in patients with type I responses (138.1 ± 0.8 mEq/l) than in patients with type II (134.3 ± 0.8 mEq/l, type III (131.9 ± 2.3 mEq/l), or type IV responses (133.9 ± 1.3 mEq/l), p < .05.

Response to alternative vasodilator agents. Twelve of the 13 patients who failed to show sustained hemodynamic improvement with captopril (five with minimal responses and seven with drug tolerance) received oral hydralazine (11 patients) or minoxidil (1 patient) 24 hr after the withdrawal of captopril to determine whether they were still responsive to other vasodilator drugs. Hydralazine (300 to 600 mg over 24 hr) produced marked increases in cardiac index (1.60 ± .14 to 2.51 ± .15 l/min/m²) and decreases in mean arterial pressure (92.4 ± 6.2 to 71.2 ± 4.4 mm Hg), left ventricular filling pressure (28.5 ± 0.8 to 21.5 ± 1.4 mm Hg), and systemic vascular resistance (2445 ± 359 to 1114 ± 138 dyn-sec-cm⁻²), all p < .001, without changes in mean right atrial pressure or heart rate. One patient who had previously developed tolerance to hydralazine responded to oral minoxidil (40 mg over 24 hr) in a fashion similar to that noted in the other 11 patients taking hydralazine.²¹

Discussion

Although the immediate effects of angiotensin-converting enzyme inhibition with captopril are thought to be sustained in most patients with severe chronic heart failure,¹ ² there is little information concerning the relationship between the short- and long-term responses to the drug. Although patients who demonstrate marked effects with first doses of captopril often improve clinically during long-term treatment,²¹ ²⁴ others with similar initial responses may not benefit because these hemodynamic effects become rapidly attenuated;²¹ still others may improve with long-term therapy despite the occurrence of early hemodynamic tolerance.⁷ On the other hand, although captopril is often ineffective in patients who do not respond to short-term therapy, some individuals appear to benefit from prolonged treatment despite minimal initial effects.⁶ Because these various patterns of response have largely been the subject of single case reports, the frequency of occurrence of such response patterns has not been defined, and hence the clinical importance of these observations is not known.

Our findings indicate that patients with heart failure demonstrate at least four hemodynamic patterns of response to captopril therapy. Approximately one-fifth (18%) of patients had little hemodynamic change during immediate and short-term treatment and generally failed to show long-term improvement (type I response). About one-half (55%) of patients demonstrated marked hemodynamic benefits with first doses of the drug, which were sustained after 48 hr and after 2 to 8 weeks (type II response). The remaining patients (27%) had immediate responses to captopril that became partially or completely attenuated early or late in the course of treatment. Of the 12 patients who developed attenuated responses within the first 48 hr, seven showed a spontaneous return of the hemodynamic effects of first doses of the drug during long-term therapy (type III response). Tolerance was not reversible (type IV response) in the other five patients nor in two others in whom a loss of drug effect was observed only during prolonged treatment. Most of our patients (6/9) who failed to show short-term responses to captopril also failed to improve with long-term therapy, and most of the patients (35/42) who responded initially had sustained circulatory effects; that is, the response to the initial dose of captopril reflected the long-term effects of the drug in 80% of our patients with heart failure. These findings are similar to those of Case et al.,¹⁹ ²⁵ who proposed the use of the first-dose response to captopril to predict the long-term effects of the drug in patients with systemic hypertension.

We could not clearly define those factors determining the type of hemodynamic response to captopril in an individual patient with heart failure. The failure to respond to short-term therapy in the nine patients who showed a type I pattern appeared to be related to the low plasma renin activity and normal serum sodium concentration that characterized this group; before treatment, all patients had a plasma renin activity less than 2 ng/ml/hr and a serum sodium concentration of 135 mEq/l or greater. This finding is consistent with the concept that captopril exerts its short-term effects in heart failure by inhibition of angiotensin-dependent peripheral vasoconstriction²⁴ and supports the findings of those investigators who have reported a close relationship between plasma renin activity, serum sodium concentration, and short-term responses to the drug.⁶ ²⁶ ²⁷ However, we found a plasma renin activity of less than 2 ng/ml/hr in nearly 30% of patients who had initial and sustained hemodynamic improvement (type II response); only the occurrence of reactive hy-
perreninemia after first doses of captopril in these patients proved to be a reliable means of distinguishing responders from nonresponders. Therefore the finding of a low plasma renin activity before treatment cannot be used to select patients unlikely to respond to captopril therapy. The limited usefulness of plasma renin determinations is consistent with the concept that mechanisms other than angiotensin inhibition may play an important role in the response to captopril, i.e., potentiation of bradykinin, stimulation of vasodilator prostaglandins, or attenuation of sympathetic nervous system responses.

Three of the nine patients with minimal responses to initial doses of captopril subsequently showed hemodynamic and clinical improvement; delayed responses have also been described in hypertensive patients. All three patients had low plasma renin activities with minimal changes after first doses of the drug, but long-term therapy produced increases in plasma renin activity as well as hemodynamic responses to short-term drug administration. The mechanism of these delayed responses to captopril is unknown but may be related to a diuretic effect of the drug mediated by a reduction in plasma aldosterone levels; all three of our patients who showed delayed responses lost weight during captopril therapy, a response not seen in the other six patients who had minimal initial effects. Since angiotensin may stimulate aldosterone secretion at suppressor concentrations, captopril might be able to suppress aldosterone secretion (and thereby potentiate a diuresis) in the absence of any observed short-term central hemodynamic effects. Insofar as a positive sodium balance may attenuate the responses to captopril in patients with heart failure, diuresis may restore hemodynamic and humoral responsiveness to the drug, which would explain the appearance of delayed effects.

A rapid attenuation of effect was observed within the first 48 hr in 12 of the 42 patients (29%) who had initial beneficial effects; in seven of these patients, however, continued unaltered therapy with captopril for 2 to 8 weeks produced a spontaneous restoration of the drug’s initial effects. This pattern has been designated a “triphasic response” by Case et al., who observed a similar transient loss of effect in patients with systemic hypertension after 1 to 2 days of treatment with captopril, followed by restoration of the initial response after 7 to 10 days of continued therapy. Although others have suggested that a triphasic pattern of response might occur in patients with heart failure, the supporting evidence was based on noninvasive assessments of left ventricular function, which exhibit only small changes during the course of captopril therapy. Our findings therefore represent the first hemodynamic evidence that a triphasic response may occur in patients with heart failure treated with captopril.

In hypertensive patients a triphasic response is frequently observed in patients with elevated plasma renin activities; the mean plasma renin activity was 9.5 ng/ml/hr in the patients with systemic hypertension evaluated by Case et al., a value similar to that noted in our patients with heart failure who demonstrated a triphasic response (9.4 ng/ml/hr). Because a markedly elevated plasma renin activity appears to be uncommon in patients with heart failure who are clinically stable, the frequency of a triphasic response in our patients with heart failure was low (14%); the occurrence of such responses might have been more frequent had we evaluated patients during periods of clinical decompensation. Case et al. observed a triphasic response in half of their hypertensive patients; however, many of their patients were selected for therapy because they had renovascular hypertension and thus had higher plasma renin activities than would have been expected in an unselected population of patients.

The mechanisms underlying the occurrence of a triphasic response in patients with hypertension and heart failure remain unclear. A transient loss of inhibition of converting enzyme activity seems unlikely, since in hypertensive patients aldosterone suppression continues unchanged during the period of attenuated response. Alternatively, activation of counteractive vasoconstrictive forces (i.e., sympathetic nervous and renin-angiotensin systems) may occur in patients with hypertension and heart failure and may attenuate the hemodynamic responses to therapy; such forces may themselves become attenuated with continued therapy and permit restoration of initial drug responses. However, confirmatory neurohumoral evidence to support this hypothesis is not yet available. Late restoration of hemodynamic effects may also be potentiated by the diuretic actions of captopril, which were particularly marked in this group of patients, most of whom experienced a weight loss of at least 2 kg during the study. Regardless of the mechanism of the triphasic response, the finding of hemodynamic attenuation early in the course of captopril therapy does not preclude a long-term favorable effect of the drug.

Although tolerance has been reported frequently during the administration of other vasodilator drugs in patients with heart failure, it has rarely been reported during therapy with captopril. Tolerance to the long-
The term effects of captopril occurred in seven patients (14%). Such tolerance occurred both early (within 48 hr) and late (after 2 to 8 weeks) and could not be reversed by increments in dose. Tolerance was reversed by diuresis in the patient who had marked fluid retention during the course of therapy; fluid retention frequently accompanies tolerance to other vasodilator drugs\(^\text{40}\), \(\text{41}\) and has been reported to attenuate the hemodynamic responses to captopril in heart failure.\(^\text{39}\) However, weight changes did not accompany captopril therapy in the other patients who showed tolerance. Alternatively, tolerance might be the result of sustained activation of counteractive vasoconstrictor forces; however, such activation is least likely to occur in patients with a severely depressed cardiac index,\(^\text{37}\), \(\text{38}\) which characterized most of the patients in this group. If such forces had been activated in our patients who demonstrated tolerance, rebound hemodynamic changes would have been expected after captopril withdrawal,\(^\text{36}\), \(\text{38}\) and these were not observed. Our evidence indicates that tolerance was specific to angiotensin-converting enzyme inhibition, since our patients were still responsive to direct-acting vasodilators (i.e., hydralazine) but not to alternative inhibitors of the converting enzyme (i.e., enalapril). Yet the sustained elevation in plasma renin activity that accompanied long-term therapy in these patients, together with the acute reactive hyperreninemia that followed the administration of enalapril and double doses of captopril, suggests that the angiotensin-converting enzyme was still inhibited. Hence the mechanism underlying tolerance to captopril may involve a step beyond converting enzyme inhibition, i.e., alteration in the number and/or affinity of angiotensin II receptors.\(^\text{42}\) Drug-specific tolerance to other cardiovascular agents used in the treatment of severe heart failure has also been attributed to changes in receptor structure or number.\(^\text{5}, \text{43}, \text{44}\)

Both groups of patients with initial and long-term beneficial responses to the drug (types II and III) showed, after first doses of captopril, an increase in plasma renin activity, which gradually declined toward pretreatment values during long-term therapy. A similar decrease in plasma renin activity during the course of treatment of heart failure with captopril was also observed by Dzau et al.\(^\text{24}\) and was attributed to the diminished stimulation of the renin-angiotensin system that would be expected to accompany an improvement in the heart failure state.\(^\text{35}\) This hypothesis is supported by our observation that patients who developed tolerance to captopril and who consequently did not improve hemodynamically or clinically, did not demonstrate a progressive decrease in plasma renin activity toward pretreatment values during the course of therapy.

The findings of this study must be interpreted in the context of certain limitations and precautions. Although we evaluated a large number of patients, the duration of captopril therapy was only 2 to 8 weeks; the frequency of the patterns of response that we delineated may have differed had the treatment period been longer. Had repeat evaluation been performed after 3 or 6 months, we might have demonstrated a higher frequency of hemodynamic tolerance; such tolerance may not occur for several months during long-term treatment with hydralazine.\(^\text{5}\) On the other hand, such prolonged therapy might also permit a greater frequency of delayed responses in patients with minimal initial responses as well as the spontaneous restoration of first-dose effects in a patient in whom the appearance of tolerance at the time of repeat evaluation merely represented the attenuated phase of a triphasic pattern. However, we chose a treatment period of 2 to 8 weeks because we wished to maintain intense supervision of medications and diet; longer periods of such close observation were not feasible. Furthermore, experience in hypertensive patients had previously shown that the response seen after 10 days of treatment with captopril accurately reflected the effects of long-term therapy.\(^\text{19}, \text{25}\)

In conclusion, although the effects of first doses are frequently sustained, the occurrence of delayed, attenuated, and triphasic responses in one-third of our patients receiving captopril indicates that a complex and variable relationship exists between the early and late hemodynamic effects of this drug in patients with severe chronic heart failure. The existence of such discordant responses raises important questions concerning the value of conducting short-term invasive hemodynamic testing in an attempt to guide the choice of therapeutic agents in the management of severe heart failure. Further work is needed to elucidate the pathophysiologic mechanisms that underlie these observations and to determine the frequency and causes of such hemodynamic response patterns during treatment with other vasodilator drugs.

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