Functional Renal Insufficiency During Long-Term Therapy with Captopril and Enalapril in Severe Chronic Heart Failure

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Renal function was evaluated in 104 patients with severe chronic heart failure whom we treated with captopril or enalapril. Seventy patients showed no change or an improvement in renal function (group A), and 34 patients developed functional renal insufficiency (group B). Before converting-enzyme inhibition, group B patients received higher doses of furosemide ($p < 0.02$) and had lower central venous pressures ($p < 0.05$) than group A patients. After 1 to 3 months of converting-enzyme inhibition, an excessive reduction in left ventricular filling pressure (to less than 15 mm Hg) or mean arterial pressure (to less than 60 mm Hg) was noted in 28 of 34 (82%) patients in group B but in only 22 of 70 patients in group A (31%) ($p < 0.001$). At the end of the study, drug-induced azotemia resolved after a reduction in the dosage of diuretics, despite unaltered treatment with captopril and enalapril. Hence, the deterioration of renal function after converting-enzyme inhibition in heart failure is not a toxic or immunologic reaction to therapy but results from specific hemodynamic events that can be ameliorated by sodium repletion.

INHIBITION OF THE angiotensin-converting enzyme is an established approach to the management of patients with severe chronic heart failure (1-3). Marked decreases in intracardiac filling pressures and systemic vascular resistance are seen during short- and long-term treatment with both captopril and enalapril (4, 5), and this hemodynamic improvement is generally followed by alleviation of dyspnea and fatigue and an increase in exercise tolerance (2-7). These benefits are commonly accompanied by a notable natriuresis, correction of preexisting hyponatremia, and a reduction in the need for concomitant treatment with potassium supplements (8, 9).

Little is known, however, about the effects of long-term therapy with converting-enzyme inhibitors on renal function in patients with severe chronic heart failure. Although antagonism of angiotensin-induced renal vasoconstriction might be expected to improve renal blood flow (10, 11), the marked decreases in systemic blood pressure that can accompany treatment with captopril and enalapril may reduce renal perfusion and lead to marked azotemia (12-14). The complex interaction of these two opposing physiologic events may explain why renal function has been reported to improve during treatment with these drugs in some patients with congestive heart failure (15-19) but to deteriorate in others (19-23).

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Little information is available, however, concerning the frequency with which significant changes in renal function occur during long-term converting-enzyme inhibition, the hemodynamic factors that underlie such changes, and the therapeutic management of drug-induced azotemia. Previous studies (14-22) have generally been only short-term evaluations in small numbers of patients, who did not have cardiac catheterization or long-term follow-up. In the present study we evaluated changes in renal function in 104 patients with severe chronic heart failure who underwent invasive hemodynamic studies during both short-term and long-term treatment with captopril and enalapril.

Methods

PATIENT POPULATION

One hundred four patients with severe chronic heart failure received long-term therapy with captopril or enalapril. The group comprised 78 men and 26 women, aged 27 to 83 years (mean, 63). The cause of heart failure was ischemic heart disease in 65 patients, primary dilated cardiomyopathy in 33 patients, and primary mitral or aortic valvular regurgitation in 6 patients. All had a left ventricular ejection fraction of less than 30% as determined by radionuclide ventriculography. Twenty-nine patients had diabetes mellitus; 34 patients had a past history of systemic hypertension. All patients had dyspnea or fatigue (or both) at rest or on minimal exertion but were evaluated while clinically stable. No patient had had an acute myocardial infarction within 4 weeks or an acute exacerbation of heart failure within 2 weeks.

HEMODYNAMIC ASSESSMENT AND DRUG ADMINISTRATION

Each patient received captopril or enalapril under controlled study conditions for 1 to 3 months, and the hemodynamic effects of each drug were assessed by two right-heart catheterizations, the first done immediately before the initiation of therapy and the second at the end of the treatment period.

At the beginning of the trial (for at least 5 days before the study), all patients received constant dosages of digoxin and diuretics, and all previous therapy with vasodilator drugs was discontinued. All patients were fed a salt-restricted diet and were entered into the study when their body weight, blood urea nitrogen, and serum creatinine concentration had remained unchanged for 4 days. Right heart catheterization and arterial cannulation were then done for measurement of intracardiac and systemic pressures, respectively (24). Left ventricular filling pressure was estimated by 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 computer using iced injectate.

Mean arterial pressure, heart rate, left ventricular filling pressure, mean right atrial pressure, and cardiac output were measured repeatedly (with a variation of less than 10%) to ensure stability of the hemodynamic state before drug administration.

Each patient then received an initial dose of 25 mg of captopril orally, after which all hemodynamic variables were determined every 30 minutes for 3 hours. Patients were then treated with either captopril (86 patients) or enalapril (18 patients) according to research protocols that were active at the time the patients were seen. Pretreatment demographic, hemodynamic, and clinical data and the initial response to captopril were not used to determine the choice of a converting-enzyme inhibitor. The dosage of captopril was based on each patient's pretreatment renal function (4, 8) and ranged from 75 to 300 mg/d (four patients received 450 mg/d). The dosage of enalapril was 40 mg/d orally, except in one patient who received 20 mg/d.

For the next 1 to 3 months, dosages of digitalis, diuretics, and captopril or enalapril remained unaltered, and the salt-restricted diet was maintained. At the end of the treatment period, right heart catheterization and arterial cannulation were again done to assess the long-term response to treatment. The procedures for the second evaluation were identical to those followed for the first study. Hemodynamic variables were measured during uninterrupted therapy for 3 hours after the administration of captopril and for 4 to 6 hours after the administration of enalapril.

BIOCHEMICAL AND HORMONAL MEASUREMENTS

Blood samples for determination of blood urea nitrogen, serum creatinine, and serum sodium concentration (in all patients) and for measurement of plasma renin activity by radioimmunoassay (in 100 patients) were collected before the first dose of captopril and then again after 1 to 3 months of treatment with captopril or enalapril (90 minutes and 4 hours after drug administration, respectively). All samples were drawn at a similar time of day, while the patient was on a constant salt-restricted diet, and after the patient had remained supine for a minimum of 4 hours. In 55 of the 104 patients, endogenous creatinine clearance was measured before and during long-term converting-enzyme inhibition using 24-hour urine specimens collected immediately before the performance of hemodynamic measurements.

Changes in the clinical status of each patient after 1 to 3 months of treatment with captopril or enalapril were assessed in terms of symptoms of dyspnea and fatigue at rest and in exercise tolerance. Because all patients had symptoms at rest or on minimal exertion, formal exercise testing was not done.

DATA ANALYSIS

Mean systemic and pulmonary artery pressures were determined by electronic filtration. Derived hemodynamic variables were calculated as follows: cardiac index = cardiac output/body surface area (expressed in $L/min \cdot m^2$); and systemic vascular resistance = 80 × (mean arterial pressure − mean right atrial pressure)/cardiac output (expressed in dynes · s · cm^{-5}). During both short- and long-term therapy, the hemodynamic responses to converting-enzyme inhibition were assessed at peak drug effect on left ventricular filling pressure and systemic vascular resistance (1.0 ± 0.5 hours after captopril and 3.0 ± 1.0 hours after enalapril).

We defined a significant deterioration in renal function during this trial as an increase in blood urea nitrogen of 20 mg/dL or more or as an increase in serum creatinine concentration of 0.4 mg/dL or more. These values were chosen so as to be 2 SD greater than the changes in these variables that occurred in a control group of 20 patients who received stable dosages of digoxin and diuretics for 4 weeks and who were not treated with converting-enzyme inhibitors (mean change in blood urea nitrogen, -0.4 ± 9.6 mg/dL, and in serum creatinine, -0.03 ± 0.21 mg/dL). Patients were divided into two groups according to the observed change in renal function during the trial: group A consisted of patients in whom renal function improved or did not change, and group B consisted of patients in whom renal function deteriorated (according to the criteria outlined above). Qualitative and quantitative differences between the two groups of patients were compared by the chi-square statistic and by the *t*-test for independent variables. The short-term and long-term hemodynamic effects of captopril and enalapril within each group were compared by repeated-measures analysis of variance. Group data are expressed as mean ± SE.

Table 1. Pretreatment Clinical and Biochemical Variables in Patients with Stable (Group A) or Worsening (Group B) Renal Function During Long-Term Converting-Enzyme Inhibition

	Group A ($n = 70$)	Group B ($n = 34$)
Age, *yrs*	62.4 ± 1.4	64.6 ± 2.4
Sex, *n*		
Men	51	27
Women	19	7
Cause of heart failure, *n*		
Ischemic heart disease	44	21
Idiopathic cardiomyopathy	22	11
Primary valvular regurgitation	4	2
History of systemic hypertension, *n/n (%)*	23/70(33)	11/34(32)
Diabetes mellitus, *n/n(%)*	13/70(19)	16/34(47)*
Captopril/enalapril, *n/n*	60/10	26/8
Captopril dosage, *mg/d*	238 ± 13	231 ± 19
Furosemide dosage, *mg/d*	89 ± 7	119 ± 10†
Body weight, *kg*	66.2 ± 1.5	62.4 ± 2.4
Blood urea nitrogen, *mg/dL*	42.9 ± 4.0	37.0 ± 4.7
Serum creatinine, *mg/dL*	1.8 ± 0.1	1.6 ± 0.1
Plasma renin activity, *ng/mL·h*	4.3 ± 0.8	6.8 ± 1.1
Creatinine clearance, *mL/min*	42.7 ± 3.7	49.6 ± 5.1

* $p < 0.01$, compared with group A.
† $p < 0.02$, compared with group A.

Results

Mild increases were seen in blood urea nitrogen (40.9 ± 3.1 to 52.3 ± 3.6 mg/dL) and serum creatinine concentration (1.7 ± 0.1 to 1.9 ± 0.1 mg/dL; both $p < 0.001$) during treatment with captopril and enalapril in our 104 patients. Renal function deteriorated significantly in 34 patients (33%) (group B), but 70 patients (group A) showed either no change (61 patients) or a notable decrease in blood urea nitrogen (≥ 20 mg/dL) or serum creatinine concentration (≥ 0.4 mg/dL) (9 patients). Creatinine clearance declined significantly in group B (49.6 ± 5.1 to 31.2 ± 2.8 mL/min, $p < 0.001$) but increased significantly in group A (42.7 ± 3.7 to 50.9 ± 4.3 mL/min, $p < 0.05$).

Patients in groups A and B were similar with respect to age, sex, cause of heart failure, and past history of systemic hypertension (Table 1). Patients in group B, however, had a greater prevalence of diabetes mellitus (16 of 34 patients [47%] compared with 13 of 70 patients [19%], $p < 0.01$) and were treated with larger daily dosages of furosemide (119 ± 10 compared with 89 ± 10 mg/d, $p < 0.02$) than patients in group A.

HEMODYNAMIC RESPONSES

Groups A and B were similar with respect to all pretreatment hemodynamic variables (Table 2), except that mean right atrial pressure was significantly lower in group B than in group A (9.8 ± 0.9 compared with 12.6 ± 0.7 mm Hg, $p < 0.05$).

After the first dose of captopril, groups A and B showed similar increases in cardiac index and decreases

Table 2. Hemodynamic and Biochemical Responses to Long-Term Converting-Enzyme Inhibition in Patients with Stable (Group A) or Worsening (Group B) Renal Function

	Group A ($n = 70$)			Group B ($n = 34$)			p Value*
	Before Treatment	Long-Term Response	p Value	Before Treatment	Long-Term Response	p Value	
Cardiac index, *L/min·m²*	1.71 ± 0.05	1.95 ± 0.05	< 0.001	1.84 ± 0.07	2.13 ± 0.08	< 0.001	NS
Mean arterial pressure, *mm Hg*	83.9 ± 1.7	69.9 ± 2.0	< 0.001	83.1 ± 2.6	62.1 ± 2.8	< 0.001	< 0.02
Left ventricular filling pressure, *mm Hg*	27.1 ± 0.6	18.7 ± 1.0	< 0.001	26.0 ± 0.9	11.4 ± 1.4	< 0.001	< 0.001
Mean right atrial pressure, *mm Hg*	12.6 ± 0.7	8.1 ± 0.8	< 0.001	9.8 ± 0.9	4.9 ± 1.0	< 0.001	NS
Heart rate, *beats/min*	83.3 ± 1.8	77.5 ± 1.8	< 0.001	86.1 ± 2.3	72.2 ± 2.5	< 0.001	< 0.01
Systemic vascular resistance, *dyn·s·cm⁻⁵*	2011 ± 75	1541 ± 68	< 0.001	2021 ± 114	1354 ± 61	< 0.001	NS
Blood urea nitrogen, *mg/dL*	42.9 ± 4.0	40.7 ± 3.7	NS	37.0 ± 4.7	76.2 ± 6.6	< 0.001	. . .
Serum creatinine†, *mg/dL*	1.8 ± 0.1	1.7 ± 0.1	NS	1.6 ± 0.1	2.2 ± 0.2	< 0.001	. . .
Creatinine clearance, *mL/min*	42.7 ± 3.7	50.9 ± 4.3	< 0.05	49.6 ± 5.1	31.2 ± 2.8	< 0.001	< 0.001
Body weight, *kg*	66.2 ± 1.5	65.1 ± 1.5	< 0.01	62.4 ± 2.4	62.7 ± 2.3	NS	< 0.05
Plasma renin activity, *ng/mL·h*	4.3 ± 0.8	14.0 ± 1.6	< 0.001	6.8 ± 1.1	25.0 ± 4.6	< 0.001	< 0.02

* Comparing groups A and B. NS = not significant. Significance values are not given for blood urea nitrogen and serum creatinine concentration because these two variables formed the basis of the definition of the two groups.
† Creatinine clearance was measured in 37 patients in group A and 18 patients in group B.

in mean arterial pressure, left ventricular filling pressure, mean right atrial pressure, heart rate, and systemic vascular resistance. In contrast, after 1 to 3 months of converting-enzyme inhibition, values for mean arterial pressure, left ventricular filling pressure, and mean right atrial pressure were significantly lower in group B than in group A (Figure 1). When the hemodynamic responses during long-term treatment were analyzed in terms of changes from pretreatment values (Table 2), the magnitude of the decrease in mean arterial pressure, left ventricular filling pressure, and heart rate was significantly greater in group B than in group A. The magnitude of the long-term changes in cardiac index and systemic vascular resistance in both groups was similar.

Individually, left ventricular filling pressure declined by 5 mm Hg or more to a level less than 15 mm Hg during long-term converting-enzyme inhibition in 22 of 34 group B patients but in only 16 of 70 group A patients (65% compared with 23%, $p < 0.001$). Mean arterial pressure fell by 20 mm Hg or more to a level less than 60 mm Hg in 12 of 34 group B patients but in only 10 of 70 group A patients (35% compared with 14%, $p < 0.05$). Mean right atrial pressure decreased 3 mm Hg or more to a level less than 5 mm Hg in 19 of 34 group B patients but in only 19 of 70 group A patients (56% compared with 27%, $p < 0.01$). Critical decreases in mean arterial pressure or in left ventricular filling pressure occurred in 28 of 34 group B patients but in only 22 of 70 group A patients (82% compared with 31%, $p < 0.0001$). Such marked differences between groups in the frequency of critical events were not seen at initiation of therapy.

BIOCHEMICAL AND HORMONAL RESPONSES

Patients with renal insufficiency before the study were not at greater risk for developing worsening azotemia during the trial than were patients with normal renal function before treatment. Pretreatment values for blood urea nitrogen, serum creatinine concentration, and creatinine clearance were similar in both groups (Table 2).

Pretreatment values for plasma renin activity were similar in groups A and B (Tables 1 and 2). Plasma renin activity increased in both groups during the trial, but the increase in group B was greater than that in group A (+17.1 ± 3.6 compared with +8.6 ± 1.8 ng/mL·h, $p < 0.02$). In contrast, body weight decreased (−1.1 ± 0.4 kg, $p < 0.01$) in group A but not in group B (Table 2).

CLINICAL RESPONSES

A similar proportion of patients in group A (42 of 70 patients, 60%) and group B (24 of 34 patients, 71%) noted alleviation of dyspnea after 1 to 3 months of treatment with captopril or enalapril. Inasmuch as the degree of deterioration of renal function in most patients in group B was mild, this decline generally remained clinically inapparent. Nine patients in group B, however, showed marked increases in blood urea nitrogen (> 50 mg/dL) or serum creatinine concentration (> 1.0 mg/dL) during the trial, 6 of whom had severe weakness and anorexia. Eight of these nine patients showed critical decreases in all three pressure variables (mean arterial pressure < 60 mm Hg, left ventricular filling pressure < 15 mm Hg, and mean right atrial pressure < 5 mm Hg) during long-term converting-enzyme inhibition.

MANAGEMENT OF FUNCTIONAL RENAL INSUFFICIENCY

Of the 24 patients in group B who improved clinically during the trial, 18 patients had worsening azotemia in association with a left ventricular filling pressure of less than 15 mm Hg. Upon liberalization of dietary salt intake and a reduction in the dosage of concomitantly administered diuretics, blood urea nitrogen and serum creatinine concentration returned to pretreatment values within 5 to 14 days in 17 of the 18 patients, despite continued treatment with captopril and enalapril in unchanged dosages;

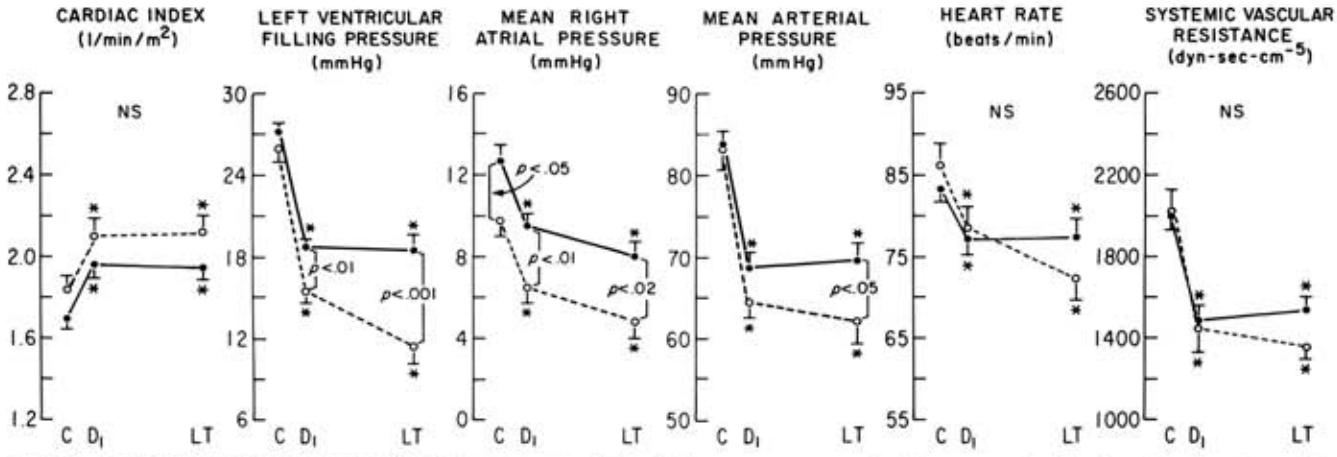

Figure 1. Cardiac index, left ventricular filling pressure, mean right atrial pressure, mean arterial pressure, heart rate, and systemic vascular resistance before (*C*), after the first dose of captopril (D_1), and during long-term converting-enzyme inhibition (*LT*) in patients with severe chronic heart failure. Values for patients in whom renal function remained constant or improved (group A, $n = 70$) during treatment are shown by the solid lines, and values for patients in whom renal function deteriorated during treatment (group B, $n = 34$) are shown by the dashed lines. Asterisks indicate a significant difference ($p < 0.01$) between each post-treatment value compared with the control (*C*) value within each group. *p* Values shown on the figure indicate a significant difference in hemodynamic variables between the two groups. Where *p* values are not designated, the observed differences were not significant (*NS*). Group data expressed as mean ± SE.

clinical benefits were maintained despite the decreased dosage of diuretics. Resolution of azotemia in 1 of the 18 patients required the withdrawal of captopril therapy; this patient was found on subsequent evaluation to have bilateral renal artery stenosis.

In six patients in group B who improved clinically during the study, worsening azotemia was associated with a left ventricular filling pressure of greater than 15 mm Hg during long-term treatment, and their dosage of diuretics was not reduced. In five patients, continued treatment with captopril or enalapril resulted in mild, stable, and well-tolerated increases in blood urea nitrogen and serum creatinine concentration during a follow-up of 3 to 18 months. One of the six patients developed progressive renal insufficiency, which persisted despite discontinuation of enalapril therapy, and died soon thereafter.

Of the ten patients in group B who did not benefit clinically from converting-enzyme inhibition, the withdrawal of captopril or enalapril therapy resulted in resolution of azotemia in all but two patients. One patient died of severe heart failure within 4 weeks, and the other improved markedly after hemofiltration therapy.

Discussion

Insofar as angiotensin II plays a major role in the pathogenesis of hemodynamic abnormalities in congestive heart failure, we might expect the improvement in cardiac performance that accompanies converting-enzyme inhibition to be translated into enhanced renal perfusion and function. Unfortunately, although both captopril and enalapril effectively redistribute blood flow to the kidneys (11), such improved renal perfusion may not result in improved glomerular function (25). Suppression of angiotensin II formation leads to loss of the hormone's vasoconstrictor actions on systemic and intrarenal efferent arterioles and (26, 27) and, thereby, to decreases in systemic blood pressure and glomerular capillary hydraulic pressure, respectively (28). The occurrence of either hemodynamic event produces little effect on renal function, but should both occur simultaneously, the fraction of renal blood flow filtered (filtration fraction) and the glomerular filtration rate may fall precipitously (12, 28).

What determines the evolution of such precarious circulatory conditions? In experimental studies in the dog and rat, the systemic and intrarenal effects of converting-enzyme inhibition have been shown to be largely dependent on changes in sodium balance (28-30), which regulates the activity of the renin-angiotensin system and modulates vascular responsiveness to angiotensin II (31). Accordingly, in the sodium-replete state, filtration fraction and glomerular filtration rate fail to change after angiotensin II blockade or suppression, regardless of whether such interference is achieved systemically or is localized to the kidneys (12, 28-30, 32-34). After salt restriction (or vena cava constriction), however, converting-enzyme inhibition is accompanied by a notable decrease in glomerular filtration rate, the magnitude of which parallels the fall in renal perfusion pressure (12, 28, 35).

SODIUM BALANCE AND RENAL RESPONSE TO CONVERTING-ENZYME INHIBITION IN HUMANS

Studies in normal persons and in hypertensive patients indicate that during treatment with converting-enzyme inhibitors, glomerular filtration is highly dependent on sodium balance. In sodium-replete persons, suppression of angiotensin II formation results in little change in renal blood flow or glomerular filtration rate (36, 37). However, should marked sodium depletion develop (while patients are salt restricted and treated with diuretics), renal function may decline during converting-enzyme inhibition, especially if treatment is accompanied by notable decreases in systemic blood pressure (13, 14). If renal perfusion pressure is critically reduced in these patients before therapy (as in patients with bilateral renal artery stenosis), converting-enzyme inhibition predictably causes functional renal insufficiency (38-41), an ef-

fect that is exaggerated by sodium depletion and can be alleviated by the administration of salt (41, 42). Yet, antihypertensive drugs that do not interfere with the renin-angiotensin system may not cause functional renal impairment under similar circumstances, despite decreases in systemic pressures similar to those seen after captopril and enalapril (38, 43). These observations emphasize the interdependent roles of sodium balance and the renin-angiotensin system in the preservation of glomerular filtration when renal perfusion is compromised.

The interaction of hemodynamic and hormonal factors that determine glomerular function is greatly intensified in congestive heart failure. Angiotensin-II-mediated systemic and efferent arteriolar vasoconstriction is more important in the maintenance of renal perfusion pressure and glomerular filtration in these patients than in normal or hypertensive persons (44-46), not only because renal blood flow is severely compromised (47) but also because renal venous pressure is markedly increased (35). Hence, when these highly activated systemic and renal microcirculatory mechanisms are blocked by converting-enzyme inhibition, renal perfusion pressure, filtration fraction, and glomerular filtration rate decline predictably in persons with low-output heart failure (45, 46, 48). Is the occurrence of such events dependent on the state of sodium balance? If so, we would expect the sodium retention that characterizes patients with congestive heart failure to protect against the development of renal insufficiency; conversely, diuretic therapy should exacerbate the azotemia. Can such changes in sodium balance explain why renal function has improved during converting-enzyme inhibition in some patients with heart failure (15-19) but has deteriorated in others (19-23)?

The Present Study: The findings of this study indicate that sodium balance does play a critical role in modulating the changes in renal function that accompany converting-enzyme inhibition in patients with severe heart failure. Several observations suggest that patients who developed functional renal insufficiency (group B) were more volume depleted before and during treatment with captopril or enalapril than were patients in whom renal function remained stable (group A). First, patients in group B had a lower mean right atrial pressure before therapy and had lower values for mean right atrial pressure and left ventricular filling pressure during therapy than did patients in group A. After 1 to 3 months of treatment, right and left ventricular filling pressures were excessively reduced in most patients in whom renal function deteriorated, whereas this reduction was infrequent in patients with stable renal function. Second, compared with patients in group A, patients in group B showed a more marked hypotensive response to long-term converting-enzyme inhibition, which was accompanied by a more marked increase in plasma renin activity. Previous work has shown that the magnitude of the hypotensive response to, and the degree of, reactive hyperreninemia after converting-enzyme inhibition are dependent on sodium balance and are attenuated after salt repletion or the expansion of intravascular volume (30, 48-50). Such reactive increases in plasma renin activity appear to provide a more sensitive index of angiotensin II dependence than basal estimates of hormonal activation (51). Third, patients in group B were treated with the highest doses of diuretics and showed resolution of drug-induced azotemia after the withdrawal of diuretics or the repletion of dietary salt. All of these observations suggest that by potentiating the actions of angiotensin II on systemic and intrarenal arterioles (42), sodium depletion enhanced the dilator response of systemic and intrarenal efferent arterioles to the suppression of angiotensin II formation. The resultant fall in renal perfusion and glomerular capillary hydraulic pressures was likely the primary factor responsible for the notable deterioration in renal function seen during the study.

Was the relative sodium depletion that we believe existed in our patients in group B present before therapy, or did it develop during treatment with the converting-enzyme inhibitors? A natriuresis commonly follows the suppression of angiotensin II formation in patients with congestive heart failure (15, 37); such a natriuretic response likely explains why body weight decreased significantly in our patients with heart failure in whom renal function remained stable (group A). Experimentally, this enhancement of urinary sodium secretion occurs even in the sodium-deplete state (30, 52), but it is totally abolished if renal perfusion pressure falls markedly (12). This may explain why body weight did not change in our patients in whom renal function deteriorated (group B), because these patients showed the most marked decreases in systemic blood pressure during the course of therapy. Consequently, it seems likely that patients in group B were sodium depleted *before* treatment with the converting-enzyme inhibitors; this depletion was most likely related to the high doses of diuretics that we administered to these patients.

How can we support the hypothesis that patients in group B were sodium depleted if they had symptoms of congestive heart failure and had markedly elevated left ventricular filling pressures at the start of the trial? Some physicians might be tempted to treat these patients with even higher dosages of diuretics in an attempt to alleviate symptoms associated with pulmonary venous hypertension. There is, however, no precise relation between left ventricular filling pressure and the magnitude of sodium retention in patients with congestive heart failure; left ventricular filling pressure is not only determined by changes in intravascular volume but also by changes in the resistance to left ventricular ejection (as well as ventricular pressure-volume relations). The degree to which these factors interact to determine the level of intracardiac filling pressures varies from patient to patient. Our data suggest that in group B, angiotensin-II-dependent systemic vasoconstriction (and not volume overload) played the principal role in the elevation of right and left ventricular filling pressures; intracardiac pressures fell more in these patients after converting-enzyme inhibition than in patients in group A, even though only group A had a notable diuresis during the study. This exaggerated neurohormonal activity in group B patients likely involves several vasoconstrictor systems, including the

sympathetic nervous system. In fact, the withdrawal of heightened adrenergic nervous system activity may be the primary mechanism by which converting-enzyme inhibitors lower intracardiac filling pressures in patients with heart failure (16); this may explain why patients in group B, who showed the most marked decreases in ventricular filling pressures, also showed the most marked reduction in heart rate during treatment. The concept that the elevation of intracardiac pressures in many patients may result from neurohormonal activation rather than from sodium retention raises important questions concerning the utility of diuretics in patients with heart failure who do not show signs of fluid retention. Further attempts at diuresis in such patients may not only fail to alleviate symptoms but may activate endogenous neurohormonal mechanisms (53) and predispose to functional renal insufficiency should these patients be treated subsequently with converting-enzyme inhibitors.

Previous Studies: Our findings explain the contrasting observations of other investigators who have evaluated the effects of converting-enzyme inhibition on renal function in patients with congestive heart failure. In patients in whom diuretic therapy was maintained, various authors (19-21) have noted marked decreases in renal blood flow, glomerular filtration rate, filtration fraction, and urinary sodium excretion after short-term therapy with captopril, the magnitude of these changes being directly related to the concomitant fall in mean arterial pressure. In contrast, Creager and coworkers (15) noted increases in renal blood flow and urinary sodium excretion and little change in glomerular filtration rate after the first doses of captopril, but their patients were in positive sodium balance because diuretics had been withheld for at least 24 hours before the study. The withdrawal of diuretic therapy may have diminished the dependence of glomerular filtration on angiotensin II (12, 28) and attenuated the hypotensive response to converting-enzyme inhibition (50), both of which act to preserve renal function.

Similar mechanisms likely account for the changes in renal function that have been reported during long-term treatment with converting-enzyme inhibitors. Although Dzau and colleagues (17, 18), Kubo and colleagues (16), Mujias and associates (19) observed little change or increases in glomerular filtration rate and urinary sodium excretion after periods of therapy varying from 5 days to 4 months, these investigators generally reduced the dosage of diuretics or permitted patients to consume a liberalized sodium diet in order to minimize the degree of systemic hypotension. In contrast, Cleland and colleagues (22, 23) maintained the sodium intake and diuretic dosage at constant levels and noted that glomerular filtration fell markedly during treatment with captopril and enalapril. In our study, we also kept sodium intake and diuretic dosages constant and thus noted changes in renal function similar to those seen by Cleland and coworkers. Unlike previous investigators, however, we did cardiac catheterization before and during long-term converting-enzyme inhibition and thus were able to identify those hemodynamic factors that contributed to the changes we and others have observed.

ADDITIONAL RISK FACTORS FOR FUNCTIONAL RENAL INSUFFICIENCY

The high prevalence of diabetes mellitus in our patients who developed renal insufficiency after converting-enzyme inhibition deserves special comment. Circulating levels of renin and aldosterone are frequently low in diabetic patients and fail to respond normally to salt depletion and other physiologic stimuli (54-57). This observation may explain why patients in group B, 16 (47%) of whom were diabetic, had basal values for plasma renin activity that were similar to those in group A, despite hemodynamic evidence of pretreatment sodium depletion. Such volume depletion may have been directly related to the high prevalence of diabetes in group B, because diabetic patients do not seem to elaborate aldosterone readily in order to defend intravascular volume (54, 55) and, hence, may be particularly sensitive to the natriuretic effects of diuretic therapy (58); such salt depletion potentiated the hypotensive effects of converting-enzyme inhibition in our study (30, 49, 50). We might have expected a diminished hypotensive response to captopril and enalapril in our diabetic patients, because the peripheral vasculature in untreated diabetics shows an attenuated vasoconstrictor response to angiotensin II (59), possibly due to a reduced density of angiotensin II receptors (57); yet precisely the opposite finding was noted. These data support experimental findings suggesting that sodium balance is a more important modulator of the activity of the renin-angiotensin system than is the diabetic state (50, 57).

Pretreatment biochemical variables did not predict changes in renal function during converting-enzyme inhibition in the present study. Patients with renal insufficiency before therapy with captopril or enalapril were not more likely to develop worsening azotemia than were patients with normal pretreatment values for blood urea nitrogen and serum creatinine. Pretreatment renal function predicts the long-term hemodynamic and clinical response to converting-enzyme inhibition (60) but not drug-induced changes in renal function. Similarly, although pretreatment values for plasma renin activity were somewhat higher in patients who developed worsening azotemia, these values were not significantly different between our two groups of patients. Yet, insofar as the reactive increase in plasma renin activity after converting-enzyme inhibition is a more sensitive index of angiotensin dependence that basal estimates of hormonal activity (51), it is likely that the degree of activation of the renin-angiotensin system at the start of the study was greater in patients in whom renal function deteriorated than in those in whom renal function was preserved. These findings are consistent with those of other studies (including our own) in which patients with high-renin heart failure were most likely to show a decline in glomerular filtration rate and filtration fraction after converting-enzyme inhibition (15, 19, 20, 61). Yet, even such patients may show an improvement in renal function during long-term therapy if doses of concomitantly

administered diuretics are reduced (19).

Finally, the long-acting converting-enzyme inhibitor enalapril was used in a somewhat higher fraction of our patients in whom azotemia worsened than in patients in whom renal function was preserved (8 of 34 [24%] compared with 10 of 70 [14%]), although this difference did not reach statistical significance in this study because of the small number of patients who received enalapril. Nevertheless, in patients with severe chronic heart failure in whom the diuretic dosage is kept constant, the risk for functional renal insufficiency during converting-enzyme inhibition is higher in patients treated with long-acting agents than in those treated with short-acting agents (62). In these highly symptomatic patients with low renal perfusion pressures and marked activation of the renin-angiotensin system, glomerular function is exquisitely dependent on the efferent arteriolar actions of angiotensin II (45, 46, 48), and thus, efforts to suppress the actions of angiotensin II continuously and completely by the use of enalapril (62) may have potentiated the occurrence of functional renal insufficiency in the present study. This risk of long-acting converting-enzyme inhibitors in patients with severe chronic heart failure has been confirmed recently in a double-blind, multicenter, comparative study of captopril and lisinopril (an investigational, long-acting, converting-enzyme inhibitor), in which the frequency of worsening azotemia was significantly greater in the lisinopril-treated group than in the captopril-treated group (18% compared with 5%) despite attempts to decrease the risk for azotemia by reducing the dosage of diuretics (63).

LIMITATIONS OF THE PRESENT STUDY

Our results must be interpreted cautiously. We did not do isotopic measurements of plasma volume or of total-body exchangeable sodium in our patients, and thus, we could not confirm that pretreatment total body sodium levels in patients who developed renal insufficiency were significantly less than levels in patients in whom renal function remained stable; future studies are needed to verify or refute our hypothesis. We did not measure renal blood flow in our patients and thus could not calculate filtration fraction; hence, we were unable to determine whether the deterioration in renal function after converting-enzyme inhibition in group B resulted from the loss of angiotensin's systemic vasoconstrictor effects or its intrarenal (efferent) arteriolar actions. Future work, however, is likely to confirm experimental observations (12, 28) that both effects are needed to produce functional renal insufficiency. Fortunately, both actions are salt sensitive, and hence, sodium repletion attenuates the fall in both systemic blood pressure and filtration fraction (12, 28, 30, 49, 50). Finally, we did not compare the effects of converting-enzyme inhibition on renal function with the effects induced by a vasodilator agent that produces equal hypotensive responses but does not interfere with angiotensin-mediated efferent arteriolar vasoconstriction (43). Unfortunately, no vasodilator agent is presently available that produces sustained hemodynamic improvement in patients with congestive heart failure and is accompanied by hypotensive effects that are as marked as those seen after converting-enzyme inhibition (1). Nevertheless, renal insufficiency may develop in patients with severe heart failure whenever severe hypotension complicates therapy with any vasodilator drug (64). Such excessive systemic vasodilatation, however, is usually due to the overzealous administration of the vasodilator agent rather than due to underlying sodium depletion, and hence, renal insufficiency in such cases may not respond favorably to interventions that restore sodium balance.

CONCLUSIONS

Functional renal insufficiency occurs during converting-enzyme inhibition in up to one third of salt-restricted patients with severe chronic heart failure treated with constant dosages of diuretics. This decline in renal function is not a toxic or immunologic reaction to therapy but is a predictable result of loss of angiotensin-II-mediated systemic and intrarenal vasoconstrictor effects, which are needed to maintain renal perfusion pressure and glomerular filtration rate in low-output states. Our findings indicate that the occurrence of functional renal insufficiency is related to an excessive reduction in intracardiac filling pressure and systemic blood pressure, may be exacerbated by interventions that increase the dependency of the circulation on angiotensin II (diuretic therapy), and thus may be alleviated by a reduction of the dosage of diuretic drugs or by liberalization of dietary salt intake without the need for discontinuation of therapy. This latter observation is important, because patients with heart failure who develop progressive increases in blood urea nitrogen and serum creatinine concentration during treatment with converting-enzyme inhibitors usually have benefited clinically from therapy and will develop symptomatic deterioration should treatment be withdrawn out of inappropriate fears of drug-related nephrotoxicity. In our experience most patients with heart failure who have responded favorably to therapy with captopril and enalapril will experience resolution of drug-induced azotemia without clinical exacerbation of their heart failure when efforts are made to replete total body stores of sodium.

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