PATHOPHYSIOLOGY AND NATURAL HISTORY

CONGESTIVE HEART FAILURE

Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure

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ABSTRACT Although past reports have identified a variety of prognostic factors in patients with severe chronic heart failure, previous studies have not evaluated the interaction of prognostic variables and drug treatment. We analyzed the association of 30 clinical, hemodynamic, and biochemical variables with survival in 203 consecutive patients with severe heart failure; all variables were assessed just before initiation of treatment with a variety of vasodilator drugs, and all patients were subsequently followed for 6 to 94 months. By regression analysis, pretreatment serum sodium concentration was the most powerful predictor of cardiovascular mortality, with hyponatremic patients having a substantially shorter median survival than did patients with a normal serum sodium concentration (164 vs 373 days, p = .006). The unfavorable prognosis for hyponatremic patients appeared to be related to the marked elevation of plasma renin activity that we noted in these individuals (10.0 ± 2.0 ng/ml/hr), since hyponatremic patients fared significantly better when treated with angiotensin converting–enzyme inhibitors than when treated with vasodilator drugs that did not interfere with angiotensin II biosynthesis (median survival 232 vs 108 days, p = .003). In contrast, there was no selective benefit of converting–enzyme inhibition on the survival of patients with a normal serum sodium concentration, in whom plasma renin activity was low (1.9 ± 0.3 ng/ml/hr). This interaction between serum sodium concentration, drug treatment, and long-term outcome suggests that the renin–angiotensin system may exert a deleterious effect on the survival of some patients with chronic heart failure, which can be antagonized by converting enzyme inhibition, and provides a clinical counterpart for the similar prognostic role that has been postulated for angiotensin II in experimental preparations of heart failure.

determining the severity of hemodynamic and clinical impairment in patients with severe chronic heart failure, but the role of these mechanisms in determining survival is unclear. Patients with heart failure who have the most marked elevation of plasma catecholamines have the most unfavorable long-term prognosis; yet, as with other proposed predictors of mortality, it remains uncertain whether neurohormonal activation is the result of a more advanced degree of heart failure or whether it contributes directly to the progression to terminal left ventricular dysfunction or sudden death. Although neurohormonal inhibitors appear to retard the progressive deterioration of cardiac function that is seen in experimental preparations of heart failure, similar data are lacking in patients, largely because previous clinical studies have not controlled for drug treatment.

In this report we analyzed the determinants of survival in a large group of patients with severe chronic heart failure immediately before treatment with a variety of vasodilator agents, and more importantly, evaluated the interaction of these prognostic variables with subsequently administered drug therapy.

Methods

Patient population. Between December 1976 and May 1984, we treated 203 patients with severe chronic heart failure with vasodilator drugs. All patients had dyspnea and fatigue at rest or on minimal exertion despite therapy with digitalis and diuretics; all patients had a left ventricular ejection fraction less than 30% by echocardiography or by contrast or radionuclide ventriculography. There were 145 men and 58 women, ranging in age from 27 to 89 years (mean 64 years). The cause of heart failure was ischemic heart disease in 120 patients, primary dilated cardiomyopathy in 62 patients, and severe mitral and/or aortic regurgitation in 21 patients, eight of whom had undergone valve replacement surgery at least 1 year before evaluation. All patients were evaluated during a period of clinical stability; no patient had experienced a myocardial infarction within 4 weeks or an acute exacerbation of congestive heart failure within 2 weeks. Patients who had received long-term therapy with inotropic agents were excluded from this analysis.

Study protocol. After clinical stabilization on a 2 g sodium diet and constant doses of digoxin and diuretics, all patients underwent right heart catheterization to guide the selection of a vasodilator drug. The procedures that we followed have been published in detail previously; all patients had pulmonary capillary wedge pressure of 15 mm Hg or more. The selection of a specific agent was determined by individual responses and the agents available to us at the time each patient was evaluated. Drug treatment was not randomized. In general, a series of drugs was tested in each patient until a satisfactory short-term hemodynamic effect was observed at a dose that produced no adverse reactions. Drug therapy was then continued for 1 to 3 months, at which time the efficacy of the selected agent was evaluated clinically and, in the majority of the patients, by repeat right heart catheterization. If no clinical or hemodynamic benefits were observed or if adverse reactions occurred that prohibited continued treatment, alternative vasodilator agents were sought during second and third right heart catheterization procedures until a drug was found that was effective and well tolerated, until no such agent was discovered, or until death occurred. If no drug proved valuable during the course of multiple evaluations, patients were generally continued on treatment with the vasodilator agent that had been most recently used. If it had been well tolerated. By following such a protocol, we were able to arrive at a single vasodilator drug for each patient, which was considered the primary therapeutic intervention for purposes of this study.

Two groups of patients were identified. Eighty-six patients received long-term therapy with angiotensin-converting-enzyme inhibitors as their primary therapeutic intervention: captopril (75 to 300 mg daily, 77 patients) or enalapril (20 to 40 mg daily, nine patients). One hundred and seventeen patients received long-term treatment with drugs that did not interfere with angiotensin II biosynthesis: hydralazine (150 to 3000 mg daily, 105 patients), prazosin (15 mg daily, seven patients), or isosorbide dinitrate (80 to 320 mg daily, five patients). All efforts were made in each patient to maintain treatment with the drug designated as the primary therapeutic intervention for the duration of his/her life. Despite our efforts, however, 27 patients treated with hydralazine discontinued the drug more than 4 weeks before death or most recent follow-up because of the late occurrence of drug failure or adverse reactions; 19 of these patients subsequently received long-term treatment with other vasodilator drugs that did not interfere with angiotensin II biosynthesis (nitrates, minoxidil, or prazosin), three patients received long-term therapy with captopril, and five patients received no alternative vasodilator therapy. Seven patients who were treated with captopril or enalapril discontinued the drug more than 4 weeks before death or most recent follow-up examination because of late occurrence of drug failure or adverse reactions; none received alternative long-term treatment with direct-acting vasodilators. Therefore, only three patients crossed over to the alternate therapeutic category (hydralazine to captopril) during the course of the trial.

Data analysis. Long-term survival was assessed from the day of initiation of treatment with the drug that comprised the patient's primary therapeutic regimen to the day of death or to November 1, 1984; each patient was followed for at least 6 months. In most cases we used multiple sources to confirm the date of death, including hospital records, patient's physician, patient's family, and death certificates. The cause of death was ascribed to progressive heart failure, sudden cardiac death (unexpected circulatory collapse occurring in a clinically stable patient), an acute identifiable cardiac event (myocardial infarction or pulmonary embolism), or noncardiac causes. Patients were considered "lost" if the long-term clinical outcome was unknown (11 patients, survival calculated to date of last visit), if therapy was altered to a drug of a different therapeutic class (three patients, survival calculated to date of change), or if the death resulted from noncardiac causes (six patients, survival calculated to date of death).

The following 30 pretreatment variables were assessed for their potential association with survival: age and sex; cause and duration of heart failure; functional class; history of diabetes mellitus, hypertension, or angina pectoris; cardiac index, stroke volume index, left ventricular filling pressure, mean systemic arterial pressure, mean pulmonary arterial pressure, mean right atrial pressure, heart rate, systemic and pulmonary vascular resistances, right and left ventricular stroke work indexes, and left ventricular ejection fraction (by radionuclide cineangiography); serum sodium concentration, plasma renin activity (by radioimmunoassay), blood urea nitrogen, serum creatinine concentration, and uric acid; serum glutamyl-oxalate and glutamyl-pyruvate transaminases, alkaline phosphatase, and bilirubin;
and hematocrit. Derived hemodynamic parameters were calculated according to standard methods.\textsuperscript{14}-\textsuperscript{19}

All pretreatment hemodynamic and biochemical variables were assessed within 24 hr before the initiation of treatment with the drug that comprised the patient’s primary therapeutic intervention. All measurements were performed under steady-state conditions, after patients had been clinically stable for at least 2 weeks and after they had been treated with constant doses of digoxin and diuretics (and no other cardioactive drugs) for at least 5 days; during this time they were fed a 2 g sodium diet, had free access to water, and maintained stable body weights and renal function. All measurements (except those of plasma renin activity and left ventricular ejection fraction) were obtained in triplicate in each patient to ensure stability. All hemodynamic and hormonal variables were assessed simultaneously, after patients had been supine at least 12 hr and 12 to 18 hr after the last doses of digoxin and diuretic.

Twenty-eight of the 30 pretreatment variables noted above were entered into a Cox proportional-hazards model\textsuperscript{20} with the use of stepwise regression analysis (Biomedical Computer Programs, BMDP-2L). Left ventricular ejection fraction and plasma renin activity were determined within 24 hr before the initiation of drug therapy in only 112 and 96 patients, respectively, and thus, were not entered into the Cox regression analysis. Cumulative survival curves were constructed by Kaplan-Meier survivorship methods,\textsuperscript{21} and differences between survival curves were tested for significance by both Mantel-Cox log-rank and Wilcoxon-Breslow methods.\textsuperscript{22, 23} Qualitative and quantitative comparisons of pretreatment hemodynamic, clinical, and biochemical variables between patient subgroups were performed by the chi-square statistic and by the Wilcoxon two-sample rank-sum test, respectively. Group data are expressed as mean ± SEM.

Results

The hemodynamic and biochemical characteristics of the 203 patients with severe chronic heart failure in our study are summarized in table 1.

Cause of death and cumulative survival rates. During the duration of follow-up (6 to 94 months), there were 155 deaths. Fifty-eight patients died suddenly, 84 patients died from progressive congestive heart failure, seven patients died from an acute identifiable cardiac event (myocardial infarction or pulmonary embolism), and six patients died from noncardiac causes. For the total population, the 1 year, 2 year, and 3 year cumulative survival rates were 42%, 24%, and 14%, respectively.

Univariate predictors of survival before stepwise regression. The following variables were significantly correlated (by univariate analysis) with cardiovascular mortality: serum sodium concentration; serum creatinine concentration; serum bilirubin; age; cardiac, stroke volume, and right and left ventricular stroke work indexes; mean right atrial pressure; and pulmonary vascular resistance. Survival was similar for patients with and those without coronary artery disease.

Predictors of prognosis after stepwise regression analysis. After stepwise regression analysis, five variables were found to contribute independently to the prediction of survival: serum sodium concentration ($\chi^2 = 24.26$, $p < .0001$), left ventricular stroke work index ($\chi^2 = 10.40$, $p < .001$), serum creatinine concentration ($\chi^2 = 8.52$, $p = .004$), serum bilirubin ($\chi^2 = 7.13$, $p = .008$), and age ($\chi^2 = 6.79$, $p = .009$).

Among these five variables, pretreatment serum sodium concentration was the most powerful predictor of long-term prognosis. Patients with heart failure with a normal serum sodium concentration (> 137 meq/liter) fared significantly better than did patients with hyponatremia (serum Na $\leq$ 137 meq/liter; median survival 373 days vs 164 days, Breslow $p = .006$, Mantel-Cox $p = .005$; figure 1). This difference between patient subgroups was more marked when lower values for serum sodium concentration were used for purposes of stratification; the median survival of patients with severe hyponatremia (serum Na $\leq$ 130 meq/liter) was substantially shorter (99 days vs 337 days) than that of patients with a higher pretreatment serum sodium concentration (Breslow and Mantel-Cox, both $p < .001$; figure 2).

Hemodynamic and clinical correlates of hyponatremia. Patients with a normal serum sodium concentration (>137 meq/liter) were similar to those with hyponatremia with respect to age and sex, cause and duration of heart failure, presence of risk factors, daily dose of diuretics, and pretreatment hemodynamic variables reflecting right and left ventricular performance (table 2). Patients with hyponatremia, however, had significantly lower values for mean systemic arterial pressure ($p < .001$) and significantly higher values for blood urea nitrogen ($p < .001$), serum glutamyl-pyruvate transaminase ($p = .001$), serum glutamyl-oxalate

| TABLE 1 |
|------------------------|------------------------|
| **Selected clinical, hemodynamic, and biochemical characteristics of patients with severe chronic heart failure in the present study** | |
| **Age** | 64.2 ± 0.9 years |
| **Duration of heart failure** | 31.4 ± 2.6 months |
| **Cardiac index** | 1.0 ± .04 l/min/m² |
| **Left ventricular filling pressure** | 25.3 ± 0.4 mm Hg |
| **Mean systemic arterial pressure** | 82.9 ± 1.0 mm Hg |
| **Mean right atrial pressure** | 11.6 ± 0.5 mm Hg |
| **Heart rate** | 85.7 ± 1.0 mm Hg |
| **Systemic vascular resistance** | 2008 ± 48 dyne-sec-cm⁻⁵ |
| **Pulmonary vascular resistance** | 397 ± 15 dyne-sec-cm⁻⁵ |
| **Left ventricular ejection fraction** | 0.17 ± .01 |
| **Serum sodium concentration** | 135.5 ± 0.4 meq/l |
| **Blood urea nitrogen** | 43.6 ± 2.0 mg/dl |
| **Serum creatinine concentration** | 2.0 ± 0.1 mg/dl |
| **Alkaline phosphatase** | 134 ± 4 μU/ml |
| **Serum glutamyl-pyruvate transaminase** | 63 ± 9 μU/ml |
| **Serum bilirubin** | 1.3 ± 0.1 mg/dl |
| **Plasma renin activity** | 6.6 ± 1.7 ng/ml/hr |

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transaminase (p < .005), and alkaline phosphatase (p = .03) than did patients with a normal serum sodium concentration.

This biochemical evidence of impaired renal and hepatic perfusion in hyponatremic patients was associated with marked increases in plasma renin activity (10.0 ± 2.0 ng/ml/hr), whereas plasma renin activity was low in patients with a normal serum sodium concentration (1.9 ± 0.3 ng/ml/hr, p < .001 between the two groups). In the 96 patients with heart failure in whom both variables were determined simultaneously, serum sodium concentration varied linearly and inversely with plasma renin activity (r = .68, p < .001). According to the linear regression equation relating these two variables (figure 3), our lower limit of normal for plasma renin activity in patients with heart failure (2 ng/ml/hr) corresponded to our lower limit of normal for serum sodium concentration (137 meq/liter).

Interaction of serum sodium concentration, drug treatment, and survival. In patients with a serum sodium concentration of more than 137 meq/liter, the survival of patients treated with converting-enzyme inhibitors did not differ from that of patients who received drugs that did not interfere with the renin-angiotensin system (figure 4). In contrast, hyponatremic patients treated with converting-enzyme inhibitors fared significantly better than did hyponatremic patients treated with other vasodilator drugs (median survival 232 vs 108 days, Breslow p = .003, Mantel-Cox p = .02; figure 5).

In effect, converting-enzyme inhibition shifted the survival curve of hyponatremic patients with heart failure upward and to the right, so as to be superimposable on the survival curve of patients with a normal serum sodium concentration (compare figures 1 and 5). Consequently, when only patients with heart failure treated with converting-enzyme inhibitors were analyzed, serum sodium concentration was no longer a prognostic factor; patients with hyponatremia fared similarly to patients with a normal pretreatment serum sodium concentration (figure 6).

This interaction of treatment and survival in hyponatremic patients was not explicable by other factors. Patients treated with hydralazine, prazosin, and nitrates were similar to those treated with captopril and enalapril with respect to all pretreatment clinical, hemodynamic, and biochemical variables.

Of the 57 patients treated with converting-enzyme inhibitors who died from cardiovascular causes, 19 patients (33%) died suddenly, whereas 34 patients (60%) died of progressive congestive heart failure. Of the 92 patients treated with other vasodilator drugs who died cardiac deaths, 39 patients (42%) died suddenly, and 50 patients (54%) died of progressive heart failure. These differences in the mode of death between the two treatment groups were not significant.

Discussion

The findings of the present study indicate that serum sodium concentration is a primary determinant of survival of patients with severe chronic heart failure. Despite similar clinical characteristics and similar right and left ventricular performance, hyponatremic pa-
TABLE 2
Hemodynamic and clinical characteristics of patients stratified according to pretreatment serum sodium concentration

<table>
<thead>
<tr>
<th></th>
<th>Na ≤137 meq/l</th>
<th>Na &gt;137 meq/l</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.8 ± 1.1</td>
<td>63.6 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>89 men, 28 women</td>
<td>56 men, 30 women</td>
<td>NS</td>
</tr>
<tr>
<td>Etiology</td>
<td>77 ICM, 31 PDC, 9 VR</td>
<td>43 ICM, 31 PDC, 12 VR</td>
<td>NS</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>31 ± 3</td>
<td>32 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>Dose of furosemide (mg/day)</td>
<td>92 ± 5</td>
<td>81 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>1.8 ± .04</td>
<td>1.8 ± .05</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke volume index</td>
<td>21.6 ± 0.7</td>
<td>21.0 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>LV filling pressure</td>
<td>25.5 ± 0.5</td>
<td>25.2 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mm Hg)</td>
<td>81.2 ± 1.2</td>
<td>86.6 ± 1.5</td>
<td>p&lt;.001</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mm Hg)</td>
<td>39.1 ± 0.7</td>
<td>39.1 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>12.7 ± 0.6</td>
<td>11.1 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>84.5 ± 1.3</td>
<td>87.3 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne-sec-cm⁻¹)</td>
<td>1954 ± 56</td>
<td>2083 ± 84</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyne-sec-cm⁻¹)</td>
<td>398 ± 19</td>
<td>397 ± 22</td>
<td>NS</td>
</tr>
<tr>
<td>LV stroke work index (g-m/m²)</td>
<td>16.3 ± 0.7</td>
<td>17.7 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>RV stroke work index (g-m/m²)</td>
<td>8.0 ± 0.3</td>
<td>8.0 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.16 ± 0.01</td>
<td>0.19 ± 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>49.1 ± 2.8</td>
<td>36.1 ± 2.4</td>
<td>p&lt;.001</td>
</tr>
<tr>
<td>Serum creatinine concentration (mg/dl)</td>
<td>2.0 ± 0.1</td>
<td>2.0 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>10.0 ± 2.0</td>
<td>1.9 ± 0.3</td>
<td>p&lt;.001</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>11.5 ± 0.3</td>
<td>10.0 ± 0.3</td>
<td>p&lt;.05</td>
</tr>
<tr>
<td>Serum bilirubin (mg/dl)</td>
<td>1.4 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Alkaline phosphatase (mU/ml)</td>
<td>142 ± 5</td>
<td>123 ± 7</td>
<td>p&lt;.03</td>
</tr>
<tr>
<td>Serum glutamy1-pyruvate transaminase (mU/ml)</td>
<td>90 ± 18</td>
<td>27 ± 2</td>
<td>p&lt;.001</td>
</tr>
<tr>
<td>Serum glutamyl-oxalate transaminase (mU/ml)</td>
<td>73 ± 14</td>
<td>27 ± 2</td>
<td>p&lt;.005</td>
</tr>
</tbody>
</table>

ICM = ischemic cardiomyopathy; PDC = primary dilated cardiomyopathy; VR = primary valvular regurgitation; LV = left ventricular; RV = right ventricular.

FIGURE 3. Relationship between serum sodium concentration and plasma renin activity before vasodilator therapy in 96 patients with severe chronic heart failure. In the linear regression equation depicted in the graph, our lower limit of normal for serum sodium concentration (137 meq/liter) in this study corresponded to our lower limit of normal for plasma renin activity (2 ng/ml/hr).³⁴

Serum Na Concentration >137 mEq/l

FIGURE 4. Kaplan-Meier analysis showing cumulative rates of survival in patients with heart failure and a normal serum sodium concentration (>137 meq/liter) stratified into two groups based on treatment. The prognosis of patients treated with converting enzyme inhibitors (CEI) was similar to that of patients who received drugs that did not interfere with the renin-angiotensin system (Non-CEI) (p = .58, Wilcoxon-Breslow).
Patients with heart failure and hyponatremia (pretreatment serum sodium concentration \(<137 \text{ meq/liter}\)) stratified into two groups based on treatment. Patients treated with converting-enzyme inhibitors (CEI) had a significantly more favorable long-term prognosis than did patients who received drugs that did not interfere with the renin-angiotensin system (Non-CEI) (p = .003, Wilcoxon-Breslow).

Patients treated with converting-enzyme inhibitors had a significantly poorer long-term prognosis than did patients with a normal serum sodium concentration. Insofar as activation of the renin-angiotensin system plays a central role in the pathogenesis of hyponatremia in severe heart failure,\(^{25}\) we suspected that the unfavorable outcome in these patients was causally related to the markedly elevated levels of plasma renin activity we and others have measured in these individuals.\(^{25-30}\) An analysis of the interaction of treatment and survival in our patients supports this hypothesis. Hyponatremic patients fared significantly better when treated with converting-enzyme inhibitors than when treated with vasodilator agents that did not interfere with angiotensin II biosynthesis; in contrast, we observed no interaction between therapeutic drug class and the long-term outcome in patients with a normal serum sodium concentration, in whom plasma renin activity was low. Converting-enzyme inhibition shifted the unfavorable survival curve of hyponatremic patients with heart failure upward and to the right, so as to be superimposable on the more favorable survival curve of patients with a normal serum sodium concentration. These data suggest that the renin-angiotensin system may exert a deleterious effect on the survival of some patients with severe heart failure, and that this effect may be antagonized by treatment with converting-enzyme inhibitors.

Previous investigations have underscored the importance of serum sodium concentration in patients with severe chronic heart failure. Dzau et al.\(^{26}\) have proposed that patients with heart failure are not homogenous but can be stratified into two groups based on serum sodium concentration. Patients with a normal serum sodium concentration tend to be clinically stable and react appropriately to circulatory stress,\(^{26, 31, 32}\) whereas (despite similarly compromised cardiac performance) patients with hyponatremia are clinically decompensated,\(^{26}\) have high circulating levels of stress hormones,\(^{31}\) frequently have prerenal azotemia,\(^{26, 27}\) and are limited in their ability to respond to interventions that further decrease cardiac output.\(^{32}\) Our findings support these observations. Patients with low and normal values for serum sodium concentration showed similar degrees of right and left ventricular dysfunction, but only hyponatremic patients demonstrated evidence of impaired peripheral perfusion; mean systemic arterial pressure was lower and abnormalities of renal and liver function were more marked in these patients than in patients with a normal serum sodium concentration. These differences were not due to differences in the dose of concomitantly administered diuretics. The expansion of extracellular volume that characterizes the heart failure state appears to be insufficient to sustain systemic perfusion in hyponatremic patients; instead, circulatory homeostasis is maintained by the stimulation of neurohormonal forces, especially the renin-angiotensin system.\(^{33}\)

**FIGURE 5.** Kaplan-Meier analysis of cumulative rates of survival in patients with heart failure and hyponatremia (pretreatment serum sodium concentration \(<137 \text{ meq/liter}\)) stratified into two groups based on treatment. Patients treated with converting-enzyme inhibitors (CEI) had a significantly more favorable long-term prognosis than did patients who received drugs that did not interfere with the renin-angiotensin system (Non-CEI) (p = .003, Wilcoxon-Breslow).

**FIGURE 6.** Kaplan-Meier analysis of cumulative rates of survival in patients with heart failure treated with converting-enzyme inhibitors stratified into two groups based on pretreatment serum sodium concentration (>137 vs \(<137 \text{ meq/liter}\)). In these patients who received captopril and enalapril, the long-term prognosis of patients with a normal serum sodium concentration was similar to that of patients with hyponatremia (p = .45, Wilcoxon-Breslow).
Activation of the renin-angiotensin system in hyponatremic patients serves a number of beneficial roles. The elevated levels of angiotensin II primarily support systemic blood pressure; hence, hyponatremic patients are particularly likely to experience profound hypotension when angiotensin biosynthesis is suppressed by converting-enzyme inhibition. Angiotensin II also serves to preserve renal function in low-flow states, either by a direct constrictor effect on postglomerular efferent arterioles to increase filtration fraction or by stimulating the release of prostaglandins that help to maintain renal blood flow as cardiac output declines. Circulating levels of vasodilating prostaglandins are markedly elevated in hyponatremic patients with congestive heart failure and interact with the renin-angiotensin system to regulate systemic vascular resistance and preserve regional blood flow. These beneficial effects of angiotensin II in hyponatremic patients, however, are not gained without a price. By causing direct vasoconstriction, by facilitating the vasoconstrictor actions of the sympathetic nervous system, and by promoting sodium retention by the kidney by stimulating the synthesis of aldosterone, angiotensin II serves to further exacerbate loading conditions in the heart, leading to worsening dyspnea and fatigue. By increasing the production of mineralocorticoids, angiotensin II may exacerbate diuretic-induced potassium depletion, which may predispose to the provocation of complex ventricular tachyarrhythmias. The impaired systemic perfusion and the high circulating levels of angiotensin interact to provide a nonosmotic stimulus to the release of vasopressin, the levels of which are elevated in patients with high-renin heart failure and the antidiuretic effects of which may contribute significantly to the development of hyponatremia. In addition, angiotensin may directly stimulate the thirst center and limit free water clearance in these patients; both events serve to further lower serum sodium concentration. The resulting hyponatremia may be sufficiently severe to cause temporary or permanent neurologic dysfunction and death. Hence, through activation of both diuretic and polydipsic mechanisms, the renin-angiotensin system emerges as the most important pathogenetic factor in the evolution of hyponatremic heart failure; interventions that exacerbate or correct the hyponatremic state (diuretics and captopril, respectively) appear to do so by stimulating or interfering with formation of angiotensin II.

Our data suggest that these detrimental effects of angiotensin II, each acting alone or in concert, may shorten survival in patients with severe chronic heart failure. The cumulative survival curve for hyponatremic patients was shifted downward and to the left (figure 1 and 2) compared with that for patients without notable activation of the renin-angiotensin system. Furthermore, compared with treatment with direct-acting vasodilators, converting-enzyme inhibition selectively shifted the cumulative survival curve of hyponatremic patients upward and to the right so as to be superimposable on the survival curve of patients with a normal serum sodium concentration (figures 4 and 5). These apparent beneficial effects of captopril and enalapril on survival may be mediated by a number of interactive mechanisms. Converting-enzyme inhibition decreases the markedly elevated left ventricular wall stress of patients with congestive heart failure that may lead to progressive cardiac dilatation and death. Captopril and enalapril also preserve total body levels of potassium and reduce circulating levels of catecholamines; either mechanism may prevent the complex ventricular tachyarrhythmias that result in sudden death. The decrease in plasma levels of norepinephrine may further ameliorate ventricular wall stress, prevent the occurrence of stress-related hypokalemia, and avert the potentially direct toxic effects of catecholamines on the myocardium. Since we did not note significant differences in the mode of death between our two treatment groups, it is likely that multiple mechanisms were responsible for the favorable effects that we observed.

Our results differ from those of previous studies that have attempted to delineate specific factors that predict the long-term outcome in patients with severe chronic heart failure. Some investigators have noted an association between the severity of left ventricular dysfunction and the duration of survival, but many of these studies did not employ stepwise regression analysis (as we did) to correct for interdependence among potential prognostic factors. Other reports have noted a relationship between the degree of functional impairment and mortality; fortunately, because nearly all of our patients were in New York Heart Association class IV, we were able to analyze survival in a functionally homogenous population without a wide range of symptoms. Still other studies have found that the detection of malignant ventricular arrhythmias by ambulatory electrocardiography identifies a patient population at high risk of death. We did not perform such monitoring systematically in our patients and thus cannot comment as to the prognostic significance of ventricular arrhythmias; recent observations, however, suggest that the occurrence of potentially lethal ventricular ectopic rhythms in patients with heart failure reflects
advanced hemodynamic and functional impairment and may not be an independent determinant of survival. None of these previous reports evaluated serum sodium concentration as a potential prognostic variable. Furthermore, none of these trials pursued a potential cause and effect relationship; treatment directed at the amelioration of these previously proposed prognostic factors has not been demonstrated to prolong survival.

Only one previous study has evaluated the importance of serum sodium concentration and plasma renin activity as determinants of survival in patients with severe chronic heart failure. In 106 patients with heart failure Cohn et al. also noted associations between a high plasma renin activity and a low serum sodium concentration and mortality by univariate analysis, but both factors were overshadowed by the primary importance of plasma catecholamines in determining long-term clinical outcome in their patients. Unfortunately, interaction effects were not analyzed, and the number of patients treated with converting-enzyme inhibitors was not specified. We consider these omissions to be of great importance. Our findings indicate that converting-enzyme inhibition shifts the survival curve of patients with hyponatremia so as to be superimposable on the survival curve of patients with hyponatremia so as to be superimposable on the survival curve of patients with a normal serum sodium concentration (figure 6); i.e., captopril and enalapril neutralize the prognostic importance of serum sodium concentration and plasma renin activity in patients with heart failure. Were a large number of patients with heart failure in the series of Cohn et al. treated with converting-enzyme inhibitors (as is likely), the predictive power of plasma renin activity and serum sodium concentration would have been diminished, permitting the emergence of other factors as primary determinants when stepwise regression analysis was performed; similar observations have been made by Creager et al. More importantly, Cohn et al. were unable to support a cause and effect relationship between plasma catecholamines and survival; they could not determine whether elevated circulating levels of catecholamines reflected the greater severity of a more fundamental disease process or whether they exerted a direct detrimental effect on the myocardium, since no interventions (such as β-blockers) were used that could be analyzed for potential interaction with survival in high-risk subgroups. We did not measure plasma catecholamines in most of our patients, and thus cannot comment on their predictive value; other investigators, however, have not found plasma catecholamines to be the primary correlate of survival. On the other hand, by stratifying patients into hormonal subgroups and analyzing the interaction of treatment and survival, we were not only able to identify hyponatremic patients as being at high risk, but were also able to suggest that by correcting hyponatremia, converting-enzyme inhibition may ameliorate its prognostic import.

Our data establish a prognostic role for serum sodium concentration in patients with severe chronic heart failure based on values for this variable that were determined under carefully controlled steady-state conditions. Measurements of serum sodium concentration were performed after 5 days of bed rest in the hospital while patients were taking constant doses of digoxin and diuretics (and no other cardioactive drugs). All patients were fed a 2 g sodium diet, had free access to water, and had stable body weights and renal function. We have previously shown that, under such circumstances, measurements of serum sodium concentration show little variability and correlate closely with simultaneous determinations of plasma renin activity. In contrast, patients who have recently undergone a notable diuresis are likely to have marked activation of the renin-angiotensin system, but this will not be reflected in a fall in serum sodium concentration until steady-state conditions are achieved. Such equilibration occurs as angiotensin II stimulates the central nervous system to promote the release of vasopressin as well as to increase thirst. Hence, it is critical that these patients have free access to water. Should water intake be restricted, the homeostatic actions of angiotensin II cannot be fully expressed, and measurements of serum sodium concentration may not accurately reflect the activity of the renin-angiotensin system. In addition, such restriction (although frequently prescribed) is rarely successful in producing long-term correction of the hyponatremic state, since patients cannot comply because of extreme thirst.

The findings of the present study need to be interpreted cautiously. We studied only severely limited patients with heart failure; factors other than serum sodium concentration may be important in determining the prognosis of patients with early and mild heart failure in whom hyponatremia is an unusual occurrence. Our hypothesis that activation of the renin-angiotensin system was associated with an unfavorable long-term survival was not based on a direct correlation of plasma renin activity with mortality, because renin was measured in less than half of our patients and principally in those treated with captopril and enalapril, which would have neutralized the predictive value of this hormone. Our observation, however, that con-
verting-enzyme inhibition antagonized the unfavorable outcome in hyponatremic patients suggests that the prognostic importance of serum sodium concentration was related to its ability to reflect the biologic activity of angiotensin II. We should also note that most of our patients treated with hydralazine, prazosin, and nitrates received these drugs between 1976 and 1981, whereas most patients who received captopril and enalapril were treated between 1980 and 1984; our results, therefore, may reflect a change in the natural history of the disease or in our referral patterns during the study. Our data indicate, however, that neither explanation is likely. The prevalence of specific prognostic factors in our patients did not change during the 8 year period of observation. Furthermore, had there been an improvement in survival during the trial unrelated to treatment, we would have expected to see a shift in both of our patient subgroups (regardless of serum sodium concentration), but patients with hyponatremia were selectively benefitted. Had survival improved because of the referral of less ill patients (i.e., those with a normal serum sodium concentration), we would have observed a favorable effect on prognosis only in these patients; just the opposite trend was noted.

Most importantly, we must emphasize that this study (as were all previous survival studies) was a retrospective analysis of patients whose treatment was not controlled, randomized, or blinded. Hence, we cannot use its findings to conclude that any drug alters survival in patients with congestive heart failure. Our observations simply establish the existence of a significant interaction between serum sodium concentration, converting-enzyme inhibition, and survival, which permits the formulation of hypotheses that can be confirmed or refuted in prospective, randomized, clinical trials. Aside from exactly reproducing our findings, such trials have three possible outcomes with regard to the concepts that we have outlined in this report. They may indicate that no agent favorably modifies the long-term outcome in patients with advanced left ventricular dysfunction; our data suggest that this might occur if patients with hyponatremia were excluded from these trials. Alternatively, future studies may show that all classes of vasodilator drugs favorably influence the survival of these patients. Our data suggest, however, that converting-enzyme inhibitors may exert a selective advantage in patients with hyponatremia. Such an advantage might explain the findings of Furberg and Yusuf who, by pooling the short-term survival data derived from placebo-controlled trials, noted a trend toward improved survival in patients with heart failure treated with converting-enzyme inhibitors but not in patients treated with direct-acting vasodilator drugs. The favorable effects of long-term β-blockade on the mortality of patients with heart failure in uncontrolled trials may also arise from their ability to suppress renin release from the kidney. Finally, long-term trials may show that converting-enzyme inhibitors are superior to other vasodilator drugs in prolonging life in all patient subgroups, regardless of serum sodium concentration; our data suggest, however, that such superiority would be easier to establish in hyponatremic patients, not only because of their higher event rate, but also because of the role played by angiotensin II in producing the hyponatremic state.

In conclusion, our findings indicate that pretreatment serum sodium concentration is the most powerful predictor of long-term prognosis in patients with severe chronic heart failure who are candidates for vasodilator therapy. Our observation that this prognostic relationship is modified by converting-enzyme inhibition suggests that the renin-angiotensin system exerts a deleterious effect on long-term outcome in patients with heart failure that is similar to that which has been proposed for this hormonal system in patients with hepatic cirrhosis and chronic obstructive lung disease. These data provide a clinical counterpart to the prognostic role that has been postulated for the renin-angiotensin system in experimental preparations of chronic heart failure.

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