

Natural History of Patients with Congestive Heart Failure

Potential Role of Converting Enzyme Inhibitors in Improving Survival

BERTRAM PITT, M.D.

Ann Arbor, Michigan

To alter the natural history of congestive heart failure and change the poor prognosis for patients with this condition will require new insights into its pathogenesis as well as the development of strategies to alter the neurohumeral and serum electrolyte abnormalities associated with congestive heart failure, which are often exaggerated by current therapeutic approaches. Although improvement in hemodynamics and exercise tolerance in patients with congestive heart failure remains important, the emphasis of therapeutic goals should be shifted to prevent further cardiac deterioration and to prevent sudden cardiac death. The use of converting enzyme inhibitors holds promise for a beneficial effect on the altered hemodynamic, electrolyte, and neurohumeral abnormalities associated with congestive heart failure. If further prospective randomized trials confirm the beneficial effects of these agents in reducing the mortality rate among patients with congestive heart failure, it is likely that these benefits will have stemmed from their effects on neurohumeral factors and serum electrolyte abnormalities rather than from their effects on hemodynamics.

McKee et al [1] in 1971 on the basis of their observations in the Framingham study found that, despite the use of digitalis and diuretics, the probability of dying within five years from the onset of congestive heart failure was 62 percent for men and 48 percent for women. They stated that "despite earlier recognition and increasingly sophisticated and potent treatment of congestive heart failure its clinical course and prognosis remain surprisingly grim and not much better than cancer in general."

Since the 1960s, the period during which the patients in the Framingham study were followed, much has changed. The most common cause of congestive heart failure in the Framingham study was hypertensive heart disease. Advances in understanding the pathogenesis and therapy of hypertension over the past five years have made this entity a less common cause of congestive heart failure. The incidence of hospital discharges for congestive heart failure per 100,000 population, however, continues to rise [2]. The major causes of congestive heart failure in the 1980s are ischemic heart disease and idiopathic cardiomyopathy. Rapid progress in the development of noninvasive diagnostic techniques, including echocardiography, radionuclide ventriculography, computed tomographic imaging, and most recently nuclear magnetic resonance imaging, has improved the diagnostic evaluation of patients with congestive heart failure. New forms of therapy introduced over the past decade including vasodilators, nonglycoside inotropic agents, and novel antiarrhythmic agents have found wide application in patients with congestive

From the Division of Cardiology, Department of Internal Medicine, University of Michigan Hospitals, Ann Arbor, Michigan. Requests for reprints should be addressed to Dr. Bertram Pitt, Division of Cardiology, Department of Internal Medicine, University of Michigan Hospitals, 1500 East Medical Center Drive, TC-3910-0366, Ann Arbor, Michigan 48109-0366.

heart failure. Despite these advances in diagnosis and therapy, the statement made by McKee et al [1] regarding the prognosis of patients with congestive heart failure unfortunately remains true. Studies in the 1980s utilizing current diagnostic and therapeutic techniques reveal a mortality rate among patients with congestive heart failure similar to that reported by McKee et al [1] more than 25 years ago. Wilson et al [3] noted that the mortality rate among patients with this condition is similar regardless of whether the etiology is due to ischemic heart disease or idiopathic cardiomyopathy. Approximately half of the deaths due to congestive heart failure result from progressive congestive heart failure and the other half from sudden cardiac death [3].

In a recent survey of all published randomized trials of direct-acting arterial and/or venous dilators, Furberg and Yusuf [4] failed to find any significant trend indicating a reduction in the mortality rate. Similarly, there are no data suggesting that the newer inotropic agents, either beta agonists or phosphodiesterase inhibitors, have favorably altered mortality. In fact, what little data that are available concerning inotropic agents suggest the possibility of an adverse effect upon mortality [5].

In some studies, ambulatory electrocardiographic recording and/or electrophysiologic testing have been shown to predict sudden cardiac death in patients with chronic congestive heart failure [6]. There is, however, no convincing data to suggest that suppression of ventricular ectopic activity by antiarrhythmic therapy has reduced the incidence of sudden cardiac death in patients with congestive heart failure due to ischemic heart disease or idiopathic cardiomyopathy. The antiarrhythmic agents that have been evaluated have been found to be either poorly tolerated and/or to have a proarrhythmic effect. The only therapy suggested to reduce mortality in patients with chronic congestive heart failure are the converting enzyme inhibitors [4]. Although data on the effectiveness of these agents in reducing mortality in patients with congestive heart failure are as yet limited and only suggestive, their mechanism of action and effects on serum electrolytes and neurohumeral factors offer promise for the future. Several large randomized trials of converting enzyme inhibitors in patients with congestive heart failure are currently under way and should over the next several years provide important data on the natural history of patients with congestive heart failure as well as a better assessment of the role of these drugs in congestive heart failure.

ELECTROLYTE ABNORMALITIES IN PATIENTS WITH CONGESTIVE HEART FAILURE

The need for potassium replacement in patients with congestive heart failure, many of whom are receiving potent diuretics, is well known, as is the role of hypokalemia in predisposing to arrhythmias in patients taking digitalis.

Despite this knowledge and the extensive use of potassium supplements, the incidence of hypokalemia in patients with congestive heart failure remains disappointingly high. Johansson [7] found that in the 1980s the incidence of hypokalemia in patients with congestive heart failure who were taking diuretics was 20 to 25 percent. In other reports, the incidence of hypokalemia in patients taking diuretics for congestive heart failure is as high as 65 percent [8]. Johansson emphasized that the currently available potassium supplements are often ineffective in correcting diuretic-induced hypokalemia. The importance of hypokalemia in predisposing toward ventricular arrhythmia has recently been re-emphasized by Nordrehaug et al [9] who found a high correlation between serum potassium levels and the probability of ventricular tachycardia in patients with acute myocardial infarction. The importance of potassium replacement in preventing sudden cardiac death is emphasized by the findings of Bertuso et al [10], which showed that potassium replacement was effective without concomitant antiarrhythmic therapy in preventing sudden cardiac death in patients who had a previous diagnosis of sudden death associated with hypokalemia.

Although the importance of detecting and correcting diuretic-induced hypokalemia in patients with congestive heart failure is well recognized, the role of magnesium is less well appreciated. In patients with congestive heart failure, skeletal muscle potassium was found to be reduced to 40.5 ± 5.02 mm/mol 100 g, compared with 44.6 ± 4.0 in control patients. Skeletal muscle magnesium was also reduced to 3.95 ± 0.40 mm/ml 100 g, compared with 4.34 ± 0.29 in control patients [8]. A good correlation has also been found between serum magnesium levels and the incidence of ventricular ectopic beats [11,12]. In some patients with congestive heart failure, hypokalemia can only be corrected after administration of magnesium [13]. Burch and Giles [14] reviewed the cardiac causes of hypomagnesemia and the role of hypomagnesemia in predisposing toward ventricular arrhythmias and sudden cardiac death a decade ago. Diuretics such as furosemide cause a loss of magnesium as well as potassium. Congestive heart failure alone without diuretic therapy may also lead to hypomagnesemia. Hypomagnesemia, as well as hypokalemia, have been implicated in the occurrence of torsade de pointes. Kay et al [15] described 32 patients with torsade de pointes and noted prolongation of the QTc interval prior to development of torsade de pointes in 30 of the 32. The prolonged QTc interval was often associated with hypokalemia and/or hypomagnesemia. The episodes of torsade de pointes occurred in conjunction with the use of antiarrhythmic agents despite the fact that the blood levels of the antiarrhythmic agents were within the therapeutic range. The development of torsade de pointes was not benign in that death in five of the 32 patients was a direct result of this arrhythmia.

mia. This study emphasizes the danger of administering antiarrhythmic agents to patients with congestive heart failure who frequently have hypokalemia and/or hypomagnesemia. Hypokalemia is often considered of importance when the serum potassium level is below 3.4 meq/liter. However, in patients receiving antiarrhythmic agents, torsade de pointes has been found to occur at potassium levels of 3.9 meq/liter or less [16]. This has led to the suggestion that in patients receiving antiarrhythmic agents, serum potassium levels should be maintained at 4.0 meq/liter or above. In fact, the determination of potassium and/or magnesium depletion by plasma sampling detects only a fraction of the patients with total body potassium and/or magnesium depletion.

The frequent occurrence of hypokalemia and/or hypomagnesemia in patients with congestive heart failure treated with furosemide and other potassium-like diuretics and the increasing recognition of the dangers of hypokalemia and/or hypomagnesemia in predisposing to ventricular tachycardia make more intensive efforts to detect and correct hypokalemia and hypomagnesemia in these patients important. The maintenance of serum potassium and magnesium levels by the use of converting enzyme inhibitors may be an important part of their beneficial role in patients with congestive heart failure and may explain their ability to improve mortality [3]. Potassium-sparing diuretics and/or converting enzyme inhibitors have as yet been underutilized in patients with congestive heart failure. Although hyperkalemia is a recognized risk of using potassium-sparing diuretics, the failure of current strategies to protect against hypokalemia and/or hypomagnesemia and the association of these electrolyte abnormalities with ventricular arrhythmias suggests that hypokalemia rather than hyperkalemia may be a greater risk to the patient with congestive heart failure.

NEUROHUMERAL ABNORMALITIES IN CONGESTIVE HEART FAILURE

Plasma norepinephrine levels have been found to be elevated in patients with congestive heart failure and to indicate a poor prognosis. Patients with plasma norepinephrine levels above 800 pg/ml have a high mortality rate of approximately 90 percent in two years [17]. Although the elevated levels of norepinephrine may only reflect the underlying ventricular dysfunction [18], they may contribute to the risk of death in patients with congestive heart failure by predisposing to myocardial cell necrosis and, hence, progression to cardiac failure and/or hypokalemia

and, therefore, sudden death. Direct-acting vasodilators, which may further increase catecholamine concentration as a result of reflex sympathetic activation, might be detrimental. The ability of converting enzyme inhibitors to cause vasodilatation without a secondary increase in norepinephrine levels may be an important factor in their beneficial effect in patients with congestive heart failure.

Among other neurohumeral abnormalities in congestive heart failure, plasma renin levels are elevated. During exercise, plasma renin levels increase significantly in patients with congestive heart failure, compared with levels in normal control subjects [19]. The activation of the renin-angiotensin system during exercise in patients with congestive heart failure could lead to an increased afterload and further left ventricular compromise. Of greater concern is the fact that the activation of the renin-angiotensin system results in catecholamine stimulation and hypokalemia, both of which, as mentioned earlier, may contribute to the increased risk associated with congestive heart failure. The ability of converting enzyme inhibitors to inhibit the formation of renin and therefore to protect against further increases in plasma catecholamines and hypokalemia may in part account for their beneficial effects in patients with congestive heart failure. The beneficial effects of converting enzyme inhibitors on plasma renin levels in patients with congestive heart failure is in contrast to the effect of furosemide, which causes a significant increase in the plasma renin level with potential adverse hemodynamic, neurohumeral, and electrolyte effects. The ability of furosemide and other diuretics to cause hypokalemia and/or hypomagnesemia and hyperreninemia in patients with congestive heart failure may be an important reason for our inability to alter mortality rates in these patients.

Another neurohumeral abnormality in patients with congestive heart failure is an elevated plasma level of atrial natriuretic factor [20]. The level of plasma atrial natriuretic factor appears to be increased in patients with congestive heart failure in response to atrial distension. This factor, when given intravenously to patients with congestive heart failure, causes an increase in cardiac output and naturesis [21]. The fact that patients with severe congestive heart failure have markedly elevated levels of atrial natriuretic factor [20] suggests tolerance to the effects of this factor and/or the development of other mechanisms that inhibit naturesis. The pathogenesis and prognostic role of atrial natriuretic factor in patients with congestive heart failure and the role of converting enzyme inhibitors in relation to this factor remain to be determined.

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