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EDITORIAL

Prognosis in Congestive Heart Failure: What Information Can Best Predict the Future?

The incidence of chronic congestive heart failure (CHF) has increased drastically during the past decade, with over three million patients in the United States affected. Approximately 400,000 new cases of heart failure are diagnosed each year, despite the widespread use of antihypertensive therapy and the advances made in acute intervention during myocardial infarction. CHF is currently the most common hospital discharge diagnosis in patients over 65 yr of age. Although ischemic heart disease accounts for the majority of cases, other etiologies include hypertensive heart disease, dilated cardiomyopathies (particularly idiopathic, alcoholic, and those consequent to viral myocarditis), and progressive valvular heart disease. Once overt heart failure symptoms have developed, death is usually inevitable, with progressive heart failure accounting for 60% of deaths and sudden deaths the remainder (*1*).

Despite major advances made in the medical and surgical treatment of patients with impaired left ventricular function and symptomatic CHF, it has become evident that a high mortality rate is still associated with chronic heart failure. The Framingham Study suggested a 10% annual mortality rate once symptoms had developed (*2*). The recently published V-HeFT II and SOLVD studies reported 5-yr mortality rates approaching 50% despite medical therapy (*3*, *4*). The CONSENSUS trial reported a 1-yr mortality in patients with severe NYHA Class IV symptoms of 52% despite vasodilator therapy (*5*). The need to prospectively identify those CHF patients who are at greatest risk for early mortality has become increasingly important since cardiac transplantation may serve as an effective treatment option for at least a subgroup of these individuals. A variety of mortality studies have identified clinical, hemodynamic, and laboratory factors that correlate with outcome in CHF patients and have recently been summarized in a review by Vagelos et al. (*6*). Factors associated with increased mortality include heart failure etiology, severity of right and left ventricular systolic dysfunction, extent of neurohumoral and sympathetic nervous system activation, degree of hemodynamic derangement, presence of ventricular arrhythmias, and degree of functional impairment—either determined symptomatically by NYHA classification or objectively on exercise testing.

Clinical features that have proven useful in predicting poor outcome include age greater than 55 yr at presentation, cardiothoracic ratio greater than 0.55 by chest film, the presence of a chronic third heart sound, and evidence for right heart failure (*7*). Most studies have confirmed that CHF due to ischemic heart disease is associated with a poorer prognosis than that associated with idiopathic or alcoholic cardiomyopathy. Although Cohn et al. (*8*) identified plasma renin and norepinephrine levels as independent predictors of mortality and confirmed that the higher the plasma norepinephrine level, the greater the likelihood of death due to progressive CHF, this type of neurohumoral profiling is rarely undertaken in the initial evaluation of patients with heart failure.

The relationship between left ventricular ejection fraction (LVEF) and survival varies depending upon the population study. This relationship is strongest in postmyocardial infarction populations, including those with symptomatic CHF. An LVEF less than 0.30 has consistently been shown to be predictive of excess mortality in patients whose CHF is due to ischemic heart disease. The association between LVEF and outcome in patients with idiopathic dilated cardiomyopathy is less clear, although it certainly exists when systolic function is markedly impaired (LVEF less than 0.20). Only recently has impairment in right ventricular ejection fraction become recognized as an important indicator of prognosis in CHF patients (*9*). Quantitative assessment of maximal oxygen uptake with treadmill or bicycle ergometry can add objective prognostic information. A peak oxygen uptake of less than 10–12 ml/kg/min has been associated with a 1-yr mortality rate approaching 80% (*10*). Despite the useful prognostic information derived from these studies, efforts to extrapolate from the group data the prediction of outcome in an individual CHF patient have proven problematic and argues the need for better noninvasive diagnostic modalities.

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In this issue of the *Journal*, Merlet et al. (*11*) report on the utility of ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) in predicting short-term outcome in patients with chronic CHF. Though MIBG shares the same uptake and storage mechanisms as myocardial norepinephrine (i.e., the uptake-one system of neuronal uptake), it is not metabolized by catechol-o-methyl transferase or monoamine oxidase. MIBG imaging thus represents a novel tool to assess presynaptic adrenergic activity in the failing myocardium in which abnormalities of norepinephrine uptake and release as well as decreased total myocardial norepinephrine content have been reported. The authors have demonstrated in a carefully designed prospective study of 90 patients with moderate to severe CHF owing to either ischemic cardiomyopathy (n = 24) or idiopathic dilated cardiomyopathy (n = 66) that a decrease in myocardial uptake of ^{123}I-MIBG was associated with a significantly greater likelihood of death due to progressive heart failure or arrhythmia during short-term follow-up. Those patients whose heart-to-mediastinal activity ratios (H/M) averaged less than 120% experienced 6- and 12-mo survival rates of 60% and 40%, respectively, compared to 100% survival at 12 mo for patients with higher H/M ratios (see Fig. 5).

The study population appears to have been comprised predominantly of patients with advanced heart failure as evidenced by a mean LVEF of 0.22 ± 0.08, mean CT ratio of 0.55, and left ventricular end-diastolic dimension of 67 ± 8 mm. Further proof of the severity of heart failure in the majority of patients is provided by the short time from imaging to death (mean: 7 ± 1.1 mo) or transplantation (3.9 ± 1.5 mo) for the patients who experienced an adverse outcome during follow-up. The clinical relevance of this study is strengthened by a comparison of the predictive value of ^{123}I-MIBG imaging to other known noninvasive predictors of outcome in this population, including degree of left ventricular systolic dysfunction (LVEF) and degree of cardiac dilation as quantified by the echocardiographically determined left ventricular end-diastolic diameter. Multivariate analysis confirmed that MIBG uptake was more predictive of survival than radionuclide or echocardiographic indices.

As with most carefully conducted clinical studies, this report raises a number of important questions regarding the general applicability of these findings to the management of a larger subset of patients with chronic heart failure. As previously mentioned, the study population was small (n = 80), after transplant recipients had been excluded, and was composed of predominantly advanced heart failure as judged by the marked impairment in LVEF and short duration of survival. It remains unproven whether the extent of MIBG uptake will be as predictive of outcome in patients with less severe heart failure and better preserved systolic function. Further, no information was provided regarding whether MIBG uptake was more useful in predicting sudden deaths or those due to progressive heart failure. It is tempting to speculate that this technique might identify that group of patients whose myocardial norepinephrine uptake is most markedly impaired and who are most likely to die of progression of their CHF symptoms, but no data are provided to support this hypothesis. Another correlate of extreme interest would have been the relation between cardiac MIBG uptake and either myocardial norepinephrine stores as determined by endomyocardial biopsy or circulating plasma norepinephrine levels. Both of these measures of adrenergic activity have previously been validated as prognostic indicators in this population (*12*). Another significant limitation to this study is the small number of patients with CHF due to ischemic heart disease. While 73% of the study patients had idiopathic dilated cardiomyopathy, this etiology accounts for fewer than 5% of all new cases of CHF per year. Whether MIBG uptake provides as much prognostic information in the postinfarction CHF population remains to be determined. Finally, the prognostic significance of diminished MIBG uptake was compared with only a limited number of echocardiographic and radionuclide predictors of outcome. Correlations between MIBG uptake and resting hemodynamics, serum sodium concentration, exercise duration, and peak oxygen uptake on exercise testing were not analyzed in this preliminary study. In a recently published report by Doi et al. (*13*), the presence of ^{201}Tl perfusion defects in CHF patients with idiopathic dilated cardiomyopathy was found to be associated with a poorer prognosis. However, when multivariate analysis of other known predictors of outcome, such as resting pulmonary capillary wedge, presence of asymptomatic ventricular tachycardia, and degree of cardiomegaly, were included, the ^{201}Tl results were no longer found to provide additional prognostic value. Whether MIBG uptake will continue to independently predict outcome in a more complete multivariate model remains to be determined.

The authors' suggestion that cardiac MIBG imaging may be employed in the decision-making process as to when to list a patient for heart transplantation should be interpreted with extreme caution. The 10 patients who subsequently underwent transplantation in this series were all excluded from analysis so their clinical profile and imaging results remain unknown. Heart transplantation is currently limited to patients with advanced NYHA Class IV CHF and marked functional limitation. The number of patients in this category is not apparent from this study. The decision to proceed with cardiac transplantation is usually based upon the combination of clinical parameters as well as noninvasive indices. Thus, patients are not listed for transplantation based solely upon heart size, left ventricular end-diastolic dimension, or even LVEF. It would be difficult to extrapolate from the data provided in this series to suggest that a patient with moderate heart

failure should undergo listing for transplantation based solely upon the presence of diminished cardiac MIBG uptake. This may in fact prove to be the case, but additional studies will be necessary to validate this approach. Currently, the maximum oxygen uptake (VO_2 max) on exercise testing has proven to be the most useful noninvasive guide in deciding when a patient is ready for transplant listing. Mancini et al. (*14*) have shown convincingly that patient survival with medical therapy is equal to that achieved with heart transplantation when VO_2 uptake exceeds 15 ml/kg/min. It is only when peak VO_2 uptake falls below 12 ml/kg/min that a survival advantage can be demonstrated for heart transplantation over the subsequent 12-mo period. A comparison of this functional parameter (VO_2 max) to cardiac MIBG imaging will be crucial in determining whether this new technique provides additional information regarding short-term prognosis that might affect listing for transplantation.

Before recommending more widespread use of cardiac MIBG imaging, it is necessary to obtain further information regarding the utility of this technique in a broader population of CHF patients, particularly those with milder forms of the disease as well as a larger number of patients with ischemic heart disease. Nonetheless, this scintigraphic technique has great appeal since it provides a physiologic basis for defining patients at risk of an adverse event based upon the presence of excessive sympathetic nervous system stimulation of the myocardium and depressed neuronal catecholamine uptake. Whether it will provide more useful physiologic information than other techniques, particularly PET and high-energy phosphate spectroscopy, will be of great interest. It is highly unlikely that any one prognostic indicator, whether it be an abnormal hemodynamic value, a measure of impaired contractility, neurohumoral excess, or even the degree of cardiac MIBG uptake, will ever provide 100% certainty with regard to outcome prognostication in patients with CHF. The ability to have several noninvasive markers to assist the clinician in identifying those patients who appear to be at particularly high risk for death and who should be targeted for early intervention—particularly listing for cardiac transplantation—is of utmost importance. This report by Merlet and his associates is encouraging and argues for further clinical studies of MIBG in a more diversified group of heart failure patients.

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