EDITORIAL

Clues to Prognosis in Congestive Heart Failure

Congestive heart failure (CHF) is common, with prevalence approximating 4.8 million people, an incidence of 400,000–700,000 new cases per year and >500,000 hospital admissions per year for treatment of its exacerbation in the United States alone (*1–3*). There is considerable mortality when the disorder is severe. Ischemic and hypertensive heart disease are the most common causes of CHF, with fewer cases being due to dilated cardiomyopathies (*4*). The widely variable prognosis in CHF has led to many studies of its determinants and of treatments to improve on its natural history. Identifying patients at the greatest risk of dying would allow better judgments of the effects of new therapies and the ability to target those most in need of cardiac transplantation (*5–7*). Important determinants of prognosis include the degree of left ventricular (LV) dysfunction (*8,9*), residual ischemia and multivessel disease after myocardial infarction (*10*), myocardial viability (*11,12*), hemodynamic abnormalities and reduced exercise capacity (*13–16*), wasting (*17*) and the inability to exercise at all (*5*). Especially important is reduced peak exercise oxygen consumption (VO_{2max}) (*15,17–19*). A severe reduction of VO_{2max} to <10–14 mL/kg/min objectively shows the limitation of total body functional capacity and is the present gold standard for selecting patients with the worst prognosis for cardiac transplantation (*5,18,19*). However, despite its demonstrated value, VO_{2max} may be affected by several important, noncardiac factors, such as motivation, age and physical deconditioning (*18*). Apoptosis of skeletal myocytes may be a factor in such deconditioning and reduced oxygen consumption (*20*).

Excess systemic neurohormonal activation, especially, but not limited to, that of plasma norepinephrine (PNE) (*21,22*), has been associated with worse CHF and a worse prognosis. Such excess sympathetic activation has been associated with myocardial β-receptor downregulation (*23,24*), norepinephrine (NE) depletion (*25*) and excess NE spillover (*26*) and shown by direct recordings from sympathetic fibers (*27*). Myocardial sympathetic innervation, NE stores and the NE uptake-1 mechanism may be assessed by ^{123}I-metaiodobenzylguanidine (MIBG) (*28–33*) or hydroxyephedrine imaging (*34,35*). For an insightful analysis of cardiac NE and MIBG kinetics the reader is referred to an article by Glowniak (*36*). In patients, Shofer et al. (*32*) showed quantitative relationships between MIBG and NE content in endomyocardial biopsies, plus a quantitative relationship to MIBG scintigraphy. There is also a modest relationship between cardiac MIBG uptake and LV ejection fraction (LVEF) (*32,37*). The MIBG technique has recently been applied to the problem of prognosis in CHF (*33,37,38*).

In a previous issue of the *Journal*, Merlet et al. (*39*) reported their experience with planar MIBG imaging as an indicator of prognosis in idiopathic dilated cardiomyopathy and compared these data with many of the conventional indices listed above. The authors performed a multivariate stepwise regression life-table analysis and obtained a posterior survival probability for each patient using a linear discriminant function applied to each prognostic variable. This information was compared with the survival status of each patient after a mean follow-up period of 27 mo. Patients who received transplants were excluded from the survival analysis. The sensitivity, specificity and positive and negative predictive values of each prognostic index were evaluated. In their study population, depressed MIBG uptake was the most sensitive and specific marker of poor prognosis, including the evaluation of VO_{2max}. In their multivariate model, the only independent predictors of mortality were depressed MIBG and the radionuclide LVEF. When MIBG was eliminated from the model, PNE was the only independent predictor of mortality. Using discriminate analysis, reduced VO_{2max} had a high negative predictive value (97%) but a weak positive predictive value (28%) for survival. In contrast, MIBG activity was far superior in its positive predictive value (78%).

Each new prognostic index should be evaluated in terms of current therapy. In the drug profile of the patients of Merlet et al. (*39*) on entry to the study, 91% were treated with angiotensin-converting enzyme inhibitors (ACE-I) and 18% with β-adrenergic blocking drugs. Both are part of current therapy and are known to improve prognosis in patients with CHF (*40–45*). Treatment with ACE-I reduces the PNE concentration in severe CHF (*21*) and increases the LVEF (*43,46*). The LVEF also increases by treatment with metoprolol (*24,30,47*) as well as by treatment with the newer classes of β-adrenergic blocking drugs such as carvedilol (*44,48*) and bucindolol (*49*). Thus, Merlet et al. (*39*) found that the MIBG data were prognostically useful even after therapy that was likely to have improved LV performance and possibly the cardiac MIBG activity as well (*30,47*). Conversely, the prognostic importance of PNE and LVEF may have been reduced because of the efficacy of these prior treatments. This and other studies of CHF prognosis have been limited by such a one-time assessment of index variables. Cintron et al. (*50*) have shown that antifailure therapy with enalapril

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or hydralazine-isosorbide dinitrate produced serial improvement in LVEF, and this effect itself was associated with improved survival. Thus, the estimation of the utility of any prognostic index should take into account current therapy and its effects.

To put the work of Merlet et al. (*39*) in perspective, first, one should recognize that ischemic cardiomyopathy is the most common cause of CHF. Infarcted tissue has little MIBG uptake (*33*), whereas myocardial viability is likely to be more important prognostically (*51*). Second, it is unlikely that the measurement of a single variable will be as valuable as a combination of factors in estimating prognosis. For instance, Aaronson et al. (*19*) showed greater value of a seven-element noninvasive prognostic index as opposed to the single element, VO_{2max}, in evaluating prognosis in CHF. Third, it will be important for such "new" data as MIBG to undergo serial evaluation and validation. Such re-evaluation has demonstrated the value of VO_{2max} in numerous trials. Recently published results from a three-center French trial (*38*) showed that in a multivariable analysis VO_{2max} was, in fact, prognostically significant, compared with MIBG uptake. In that study of 93 patients, 69 (74%) had nonischemic cardiomyopathies whereas 24 (26%) had ischemic heart disease. Thus, the characteristics of a patient population may limit our ability to generalize the prognostic value of MIBG findings.

As MIBG data emerge, such differences in results will likely be clarified. A more accurate definition of prognosis in the considerable population of patients with dilated cardiomyopathy would have an important therapeutic role, especially in selecting patients suitable for undergoing transplantation. The study by Merlet et al. (*39*) is useful and should stimulate further prospective studies using the MIBG technique.

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