Predicting Prognosis in Advanced Heart Failure

Use of Exercise Indices

Several investigators have searched for methods for predicting clinical outcome in patients with advanced heart failure, including various parameters of exercise capacity for prognostic risk stratification. These exercise indices include subjective parameters such as functional capacity (New York Heart Association [NYHA] classification) and objective parameters obtained by maximal and submaximal exercise stress testing. Functional class assessment is rather subjective and therefore often inaccurate, leading to substantially poor prognosis discriminating ability at mild to moderate levels of functional limitation.

Maximal exercise testing has thus far been the time-honored form of objective exercise assessment. An important advance in exercise testing in heart failure accrued from the work by Weber et al., wherein the investigators demonstrated that concomitant measurements of respiratory gas exchange and airflow with assessment of maximal oxygen consumption (VO2 max) and anaerobic threshold could allow demarcation of the causes of exercise intolerance into cardiocirculatory, pulmonary, and physical deconditioning. Soon thereafter, Szlachcic and colleagues investigated the prognostic importance of maximal oxygen consumption measured during upright bicycle ergometry in a cohort of 27 heart failure patients (21/27 NYHA III/IV; 6/27 NYHA II). At 1-year follow-up, heart failure patients with a VO2 max <10 mL/kg/min were found to have a mortality of 77% compared with a 21% mortality in the group with higher VO2 max (p<0.01). More recently, Mancini and associates examined a cohort of 114 patients with advanced left ventricular dysfunction referred for heart transplant consideration. These investigators demonstrated that transplantation could be safely deferred in patients with a VO2 max >14 mL/kg/min and that VO2 max was the best discriminant of 2-year survival. Data such as these have led to the widespread use of metabolic exercise assessment to determine need for and timing of heart transplantation. While most investigators agree that a VO2 max <10 mL/kg/min in the presence of severe left ventricular dysfunction is associated with a poor outcome, and a VO2 max >18 to 20 mL/kg/min predicts clinical stability and good outcome, controversy abounds in patients with a VO2 max between 10 and 18 mL/kg/min, a range most frequently encountered in patients with left ventricular dysfunction. Investigators have searched for ways to refine the discriminant function of this "gray area," by assessing measurements of percent predicted values of VO2 max adjusted for age and gen-
order, as well as the additive prognostic impact of echocardiographic diastolic indices. In a recent study of 123 patients with advanced heart failure and a mean VO$_2$ max of 16.9 mL/kg/min, it has been demonstrated that percent predicted values of VO$_2$ max were a better predictor of clinical events than weight-adjusted VO$_2$ max. This investigation also found that, although the presence of restrictive physiology was significantly correlated with VO$_2$ max, it added little in the way of prognostic information in the intermediate range VO$_2$ max. A separate investigation from our group has shed light on the presence of a gender mismatch in the predictive ability of VO$_2$ max, demonstrating that in women, percent predicted values of VO$_2$ max are more closely indicative of clinical outcome than weight-adjusted VO$_2$ max.\(^8\)

Traditional maximal exercise testing can be difficult in some patients who are limited by severe cardiac dysfunction or peripheral vascular disease. In such patients, submaximal exercise testing, with or without gas exchange data, is required to evaluate metabolic performance. When gas exchange data is available, our laboratory has used successfully the ventilation/carbon dioxide production ratio assessed at submaximal exercise, to reliably predict VO$_2$ max and prognosis.\(^9\) When cardiopulmonary testing is not available, however, submaximal tests, such as the 6-min walk test, offer the advantage of a safe and reproducible test that better approximates the usual daily activity levels of patients. Guyatt and associates\(^10\) performed the first study of the clinical utility of the 6-min walk test in heart failure patients and showed a significant correlation with functional class but failed to define a close association with results of cycle ergometer testing. This poor correlation with maximal exercise suggested that the 6-min walk test, in fact, might be a measure of a patient's ability to perform usual day to day activity, whereas the maximal exercise test may be a more artificial estimate of laboratory exercise capacity. Another important attribute of the 6-min walk test, demonstrated in serial studies, relates to the incremental improvement in test performance that occurs with concurrent encouragement and the training effect resulting from serial tests. These factors must be kept in mind when critically assessing the value of information derived from the 6-min walk test.

The first investigation to convincingly link the 6-min walk test and morbidity and mortality prediction in heart failure was accomplished by Bittner et al\(^11\) on behalf of the Studies of Left Ventricular Dysfunction (SOLVD) group. These investigators reported that the test independently and strongly predicted long-term mortality and hospitalization rates for heart failure beyond that of traditional indices such as left ventricular ejection fraction and NYHA functional class. It should be emphasized that the patient cohort studied was predominantly that of mild to moderate heart failure, with only 15% of the population suffering from severe heart failure.

In this issue of CHEST, Cahalin and colleagues (see page 325) attempt to define the prognostic utility of the 6-min walk test in 45 patients with severe heart failure (mean NYHA class 3.3±0.6) who were referred for heart transplantation. These researchers concluded that the 6-min walk test was useful in predicting VO$_2$ max and short-term survival but did not prognosticate long-term outcome. The concept of the study is an important one, since the availability of a safe, non-invasive, reproducible, and easily performable prognostic discriminator in patients with severe heart failure is clearly desirable. Several aspects of this investigation, however, merit discussion. For one, the study population was not quite representative of the commonly prevailing etiologic entities of advanced heart failure, and it displayed a predominance of nonischemic dilated cardiomyopathy (78%). Second, the majority of patients were men and therefore the findings of this study might not be generalized to women.

Although these investigators concluded that the 6-min walk test “accurately” predicted VO$_2$ max, the overall correlation was only modest (r=0.64). Based on the data presented by Cahalin and associates, we have analyzed the ability of using a cut point of 350 meters on the 6-min walk test to predict a VO$_2$ max of ≤14 mL/kg/min, a threshold at which heart transplantation becomes a considered option. The sensitivity is 71% and specificity 60%, with a positive and negative predictive value of 86% and 50%, respectively. One can, therefore, hypothesize that the 6-min walk test might serve as a reasonable preliminary screening test for stratifying patients into a “high risk” group who may require early referral for further maximal exercise testing if they fail to walk a distance in excess of 350 meters. Furthermore, as alluded to earlier, it is not surprising that the correlation of maximal exercise with the submaximal walk test was not very strong, since the two tests probably measure different aspects of exercise capacity.

The most important observation by Cahalin and colleagues relates to the relationship between short- and long-term event free survival prediction in relation to the 6-min walk test. The investigators found that while 6-month survival was predicted by the 6-min walk test, long-term survival was better discriminated by maximal exercise parameters, particularly percent of predicted VO$_2$ max. This finding is intriguing and again emphasizes the fact that the 6-min walk test and maximal exercise provide complementary information.

It is reasonable to assume that because laboratory conditions of maximal exercise call on ordinarily un-
used circulatory reserves, cardiopulmonary stress testing might be a better predictor of late outcome. Conversely, the 6-min walk test tends to define cardiac limitations during day-to-day activities; and therefore, failure to walk a distance of 300 to 350 meters might denote a state of exhaustion of cardiac reserves and thereby be predictive of short-term survival.

Why are exercise indices important in the prognostic assessment of advanced heart failure? First and foremost, risk stratification allows prediction of longevity and impending need for hospitalization. Second, accurate prognostication can allow appropriate selection of advanced treatment options in heart failure, particularly as it relates to committing scarce resources such as cardiac transplantation. Lastly, measures of exercise capacity can be serially followed to assess benefits of medical therapy. These reasons underscore the importance for the development and standardization of simple, noninvasive, safe, and inexpensive objective exercise indices. In summary, the 6-min walk test fulfills most of these criteria, and it can be used routinely in the ambulatory setting to assess short-term prognosis, particularly in centers where cardiopulmonary exercise assessment may not be readily available. Moreover, if future studies confirm the clinical utility of the 6-min walk test in advanced heart failure, the usefulness of this test might evolve to allow delineation of patients with severe heart failure who may benefit from closer surveillance and earlier clinical therapeutic intervention.

Mandep R. Mehra, MD
Carl J. Lacie, MD, FCCP
Richard V. Milani, MD
New Orleans

REFERENCES
5. Pina JL. Optimal candidates for heart transplantation: is 14 the magic number? J Am Coll Cardiol 1995; 26:436-37

Ground Glass Attenuation on CT in Patients With Idiopathic Pulmonary Fibrosis

Ground glass attenuation (GGA) of the lung parenchyma occurs when the x-ray density of the lung is greater than that of normal parenchyma, but less than that of soft tissue or consolidated lung. Ground glass attenuation and lung consolidation are both types of parenchymal opacification, and they are distinguished by the observation that only lung consolidation is dense enough to completely obscure the lung vessels and other soft tissue density structures. GGA, also called ground glass opacity or hazy increase in lung density, is much better shown on high-resolution CT than on the chest radiograph.

Careful attention to CT technique is critical for optimal detection of GGA. Detection of GGA is optimized when one uses thin sections (1 to 2 mm) and an adequate CT tube current (particularly in overweight patients), and when one photographs the images using an appropriate window level (600 to 800). GGA may be simulated if the patient takes an inadequate inspiration or if there is respiratory motion artifact. Because the attenuation of the lung is normally greatest in the dependent lung zones, prone views are frequently necessary to confirm the presence or absence of GGA in the posterior lung.

The prognostic significance of GGA in patients with idiopathic pulmonary fibrosis (IPF) has been evaluated in several articles. Wells and colleagues showed that, if GGA is the dominant finding on presentation of patients with IPF, it may be completely or partially reversible on steroids, and is associated with a significantly higher 4-year survival than that found in those with mixed reticular and ground glass opacity, or reticular opacity alone. Other studies which have used serial CT examinations to follow the temporal course of ground glass attenuation in IPF provide conflicting information, because although some areas of GGA were reversible on steroids, most such areas preceded