Heart failure (HF) is a growing epidemic and is now the most common primary diagnosis of all hospitalized patients in the U.S. Thus, the prevention, diagnosis, and treatment of patients with HF have substantial implications for health care from both the clinical and resource standpoint. When a patient presents with signs and symptoms of HF, clinicians expect to see a dilated poorly contractile left ventricle (LV). Yet almost one-half of all patients presenting with HF have a normal ejection fraction (EF) (1) and comprise a unique subset known as “heart failure with normal ejection fraction” (HFnEF). The prevalence of HFnEF has been gradually rising over the past 2 decades. Although therapies have proven effective in reducing mortality from HF with reduced EF, mortality from HFnEF remains unchanged (2). No therapies thus far have been proven to correct the abnormalities seen in HFnEF, halt its progression, or reduce its mortality. With such a huge potential impact on cardiovascular medicine, there is an urgent necessity to reduce its mortality. With such a huge potential impact on cardiovascular medicine, there is an urgent necessity to develop appropriate therapeutic strategies.

The clinical presentation of symptoms and signs of HF with documentation of a preserved EF has been the main entry criterion for the few therapeutic trials of HFnEF, such as the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Morbidity and mortality)-Preserved trial (3). It has been controversial as to whether noninvasive objective evidence of impaired diastolic filling is required for diagnosis of HFnEF (4,5). In this issue of the Journal, Persson et al. (6) present their Doppler echocardiographic data in a substudy that included a small group of the more than 3,000 patients of the CHARM-Preserved trial. These patients underwent an echocardiogram a median of 17.7 months after randomization and were classified into 4 groups on the basis of the severity of diastolic abnormalities seen on the transmitral flow velocity pattern: normal, relaxation abnormality, pseudonormal, and restrictive disease. Not all centers were using mitral annular tissue Doppler imaging (7), so N-terminal pro-B-type natriuretic peptide (NT-proBNP) was used in 61% of all patients to distinguish normal from pseudonormal patterns. The study showed that the primary end point of cardiovascular death or HF hospitalization after a mean follow-up of 18 months was strongly related to the severity of diastolic abnormality. Interestingly, the study found that 12% of all patients undergoing echocardiography had an EF of <35%. Of the remaining patients included in the study, 33% had a normal diastolic filling pattern.

This study does have limitations. The accuracy of the assessment of diastolic function might be questioned, as tissue Doppler was not routinely used. The authors included patients with concomitant abnormalities such as atrial fibrillation, and the noninvasive assessment of patients with these rhythms has not been well studied. The echo Doppler assessment of diastolic filling was done 18 months after randomization and it would have been of greater clinical value to report on the Doppler parameters at entry into the study. Finally, the classification of diastolic function using NT-proBNP is debatable (8); in a community-based study by Redfield et al. (9), the optimal sensitivity and specificity of BNP to detect moderate-to-severe diastolic dysfunction was only 75% and 69%, respectively. This means that in a population where the prevalence of diastolic dysfunction is 67% (as found in the current study by Persson et al. [6]), 28% of the patients would be misclassified if BNP levels were used for the diagnosis of moderate diastolic dysfunction (9).

Despite the limitations, the study is important for 2 reasons. First, it confirms our suspicions that in patients with a clinical diagnosis of HFnEF, the more severe the grade of diastolic dysfunction, the worse the clinical outcome. This means that assessment of the degree of diastolic filling abnormality on Doppler echocardiography provides important information for risk stratification. Second, the study found that objective evidence of diastolic dysfunction was present in only 67% of the patient population. This would imply that the clinical criteria used in large randomized trials such as the CHARM-Preserved trial may be inadequate for entry criteria into studies examining the effect of drugs on outcome in patients with HFnEF. If the criteria for “normal diastolic function” contained in this study are correct, there could be a significant inherent bias in the CHARM-Preserved study as well as other pending therapeutic studies for patients with HFnEF.

The findings from this study indicate that the current noninvasive assessment of diastolic filling is useful for risk stratification and necessary for entry diagnosis into any
therapeutic trial of patients with HFnlEF. However, although progress has been made, current approaches are overly simplistic, and we are just seeing the “tip of the iceberg.” A major problem with HFnlEF is that there is a lack of basic understanding and consensus on the pathophysiology, diagnostic strategies, and classification of this important disease (10–12). As opposed to HF with depressed EF, in which the pathophysiology and subsequent treatment have been extensively studied, there is still considerable controversy regarding the perturbations in cardiovascular function responsible for HFnlEF.

Although there is agreement that the clinical presentation of HFnlEF is simply the patient with signs and symptoms of HF and a preserved EF, there is no well-accepted explanation as to why this occurs. Three different pathophysiological theories have been advanced. The first postulate is that HFnlEF is due to an increase in the intrinsic muscle stiffness (13). The second pathophysiological concept is that HFnlEF is due to increased systolic ventricular and vascular stiffening that results in enhanced sensitivity to volume overload (14). Maurer et al. (15) recently reported a group of hypertensive HFnlEF patients with normal systolic ventric-
ular and vascular stiffness but larger LV sizes. Their findings support a third theory: HFnlEF is due to LV remodeling and dilatation with volume-dependent elevation of filling pressures. These different mechanisms may have important implications for differing therapeutic strategies.

The wide diversity in the pathophysiologic explanations for HFnlEF stems from the difficulty in studying and measuring the complex interplay of multiple interrelated events that contribute to diastolic filling of the LV. The commonly used Doppler-derived indexes are useful in determination of filling pressures, but they are only indirect measures of ventricular filling (16,17), and they do not provide information on the intrinsic diastolic properties of the LV (12). The intrinsic diastolic properties of the LV are best studied by simultaneous left ventricular volume, pressure, and stress/strain relationships under different loading conditions. This is currently possible only through complex invasive hemodynamic studies, which have limited applicability in large patient populations and are not widely available to most investigators (18). However, continued efforts from these invasive studies, combined with the development and assessment of newer, more sophisticated noninvasive imaging modalities using 3-dimensional echocardiography, tissue Doppler strain imaging, speckle tracking, and high-resolution magnetic resonance imaging scanning, will be necessary to fully understand this disorder.

The true pathophysiologic mechanism of “diastolic dysfunction” needs to be elucidated, for without this knowledge the diagnostic and therapeutic strategies for patients with HFnlEF cannot be advanced. We need to determine whether HFnlEF is one disease or if there are multiple distinct pathophysiologic disturbances leading to one clinical picture. These unknowns are illustrated in Figure 1, which shows the highly variable responses of diastolic function to interventions in individual patients. Our eventual understanding will have significant implications in directing therapy: should we only lower afterload and preload, or should we be examining drugs with the potential to affect myocardial relaxation, stiffness, and remodeling? We suspect that we will find a wide spectrum of pathophysiologic processes causing HFnlEF, which will require a wide spectrum of treatment options targeted to the underlying pathophysiology. This group of patients with HF and preserved EF is increasing in its prevalence without a foreseeable reduction in mortality. As HFnlEF is becoming the most common form of HF, there is a great need for coordinated efforts to fully address this problem.