Understanding "Diastolic" Heart Failure

Margaret M. Redfield, M.D.

Heart failure is common and costly, and it primarily affects the elderly. As the elderly population expands, there will be marked increases in the number of persons with heart failure. Epidemiologic studies have established that 40 percent to 50 percent of patients with heart failure have a normal ejection fraction (≥50 percent) without primary valve disease, a clinical syndrome that is commonly referred to as "diastolic" heart failure. Despite great progress in our understanding of and therapeutic approach to heart failure associated with systolic dysfunction, or systolic heart failure, we are now realizing that basic research and clinical investigations have failed to address nearly half of the epidemic of heart failure.

Patients with diastolic heart failure tend to be older than those with systolic heart failure; more of them are female, more have hypertension, and fewer have recognized coronary artery disease. Most studies show similar rates of diabetes, atrial fibrillation, and renal disease among patients with the two types of heart failure. Acute episodes of diastolic heart failure are often associated with hypertensive episodes or the onset of atrial fibrillation, and over the long term, patients with this disorder have exercise intolerance and a reduced quality of life. Although mortality after a diagnosis of diastolic heart failure is nearly equivalent to that after a diagnosis of systolic heart failure, the common causes of death among patients with diastolic heart failure have not been defined, and little is known about potential differences among clinical subgroups of this type of heart failure.

Heart failure is a progressive syndrome characterized by complex cardiac and systemic adaptations that vary over time. In patients with systolic heart failure, a regional or global myocardial insult leads to systolic and diastolic dysfunction, left ventricular remodeling (hypertrophy, fibrosis, and dilatation), local and systemic neurohumoral and cytokine activation, impairment of renal hemodynamic and excretory function, and vascular dysfunction. Prognostic hemodynamic categories are based on the relative derangement in cardiac output, filling pressures, and systemic vascular resistance. Chronic elevation of left atrial pressures leads to right heart failure. Progression is modulated by coexisting conditions, particularly coronary disease and renal disease. These insights have directed the development of therapeutic strategies that have ultimately been proved effective in clinical trials. This process is thus far incomplete, and genomic and proteomic paradigms for the pathophysiology of heart failure will continue to evolve.

If we contemplate the time and effort that have been required to elucidate the natural history and pathophysiology of systolic heart failure and the therapeutic approach to it, the prospect of "starting over" with diastolic heart failure may seem daunting. Whether diastolic heart failure shares most pathogenic mechanisms with systolic heart failure remains to be established. The first step in this process is to understand the fundamental abnormality in ventricular function that causes, or at least accompanies, the clinical syndrome.

It has long been recognized that patients with hypertrophic, infiltrative, or primary restrictive cardiomyopathy (many of whom are young) may present with heart failure despite having a normal ejection fraction. In these rare conditions, an abnormality in the myocardium (hypertrophy with myofiber disarray, amyloid infiltration, or extensive fibrosis) results in impairment in both the rate of active left ventricular relaxation and the compliance of the ventricle without a reduced ejection fraction or left ventricular cavity dilatation. These abnormalities in diastolic function result in an increased dependence on filling through atrial contraction, as well as higher atrial pressures to maintain filling and cardiac output. In these rare diseases, a discrete and easily understood cardiac structural alteration leads to diastolic heart failure.

It was assumed that elderly patients who presented with heart failure and a normal ejection fraction had primary diastolic dysfunction similar to that observed in these rarer conditions. However, this assumption has recently been challenged, in part because of a study involving a small number of patients with diastolic heart failure that did not find impaired relaxation or compliance and in part because of questions regarding the underlying pathological abnormalities of the myocardium that might be causing diastolic dysfunction in these patients (see Figure). In most series, only about 40

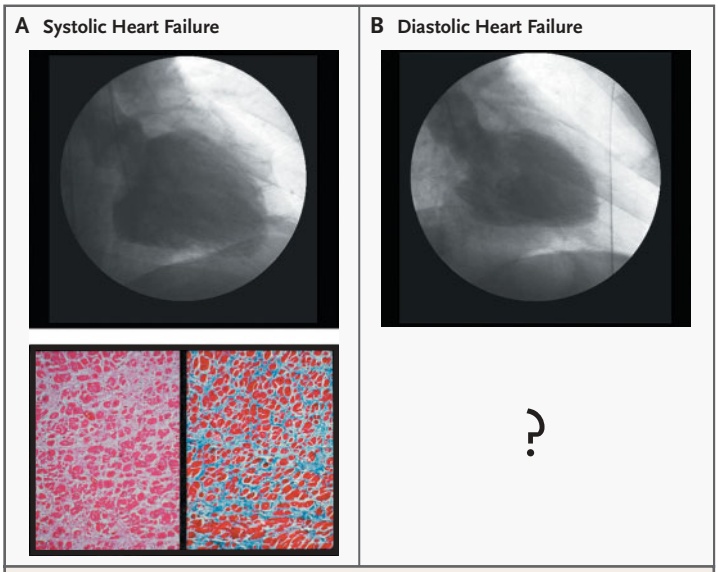

Figure. Systolic Heart Failure (Panel A) and "Diastolic" Heart Failure (Panel B).
A contrast ventriculogram (diastolic frame) from a patient with heart failure and a reduced ejection fraction (Panel A, top) shows the presence of left ventricular dilatation as seen in most patients with systolic heart failure. The characteristic pathological features of the myocardium have been well described on the basis of biopsy, autopsy, and surgical specimens, and staining with hematoxylin and eosin (Panel A, bottom left) and Masson trichrome (Panel A, bottom right) shows the typical hypertrophy and marked fibrosis. In Panel B, a contrast ventriculogram (diastolic frame) from a patient with heart failure and a normal ejection fraction underscores the absence of left ventricular dilatation common to most patients with diastolic heart failure. The characteristic pathological features of the myocardium have not been described, and fundamental questions remain regarding cardiac structure and function, clinical features, natural history, and pathophysiology.

percent of patients with diastolic heart failure meet the echocardiographic criteria for left ventricular hypertrophy, no pathological studies have been performed to establish the extent of myocardial fibrosis in patients with diastolic heart failure, and the role of ischemia in causing acute or chronic diastolic heart failure has not been defined. Indeed, some recent studies have suggested that the fundamental perturbation lies in increased arterial and systolic left ventricular stiffness — changes that result in secondary, load-dependent changes in diastolic function.

Given the complexity of heart failure, the paucity of studies in actual patients with diastolic heart failure, and the potential for heterogeneity in this condition, we must be cautious in making assumptions regarding its pathophysiology. Indeed, some suggest that it is too early to refer to heart failure in a patient with a normal ejection fraction as diastolic heart failure until more studies have established the pathophysiology involved. Thus, the study reported by Zile et al. in this issue of the *Journal* (pages 1953–1959) is particularly important. It is the largest comprehensive study to date of diastolic function in patients with diastolic heart failure, and it supports the theory that primary abnormalities in diastolic function are indeed present in patients with diastolic heart failure and that left ventricular hypertrophy is not required for diastolic dysfunction to occur. The authors acknowledge that other mechanisms may contribute to the propensity for diastolic heart failure but conclude that abnormalities in diastolic function are key.

The importance of the study by Zile et al. goes beyond their conclusions regarding the pathophysiology of diastolic heart failure. After a decade of controversy over whether this syndrome even exists, this study and a few others have begun to address the pathophysiological mechanisms that are responsible for half of the heart-failure epidemic. Further studies to confirm the findings of Zile et al. and to investigate other pathogenic mechanisms are crucial. We know little of the natural history of the disorder, particularly the mechanisms causing death in affected patients. The type and degree of neurohumoral activation, the characteristic myocardial function and pathological changes, and the systemic and renal hemodynamic profiles have not been defined. Without a better understanding of these factors, no plausible therapeutic strategies can be advanced. Although some advocate testing the same strategies used in systolic heart failure, the rationale for this approach is based largely on assumptions, and many patients with diastolic heart failure are already being treated for hypertension with the standard therapies used for systolic heart failure. Most important, without a better understanding of the pathophysiology of diastolic heart failure, opportunities for new and potentially more effective strategies may be missed.

From the Mayo Heart Failure Program and Mayo Cardiorenal Research Laboratory, Cardiovascular Division, Department of Internal Medicine, Mayo Clinic College of Medicine, Rochester, Minn.