Defining Diastolic Dysfunction

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The human intellect has an almost irresistible urge to categorize and simplify. Thus, over the years, heart failure has been classified as forward or backward, right or left, compensated or decompensated. These distinctions, which were made primarily on the basis of data obtained from the history and physical examination, provided a conceptual framework for thinking about heart failure and for rationalizing therapeutic decisions (eg, digitalis to increase cardiac output in “forward” failure). As information routinely available to the clinician has been extended from the history and physical examination to now include precise, noninvasive characterization of ventricular volumes and aortic flow, it has been increasingly recognized that the pathophysiology of heart failure cannot be assessed adequately by the older classifications. For example, it is now appreciated that “backward” heart failure with elevated ventricular filling pressures and consequent pulmonary or peripheral edema can result from either systolic or diastolic ventricular dysfunction. In fact, epidemiological and case-control studies of individuals presenting with clinical heart failure have estimated that 40% to 50% of such patients have normal systolic function and presumed diastolic heart failure.1–4 For example, Senni et al,1 from the Mayo Clinic, reported that 43% of patients with clinical congestive heart failure and adequate echocardiographic assessment of ejection fraction show normal/preserved left ventricular function. Although the prognosis of patients with heart failure and preserved systolic function has generally been regarded as intermediate between normal subjects and patients whose heart failure is associated with depressed systolic function, the recent Mayo study1 calls this into question, showing both systolic and diastolic heart failure to have a similar prognosis, at least over the first 3 to 4 years of follow-up.

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Should all patients with a clinical diagnosis of congestive heart failure and normal ventricular systolic function by echocardiogram be regarded as having diastolic heart failure? The answer to this question is simple: Of course not. Patients with sudden onset of severe mitral or aortic regurgitation may present with pulmonary edema and a normal left ventricular ejection fraction but would not be regarded by most clinicians as having diastolic heart failure. So what is diastolic heart failure? Workers in the field usually will start with the pathophysiological definition that diastolic heart failure is present when an elevated filling pressure is necessary to achieve normal ventricular filling (ie, filling of the ventricle to a normal end-diastolic volume).5 Many investigators will further subdivide diastolic heart failure into cases in which the increased resistance to diastolic ventricular filling is mechanical and external to the ventricular myocardium (eg, constrictive pericarditis, mitral stenosis) and those in which increased resistance to diastolic filling is intrinsic to the myocardium (eg, myocardial hypertrophy, fibrosis, ischemia, or infiltrative cardiomyopathies such as amyloidosis). These categorizations are far from perfect, and the interested observer can easily identify conditions or devise clinical scenarios that do not fit within this rather simple approach. The important point, however, is that even to meet this rather flawed pathophysiological definition of diastolic heart failure, knowledge of intracardiac pressures and volumes is required.

Even with precise measurements of ventricular chamber pressures and volumes, the fact that diastolic abnormalities may be functional and transient makes the timing of the clinical and investigative studies of critical importance. Just as the diagnosis of Prinzmetal’s angina may be impossible unless one carries out appropriate ECG and/or coronary angiographic studies both during and after an episode of coronary artery spasm, so it may be impossible to tell whether an episode of flash pulmonary edema in a patient with 3-vessel coronary disease was due to transient systolic or diastolic dysfunction. In fact, studies in patients with elevated left ventricular filling pressure due to acute myocardial ischemia indicate that both systolic and diastolic left ventricular dysfunction coexist in such patients,6,7 with diastolic dysfunction predominating in some but not in others.

In the context of these difficulties, the article by Vasan and Levy8 in this issue of Circulation deserves careful attention. On the basis of their extensive experience in the Framingham Study and their review of the literature, these authors propose a scheme for the definition of definite, probable, and possible diastolic heart failure. They make the cogent argument that although numerous clinical trials have examined and defined appropriate therapy for the treatment of systolic heart failure (clinical heart failure associated with depressed left ventricular ejection fraction), the optimal treatment of diastolic heart failure has not been determined. Appropriate clinical trials await the development of rigorous and widely acceptable entry criteria to define the study population. Vasan and Levy suggest that definite diastolic heart failure is present if there is definitive evidence of congestive heart failure (clinical symptoms, signs, supporting tests such as chest radiograph, typical clinical response to treatment with diuretics, with or without documentation of elevated left ventricular filling pressure or a low cardiac index) coupled with objective

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Evidence of normal left ventricular systolic function (left ventricular ejection fraction ≥50%) within 72 hours of the heart failure event and objective evidence of left ventricular diastolic dysfunction (eg, abnormal LV relaxation/filling/distensibility indices on cardiac catheterization). It is not likely that many patients in common clinical practice will meet these criteria for definite diastolic dysfunction, and therefore, Vasan and Levy propose criteria for probable diastolic heart failure that will include definitive clinical evidence of heart failure and objective evidence of normal LV systolic function within 72 hours of the heart failure event but no conclusive information on LV diastolic function. Finally, Vasan and Levy allow for possible diastolic heart failure in the patient for whom there is clinical evidence of congestive heart failure coupled with evidence of normal LV systolic function outside the 72-hour window and in whom evidence for LV diastolic dysfunction is lacking. Despite the difficulties inherent in their attempts, this classification may serve as a valuable framework that will facilitate the design of appropriate clinical trials to test the efficacy of specific therapeutic agents in the treatment of diastolic heart failure.

Certain simple deficiencies of the Vasan-Levy classification could be easily addressed by the addition of appropriate exclusion criteria. If strictly applied, their definition of probable diastolic heart failure would include individuals with acute mitral or aortic regurgitation or purely mechanical causes of diastolic heart failure (such as mitral stenosis or constrictive pericarditis); this could be avoided by adding screening for these exclusionary criteria as part of the definition. Accordingly, to have a diagnosis of probable diastolic heart failure, you would need to satisfy both the inclusionary characteristics listed in Vasan and Levy’s article and a list of exclusionary characteristics. Certain problems remain that will be difficult to sort out. For instance, it is now clear that the majority of patients with what is currently called “systolic heart failure” also have diastolic dysfunction of various degrees. In fact, there is some evidence that much of the pathophysiological derangement in patients with advanced systolic heart failure and cardiomyopathy may be a result of intrinsic abnormalities of myocyte calcium handling. Drugs or targeted gene therapy that inhibit phospholamban, inhibit the production of phospholamban, or increase the production of sarcoplasmic/endoplasmic reticulum Ca<sup>2+</sup>-ATPase (SERCA) while decreasing the phospholamban/SERCA ratio (eg, thyroid hormone) might improve both systolic and diastolic dysfunction, working primarily through a diastolic mechanism. Another problem may arise because diastolic heart failure, as defined by Vasan and Levy, will include a mixed bag of pathological entities, such as amyloidosis, ventricular hypertrophy, diffuse myocardial fibrosis, and interstitial myocardial ischemia, each of which may be expected to respond quite differently to therapeutic interventions. These important distinctions will need to be kept in mind in the design of clinical trials of potential new therapeutic approaches to diastolic heart failure. Such trials are a realistic possibility, now that it has been shown that drugs that block the renin-angiotensin system, as well as NO donors or drugs that enhance NO release, improve diastolic function in humans.

In the context of these limitations and caveats, Vasan and Levy have taken an important first step toward the development of clinical trials needed to help us identify appropriate therapy for the patient with diastolic heart failure.

References

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