Understanding Diastolic Heart Failure With Preserved Ejection Fraction
Choosing the Right Model

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Congestive heart failure (HF) is a frequent reason for hospital admission. Fifty percent of HF hospitalizations have normal ejection fraction (EF), referred to as diastolic HF (DHF). In contrast, patients with systolic HF (SHF) have reduced EF. The DHF phenotype describes patients with signs and symptoms of HF, normal EF, normal left ventricular (LV) volume, hypertension with increased relative wall thickness, LV diastolic dysfunction, and predominantly elderly women.1,2

Etiology of DHF
Longstanding hypertension may result in significant myocardial hypertrophy, appearance of a smaller ventricular chamber, increased ventricular stiffness, and delayed relaxation. Increased ventricular stiffness requires increased pressure to maintain normal filling in the presence of normal or reduced chamber volume.3 Although DHF has not been studied as extensively as SHF, limited data obtained from patients hospitalized for DHF suggest that demographic characteristics, comorbidities, and pathology differ from those with SHF. Despite these differences, DHF is similar to SHF with regard to volume overload, reduced exercise capacity, impaired quality of life, and long-term mortality.1

Casual Mechanisms
Impaired Active Relaxation
Diastole consists of active relaxation and passive filling of the ventricle. Diastolic dysfunction can be caused by mechanisms intrinsic to the cardiac muscle cells. These include changes in cardiac homeostasis resulting from abnormalities in calcium extrusion, decreased uptake of cytosolic calcium by the sarcoplasmic reticulum calcium ATPase pump (SERCA), and changes in the phosphorylation state or levels of proteins (eg, phospholamban, calmodulin, and calsequestrin) that modify SERCA.3 Because active relaxation is energy dependent, impaired diastolic filling is the first manifestation of work-induced ischemia, which is reflected by an upward shift of the LV diastolic pressure-volume relationship. Active relaxation requires the removal of cytosolic calcium during diastole (isovolumic relaxation) by SERCA, which is inhibited by phospholamban. In pathological LVH, secondary to hypertension, impaired LV relaxation is associated with decreased cardiac SERCA and increased phospholamban levels. Interestingly, SERCA levels also decrease with age, coincident with impaired diastolic function.3

Increased Passive Stiffness
Diastolic function is also determined by the passive elastic properties of the LV interacting with the active process of relaxation. LV passive compliance decreases with age and myocardial injury. Changes within the myocyte and geometric remodeling of the whole ventricle also contribute to increased passive stiffness. Myocyte hypertrophy can increase passive, as well as active stiffness. Passive stiffness is also increased in patients with focal scar or aneurysm. Infiltrative cardiomyopathies, such as amyloidosis, primarily increase passive myocardial stiffness and impair diastolic function in a similar fashion.

It has been difficult for investigators to find animal models that closely approximate DHF observed in humans. In this issue of Hypertension, Klotz et al4 have used the Dahl salt-sensitive (DS) rat as a surrogate to study pathological changes in cardiac function during development of HF. When fed a high-salt diet at 7 weeks of age, these animals retain salt and water, which leads to overt LV hypertrophy, DHF with increased LV filling pressure, and pulmonary congestion.5 At 12 weeks, Klotz et al6 found normal EF with reduced end-diastolic diastolic volume, a leftward/upward shift in the end-diastolic pressure-volume relationship, and increased end-systolic pressures.

These changes are indicative of passive diastolic dysfunction. Later (16 and 20 weeks), DS rats had additional LV hypertrophy, cardiac dilation, reduced EF, and stroke volume and increases in end-diastolic pressure and wet lung weight. Alterations in kidney mass and function in the DS rats at all stages suggest that renal dysfunction and other extracardiac factors may contribute to changes in cardiac function. The time constant for LV relaxation (τ) was significantly increased in early stages and increased to ~4 ms at later stages. Although the investigators did not consider the changes in τ to be indicative of diastolic dysfunction, a recent study has shown a strong correlation between LV end-diastolic pressure and τ in patients with definitive DHF.6 However, if Klotz et al are correct that HF in the DS rat develops independently of passive diastolic and systolic properties, this would suggest...
that a volume overload state has an important role in the DHF. It remains to be determined whether this model accurately reflects DHF in humans in the setting of long standing hypertension. Although \( \tau \) has been shown to correlate with LV end-diastolic pressure, it is a surrogate measurement of ventricular relaxation and cannot be accurately determined under all of the conditions.\(^6\)

Under ideal conditions, the fall in isovolumic ventricular pressure is approximately exponential, and the \( t_{1/2} \) (the time taken for the pressure to fall to half its initial value) or \( \tau \) can be calculated. Even in normal subjects, the pressure curve differs significantly from exponential, and the asymptote is not 0. This discrepancy may be pronounced in patients with LV hypertrophy. When left atrial pressure is raised, isovolumic relaxation may end prematurely so that the pressure curve does not approximate an exponential before filling.\(^7\)

**Perspective and Future Directions**

Several difficulties need to be overcome for a better understanding of DHF. These include the development of precise standards for the assessment of cardiac function using invasive and noninvasive techniques and validation of an animal model, which mimics DHF in humans, particularly elderly women.

**Precise Standards**

Deficiencies in understanding the pathophysiology, epidemiology, and treatment of DHF have been primarily because of the inability to accurately identify diastolic dysfunction. Despite more than a decade of work in clinical studies and research models, a simple definition of diastolic disease has not emerged. The lack of a sine qua non in individual patients and animal models has been a major impediment to identifying and quantifying disturbances in this important disease process. Delayed relaxation has been suggested to reflect diastolic dysfunction; however, raised atrial pressure overrides echocardiographic relaxation abnormality. Restrictive echocardiographic cardiac filling provides no direct information related to the underlying diastolic disease. It may be because of a specific cause or high filling pressure. It has been assumed that patients who present with DHF have diastolic dysfunction. Zile et al\(^7\) have demonstrated that a majority of DHF patients have \( \geq \)1 abnormal echocardiographic measurement. However, this study involved a selected population of relatively young, predominantly male patients who were scheduled to undergo cardiac catheterization. This is in contrast to the large clinical population of elderly, hypertensive, and predominantly female patients with DHF.\(^1,2\)

Because invasive measures of diastolic function are impractical in most patients, echocardiographic measurements are generally favored in clinical practice. However, diastolic filling of cardiac chambers is complex, and individual echocardiographic parameters have been studied with limited success. Recent advances in ultrasound technology\(^2\) have contributed to the diagnosis of DHF. Implementation of these technologies and new criteria may provide a specific diagnosis of DHF.

**Pathophysiological Mechanisms**

It remains to be determined whether DHF shares many of the same pathologic mechanisms as SHF. Traditionally, treatments for HSF have been used to treat DHS, without much proof of benefit.\(^8\) Specific treatments targeting the pathophysiology of diastolic dysfunction are lacking, and new approaches are required.\(^9\) A critical step is to understand the abnormality in LV function responsible for this clinical syndrome. In relatively uncommon conditions, such as hypertrophic, infiltrative, or primary restrictive cardiomyopathy, patients have HF despite having a normal EF. In these pathologies, hypertrophy, together with myofiber disarray, amyloid infiltration, or extensive fibrosis, impairs both active LV relaxation and increases ventricular stiffness without reducing EF or LV dilatation. The diastolic dysfunction in these abnormalities requires an increased dependence on atrial pressure and atrial contraction to maintain ventricular filling and cardiac output. Experimental studies implicate aldosterone in the genesis of myocardial fibrosis, hypertrophy, and dysfunction, and these processes may be preventable or possibly reversed.\(^10\) Improved outcomes with spironolactone in SHF have been linked to the antifibrotic effects of the drug. In addition, aldosterone has been associated with abnormal vascular function, which appears related to the development of DHF.\(^10\) However, future clinical and experimental studies are required to determine the precise links between pathological effects of aldosterone and LV diastolic dysfunction.

**Animal Models**

Klotz et al\(^7\) have clearly demonstrated that the high-salt DS rat shares the pathophysiology observed in humans with diastolic dysfunction and DHF. Future studies involving various experimental conditions (eg, exercise) will be necessary to determine whether this rat model recapitulates all of the manifestations of DHF. It may be necessary to consider a larger animal, because the DS rat, like other rodent models, has a fast heart rate (300 to 350 bpm), which often precludes obtaining reliable isovolumic relaxation times and mitral valve velocities, especially when noninvasive techniques (eg, echocardiography) are used to determine cardiac function. As with patients, it is often necessary to perform serial monitoring in animal models to determine the efficacy of a particular therapy, which makes use of cardiac catheterization impractical. Gender is also likely an important consideration when choosing an animal model. Investigators have almost exclusively used male animal models for the study of diastolic dysfunction and DHF. Male animal models may not accurately depict the pathophysiological mechanisms responsible for the gender differences observed in women who present with DHF. Difficulties in defining DHF animal models and/or humans indicate that agreement in this field remains to be achieved.

**References**


6. Aurigemma GP, Zile MR, Gaasch WH. Lack of relationship between Doppler indices of diastolic function and left ventricular pressure trac-


