CARDIOLOGY Rounds®

As presented in the rounds of the Division of Cardiology, St. Michael's Hospital, University of Toronto

Diastolic heart failure

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Congestive heart failure (HF) may be considered a condition in which cardiac output is not adequate to meet the metabolic needs of the body either at rest, or during exercise. It is usually accompanied by an increase in cardiac filling pressure and/or circulating volume. Implicit in this physiological definition is that HF can be caused by either an abnormality in systolic function resulting from a defect in expulsion of the blood (systolic HF), or in diastolic function resulting from a defect in ventricular filling (diastolic HF).

Systolic HF, which is usually caused by an impaired inotropic state, is more familiar to clinicians. Less familiar, but perhaps just as important, is diastolic HF, in which the ability of the ventricle(s) to accept blood is impaired. This problem is not uncommon and in some series, reported to account for up to 50% of patients presenting with HF.[1-5]

Diastolic function

Diastole can be divided into four phases: isovolumic relaxation, a rapid-filling phase, diastasis, and atrial contraction (Figure 1). Isovolumic relaxation is the interval between aortic valve closure and mitral valve opening, during which ventricular pressure rapidly declines without a significant change in volume. This process is energy-dependent and may be very susceptible to cellular ischemia. Most ventricular filling then occurs during the subsequent rapid-filling phase that is also partially energy-dependent. As active relaxation ends and rapid filling continues, further increases in ventricular size are limited by passive elements affecting the stiffness of the myocardium. This third or slow-filling phase is primarily dependent upon the passive properties that are not constant, but may increase as left ventricular (LV) volume increases. The last phase of diastole, atrial contraction, is normally responsible for 15%-25% of the ventricular diastolic volume, but in certain disease states, it can be as high as 40%. The atrial contribution to ventricular filling will be greater in patients with impaired early relaxation. Therefore, the ventricular diastolic pressure/volume relationship may be abnormal because of changes in active relaxation, passive compliance properties, or both (Figure 2, Table 1). Whatever the specific abnormality, the result is impaired ventricular filling and inappropriately elevated left atrial and pulmonary venous pressures.

Evaluation of diastolic dysfunction

Several non-invasive techniques have been utilized to assess diastolic function. The most commonly used methods are two dimensional- and Doppler-echocardiography, Doppler-tissue imaging, radionuclide ventriculography, magnetic resonance (MR) myocardial tagging and MR imaging.

Echocardiography

Doppler echocardiography, a noninvasive and simple procedure, may provide insight into LV diastolic dysfunction. The most commonly used Doppler parameters of diastolic dysfunction are derived from LV inflow and pulmonary venous inflow. Doppler echocardiography is capable of measuring the isovolumic relaxation time that is prolonged during abnormal relaxation. The traditional measurement of the ratio between the peak early-filling wave (E wave) and the atrial-filling wave (A wave) is a useful screening tool for abnormal LV relaxation. If the E-wave to A-wave ratio is well below that of the normal established range for the patient's age, abnormal relaxation is likely. However, as left atrial pressure rises to compensate for abnormal LV stiffness, there is a pseudonormalization of the Doppler pattern with a return of the normal ratio. Thus, patients with abnormal relaxation can have normal E/A ratios. Pseudonormalization can be detected by measuring the pulmonary venous flow. In addition, the rate of decline of the E wave (E wave deceleration time) has proven to be a useful parameter for assessing diastolic function. No one individual measurement can

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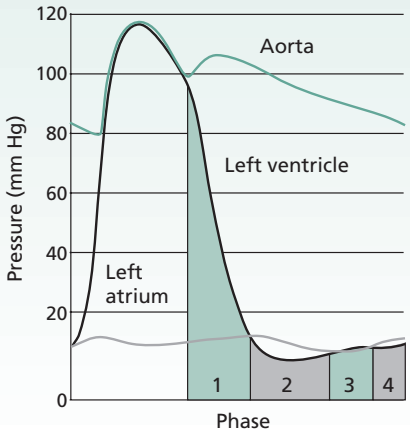
Figure 1: Four phases of diastole: (1) isovolumic relaxation (2) rapid filling, (3) diastasis, (4) atrial contraction



fully characterize LV diastolic function and no measurement is free from confounding factors. Most of the parameters are dependent on load, heart rate, and age. Several newer echocardiographic techniques hold promise for evaluating diastolic function, including acoustic quantification, color kinesis, and Doppler tissue imaging.[6-8]

Radionuclide angiography

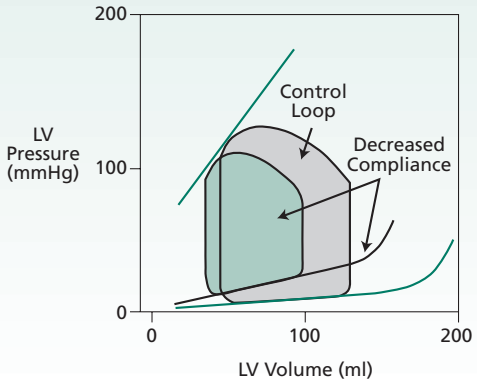
Radionuclide angiography is a method originally designed for assessing LV ejection fraction. LV filling or diastolic function can also be assessed with this procedure by analyzing diastolic time-activity curves. Radionuclide angiography measures peak filling rate, time to peak filling rate, atrial filling fraction (ie, the amount of filling with atrial contraction), and first third of fractional filling (ie, how much the LV cavity fills during the first third of diastole).

Although many investigators have tried to document reliable indicators of abnormal diastolic filling on radionuclide angiographic studies, none have been found that identify diastolic dysfunction in an individual patient. While radionuclide angiography is a powerful tool for excluding LV systolic dysfunction, its use for diagnosing diastolic dysfunction is somewhat limited.[9-10]

Magnetic resonance imaging

The technique of magnetic resonance imaging (MRI) has been shown to be of considerable use in the morphologic assessment of the heart, but functional assessment can also be obtained. Nevertheless, their clinical relevance remains to be demonstrated. Additional information may be gained from newer techniques such as MR myocardial tagging that allows the labeling of specific myocardial regions. From these tags the rotational and translational motion of the LV can be determined, which is characterized by a systolic wringing motion followed by a rapid diastolic untwisting. This untwisting motion is directly related to relaxation and may be used as a measure of the rate and completeness of relaxation as well as an estimate of early diastolic filling.[11]

Figure 2: Abnormal diastolic pressure/volume relationship



Definition of diastolic heart failure

Diastolic HF is a clinical syndrome characterized by the symptoms and signs of heart failure and accompanied by a preserved ejection fraction (EF). As a result, the condition is sometimes referred to as "heart failure with preserved systolic function." In many instances, the syndrome is a result of abnormal diastolic function. Diastolic HF occurs when the ventricular chamber is unable to accept an adequate volume of blood during diastole at normal diastolic pressures and at volumes sufficient to maintain an appropriate stroke volume. These abnormalities are caused by a decrease in ventricular relaxation and/or an increase in ventricular stiffness. Diastolic HF can produce symptoms that occur at rest or with ordinary or less than ordinary physical activity.

Diagnosis of diastolic heart failure

The diagnosis of diastolic HF cannot be made reliably at the bedside. Differentiation between systolic and diastolic heart failure cannot be made on the basis of history, physical examination, or chest radiograph alone, because markers

Table 1. Factors increasing diastolic pressure

Impaired ventricular relaxation

- Hypertrophy
- Myocardial ischemia
- Hypertension
- Collagen deposition and fibrosis
- Regional asynchrony
- Increased preload, after load
- Abnormal calcium flux
- Tachycardia

Decreased ventricular compliance

- Hypertrophy
- Hypertension
- Collagen deposition and fibrosis
- Cellular disarray
- Myocardial infiltration
- Pericardial constriction or restriction
- Right ventricle-left ventricle interactions

from these examinations occur with the same relative frequency in both systolic and diastolic HF.[12] It is for this reason that diagnostic criteria based on measurements of systolic and diastolic function have been developed.

The Working Group for the European Society of Cardiology proposed that diagnosis of primary diastolic HF requires 3 obligatory conditions to be simultaneously satisfied:[13]

- presence of signs or symptoms of congestive heart failure
- presence of normal or only mildly abnormal left ventricular systolic function
- evidence of abnormal LV relaxation, filling, diastolic distensibility, or diastolic stiffness.

However, these diagnostic criteria may be problematic for 3 reasons.

- The first obligatory condition requires the presence of signs "or" symptoms of HF; however, it is well-recognized that the mere presence of breathlessness and fatigue is not specific for the presence of HF. It would be more prudent to include specific diagnostic criteria such as the Framingham criteria.
- The second potential problem revolves around the term "systolic function." The working group defined systolic function as being normal when LV ejection fraction is ≥45%. Because EF is not a direct measure of contractility and is load-dependent, a single EF measurement is not entirely meaningful.
- The third difficulty is the requirement that a measurable abnormality in diastolic function be present. Similar to measurements of systolic function, measurements of ventricular relaxation, filling, and compliance are load-dependent. Therefore, the poor specificity, sensitivity, predictive accuracy, as well as the difficult practical aspects of measuring diastolic function, limit the application of this requirement in the clinical setting.

Definite, probable, and possible diastolic HF

Vasan and Levy proposed an extension and refinement of these diagnostic criteria by suggesting that they be divided into definite, probable, and possible diastolic HF.[14] *Definite* diastolic heart failure requires definitive evidence of HF including objective evidence of normal systolic function with EF ≥50% within 72 hours of the HF event and objective evidence of diastolic dysfunction on cardiac catheterization. If objective evidence of diastolic dysfunction is lacking, but the first 2 criteria are present, this fulfills the criteria for *probable* diastolic heart failure. If the first criterion is present and EF is ≥50%, but is not assessed within 72 hours of the HF event, this fulfills the criteria for a *possible* diastolic HF. A possible diastolic HF can be upgraded to a probable diastolic HF if one of several additional criteria is present.

The clinical application of these guidelines is limited both because they are complex and because they are empiric in nature. However, subsequent studies suggested methods to simplify the diagnostic criteria and provided objective data to validate them.

Studies by Gandi et al,[15] addressed the requirement of an EF ≥50% present within 72 hours of the HF event. This study demonstrated that in patients presenting to the emergency room with acute pulmonary edema and systolic hypertension (SBP >160 mm Hg), there were no significant differences between EF measured echocardiographically at the time of presentation (when patients had active CHF) and hours after the event (when patients were clinically stable and no longer in symptomatic HF). Therefore, the author concluded that the EF does not need to be measured coincident with the HF event. Measurement of EF within 72 hours is sufficient to meet diagnostic criteria for diastolic HF. The one possible exception to the use of this approach may be the presence of acute ischemia. However, ≥50% of the patients studied by Gandi et al had segmental wall-motion abnormalities on echocardiogram consistent with ischemic heart diseases, 2 had transient segmental wall-motion abnormalities that normalized with resolution of the pulmonary edema, and none had a significant change in EF after 72 hours. It is possible that patients with pulmonary edema caused by acute ischemia are unable to generate high systolic pressure and/or have resolution of the ischemia before echocardiographic assessment. Although it is unknown how often this occurs, it is likely to be infrequent. Thus, based on this study, to meet the diagnostic criteria for diastolic HF, EF must be ≥50% within 72 hours of the HF event. It remains to be determined whether the EF measurement can be delayed beyond 72 hours.

Zile et al[16] examined the necessity of obtaining objective evidence of diastolic dysfunction to make a diagnosis of diastolic HF. In this study, patients with a history of HF who fulfilled the Framingham criteria and had an EF ≥50% underwent diagnostic left heart catheterization and simultaneous Doppler echocardiography. None of these patients had evidence of coronary heart disease. In this group, 92% had at least 1 pressure-derived abnormality in diastolic function (including an LV end-diastolic pressure ≥16 mm Hg), 94% had at least 1 Doppler echocardiography-derived abnormality in diastolic function, and 100% had at least 1 pressure or Doppler abnormality in diastolic function. Therefore, objective measurements of LV diastolic function serve to confirm rather than establish the diagnosis of diastolic HF.

These authors concluded that the diagnosis of diastolic HF could be made without measurement of diastolic function if 2 criteria are present including symptoms and signs of heart failure (Framingham criteria) and an LV EF >50%.

Prevalence

Earlier studies suggest that diastolic dysfunction is present in one-third of patients presenting with HF and a normal EF.[17,18] Recent studies demonstrate the prevalence of diastolic HF to be between 25%-50%.[1-5] However, these studies also underscore the fact that both the prevalence and prognosis of diastolic HF may depend on age, gender, methods used to diagnose diastolic HF, the value of EF used as a cutoff value, as well as the underlying clinical disease process that caused the diastolic HF.[1-5] Whereas these determinants are largely interdependent, the most important determinant is likely to be age. Studies examining the prevalence of diastolic HF in hospitalized patients or in those undergoing outpatient diagnostic screening and prospective community-based studies have shown that in patients >70 years old, the prevalence of diastolic HF approaches 50%.[1-5,19]

Mortality and morbidity

Morbidity from diastolic HF is quite high and necessitates frequent outpatient visits, hospital admissions, as well as the expenditure of significant healthcare resources. The 1-year readmission rate approaches 50% in patients with diastolic HF. This morbidity rate is nearly identical to that for patients with systolic HF.[1-5]

The prognosis for patients with diastolic HF, although less ominous than that for patients with systolic HF, does exceed that for age-matched control patients. The annual mortality rate for patients with diastolic HF is approximately 5% to 8%. By comparison, the annual mortality rate for patients with systolic HF is approximately 10% to 15%, whereas for age-matched controls without HF, it is approximately 1%. In patients with diastolic HF, the prognosis is also affected by the etiologies of the disease. Thus, when patients with coronary artery disease are excluded, the annual mortality rate for isolated diastolic HF is approximately 2% to 3%.[20] The other determinants of mortality include age, EF cutoff, and study design. Like prevalence, these are interdependent, with the most important determinant being age (Table 2). In fact, an increasing amount of data suggests that in patients >70 years old, the mortality rates for systolic and diastolic HF are nearly equivalent.[1-5]

Table 2: Diastolic heart failure: Effects of age on prevalence and prognosis

	Age, years		
	<50 yrs old	50-70 yrs old	>70 yrs old
Prevalence	15%	33%	50%
Mortality	15%	33%	50%
Morbidity	25%	50%	50%

Mortality = 5-year mortality rate
Morbidity = 1-year rate of hospital admission for heart failure.[19]

Management

Treatment of diastolic HF remains empiric. To date, there have been no randomized, double-blind, placebo-controlled, outcome trials performed in patients with diastolic HF. Consequently, the guidelines for the management of diastolic HF are based on clinical investigations in relatively small groups of patients, clinical experience, and concepts based on pathophysiological mechanisms. Therefore, an ideal treatment strategy for patients with diastolic dysfunction has not been devised and medical therapy of diastolic dysfunction is often empirical and lacks clear-cut pathophysiological concepts. Nevertheless, four treatment approaches have been proposed:

Reduction of central blood volume: diuretics

Diuretics are effective in reducing pulmonary congestion in patients with diastolic dysfunction by shifting the pressure–volume relation downwards. However, their positive effect on LV chamber stiffness is indirect and caused particularly by a reduction in systemic blood volume and the lowering of right atrial blood volume with a decrease in pericardial constraint. However, diuretics must be used judiciously because the volume sensitivity of patients with diastolic dysfunction bears the risk that excessive diuresis can result in a sudden drop of stroke volume.[21]

Maintenance of atrial contraction and control of heart rate (beta-blockers, antiarrhythmics)

Beta-blockers have been used for many years to control blood pressure and thus, to reduce myocardial hypertrophy. The positive effect on diastolic dysfunction that has been investigated in the last 2 decades is mainly due to heart-rate slowing and not to primary improvements in isovolumic relaxation. However, the antihypertensive action of beta-blockers with regression of LV hypertrophy also seems to be important for improvement of diastolic filling. Despite the lack of a direct effect of beta-blockers on myocardial relaxation and the passive elastic properties of the myocardium,[22] these drugs can be used in diastolic failure, especially in the presence of hypertension or coronary artery disease and atrial or ventricular arrhythmias.

Improvement of LV relaxation: calcium channel blockers

Calcium channel blockers (CCBs) have been shown to improve myocardial relaxation and enhance diastolic filling. These drugs may be effectively matched to the pathophysiology of relaxation disturbances because of their ability to decrease cytoplasmic calcium concentrations and reduce afterload. However, an increase in E-velocity after calcium-blockade was recently described that was not related to impairment in diastolic function, but to an increase in diastolic filling pressure. CCBs with negative dromotropic action (eg, verapamil or diltiazem) may also improve diastolic filling by reducing heart rate.[23-28] In patients with hypertension, CCBs, as well as beta-blockers, have been shown to reduce muscle mass; this can result in an improvement in the passive elastic properties of the myocardium. CCBs of the verapamil type are first-line drugs in patients with hypertrophic cardiomyopathy because of their beneficial effects on relaxation and diastolic filling, which are often severely abnormal in these patients.[25,26]

Regression of LV hypertrophy (decrease in wall thickness and removal of excess collagen by ACE inhibitors and angiotensin receptor blockers)

Not only do angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) lower blood pressure, they also may elicit a direct effect on the heart via the local renin-angiotensin system. These effects are essential for the regression of LV hypertrophy and improvement in the elastic properties of the myocardium.[29-31] Several trials have documented that LV

Table 3. Clinical trials of diastolic heart failure.[33,34]

Trial	Comparison	Follow-up	Diagnostic criteria for DHF	Other important inclusion/ exclusion criteria	Main outcomes
PEP-CHF	Placebo Perindopril	1,000 Minimum 18 months	3 of 9 clinical and 2 of 4 echocardiographic criteria	Age >70 yrs Diuretics Hospital admission in last 3 months	Death of HF-related hospitalization
CHARM	Placebo Candesartan	2,500 Minimum 24 months	EF >40%	None	Death or hospitalization for cardiovascular disease
I-PRESERVE	Placebo Irbesartan	3,600 Approx. 48 months	EF ≥45%	Clinical diagnosis of HF	Death and hospitalization for cardiovascular disease
SENIOR	Placebo Nebivolol	2,000 (%DHF uncertain)	EF >35% and cardiac abnormality	Age >70 years Hospital admission with HF in last 12 months	
Hong Kong	Placebo Ramipril Irbesartan	450 Minimum 12 months	Doppler criteria	Diuretics	Death or hospitalization for HF Quality of life 6-minute walk test
SWEDIC	Placebo Carvedilol	140 9 months	Doppler criteria	AF excluded	Regression of diastolic dysfunction
Wake Forest	Losartan Hydrochloro-thiazide	6 months	EF>40% Hypertension		Exercise tolerance Vo2 max
MCC-135	Placebo MCC-135	6 month	EF >40% CHF		Exercise tolerance Remodeling

AF = atrial fibrillation; DHF = diastolic heart failure; HF = heart failure; I-PRESERVE = Irbesartan in Heart Failure with Preserved Systolic Function; PEP-CHF = Perindopril in Elderly People with Chronic Heart Failure; SENIORS = Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalizations in Seniors with Heart Failure; SWEDIC = Swedish Study in Patients with Diastolic Dysfunction Treated with Carvedilol.

hypertrophy is more effectively reduced by ACE inhibitors than by other antihypertensive drugs, suggesting an effect on myocardial structure beyond that provided by reduction of pressure overload. Recent data suggest that ARBs have similar effects on LV mass and structure as the ACE inhibitors.[32]

Digoxin is not recommended, especially for diastolic HF since it can be deleterious in certain situations (hypertrophic cardiomyopathy). In patients with diastolic HF and atrial fibrillation, digoxin may be needed to control heart rate.

Ongoing trials

Randomized, double-blind, placebo-controlled, multicentre trials examining the effect of therapy on clinical outcomes have been slow to develop. Impediments to the development of these kinds of studies include a lack of recognition of the importance of diastolic HF, an inability to define a homogeneous study population, and a lack of agreement on the definition and diagnostic criteria for diastolic HF. Diastolic HF is now recognized as an important problem. Guidelines for its diagnosis have been developed and industry has supported randomized, double-blind, placebo-controlled, multicentre trials. Several trials are now under way (Table 3).

Three of these trials target neurohormonal activation in the renin-angiotensin-aldosterone system by inhibiting the angiotensin II receptor (Candesartan cilexetil in Heart failure Assessment of Reduction in Mortality and morbidity [CHARM], I-PRESERVE, and Wake Forest). The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial enrolled patients with echocardiographic evidence of diastolic dysfunction and randomized them to placebo and perindopril. The MCC-135 study targets intracellular calcium homeostasis using an agent that is proposed to improve sarcoplasmic reticulum calcium reuptake.

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