CARDIOLOGY Rounds®

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Diastolic Heart Failure: An Update for 2007

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Heart failure (HF) is currently the most common primary diagnosis in hospitalized patients in the United States and an increasing cause of mortality and morbidity in the North American population. Traditionally, HF has been described as a clinical syndrome associated with impaired myocardial contractility and left ventricular (LV) cavity dilation. Many studies, however, have shown that the clinical syndrome of HF is increasingly associated with a normal or near normal LV ejection fraction (EF). This syndrome, termed "HF with preserved LVEF", or "diastolic heart failure (DHF)," is thought to be due to abnormalities in the diastolic properties of the LV, although the precise mechanisms are still debated. This issue of *Cardiology Rounds* reviews the pathophysiology of DHF, its clinical presentation and assessment, and provides recent data on the natural history and prognosis of patients with DHF, addressing some of the current clinical controversies surrounding this condition.

Pathophysiology of DHF

Two processes determine LV diastolic function: the first is the passive elastic properties of the myocardial fibers and the second is the active adenosine triphosphate (ATP)-dependent process of LV relaxation. Under normal circumstances, in diastole, elastic recoil of the left ventricle creates a suction-like effect, which increases the left atrium-LV gradient and facilitates early rapid filling of the left ventricle. Later in diastole, the cardiac myocytes are relaxed and easily distensible, allowing for further filling at a relatively low pressure. Atrial contraction at the end of diastole provides an additional 20% to 30% of LV filling volume in normal hearts, although this usually occurs at a relatively low filling pressure.

In patients with diastolic dysfunction (DD), the cardiac myocyte is hypertrophied and the extracellular matrix exhibits a relatively larger proportion of collagen. This results in increased LV wall thickness, increased wall thickness to chamber size ratio, and increased mass to volume ratio within the left ventricle.[1,2] The overall pattern is more of a concentric hypertrophied model, as opposed to the syndrome of systolic heart failure (SHF) that more typically exhibits eccentric LV remodeling, with increased LV dimensions and volumes.

The patient with DHF often has prolonged myocyte relaxation times, an impaired rate and total extent of LV filling and, initially, a shift in filling, from the early phase in diastole to the late phase in diastole.[1,2] Overall, there is a reduction in LV distensibility and a resultant increase in LV pressure for any given LV volume. Increased wall stiffness also impairs LV relaxation during exercise and the shift in filling to the late phase of diastole causes tachycardia – which shortens the diastolic filling time – to be poorly tolerated (Figure 1). Finally, while the focus has been primarily on abnormalities in diastole, a significant body of work now suggests that systolic function may not be entirely normal in patients with DHF, with global LV function preserved by increased radial function, which compensates for reduced longitudinal function.[3-5]

Etiology of DHF

DHF is a disease entity related to a thickened and stiffened left ventricle. The most common cause of DHF is chronic systemic hypertension leading to LV hypertrophy.[1,2] Other causes of thickened or stiff hearts include aortic stenosis, hypertrophic cardiomyopathy, chronic coronary ischemia, renal insufficiency, or restrictive cardiomyopathies. In the restrictive cardiomyopathy

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Figure 1: Predisposing conditions and hemodynamic determinants of DHF

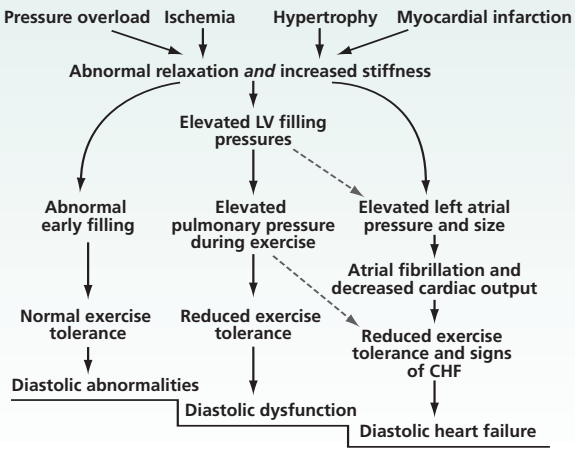


Table 1: Risk factors and conditions associated with DHF

Common

- Aging
- Female gender
- Obesity
- Hypertension
- Diabetes mellitus
- Coronary artery disease
- Chronic kidney disease
- Aortic stenosis

Uncommon

- Myocardial disorders
  - Amyloidosis
  - Sarcoidosis
  - Fatty infiltration
  - Non-infiltrative diseases
  - Idiopathic cardiomyopathy
  - Hypertrophic cardiomyopathy
  - Hypereosinophilic syndrome
  - Hemochromatosis
  - Glycogen storage disease
- Pericardial disorders
  - Constrictive pericarditis
  - Effusive-constrictive pericarditis
  - Pericardial effusion

category, etiologies for infiltrative disease such as sarcoidosis, amyloidosis, hemochromatosis, or glycogen storage disease should be considered (Table 1).

Clinical characteristics of DHF patients

Classically, DHF is a syndrome of HF that affects the elderly. In one particular review, the incidence of DHF was estimated at 15%, 33%, and 50% in patients aged <50 years, 50 to 70 years, and >70 years, respectively.[6] Patients with DHF are also more likely to be women than men, as has been shown in a number of population-based studies.[7] In addition, patients with DHF are more likely to have a history of hypertension, diabetes, chronic kidney disease, and obesity, and more likely to have related comorbidities (eg, atrial fibrillation). Despite the large amount of data on the underlying risk factors and clinical characteristics of patients presenting with DHF, it remains impossible to distinguish DHF from SHF based on clinical assessment alone.

Assessment of LV diastolic function

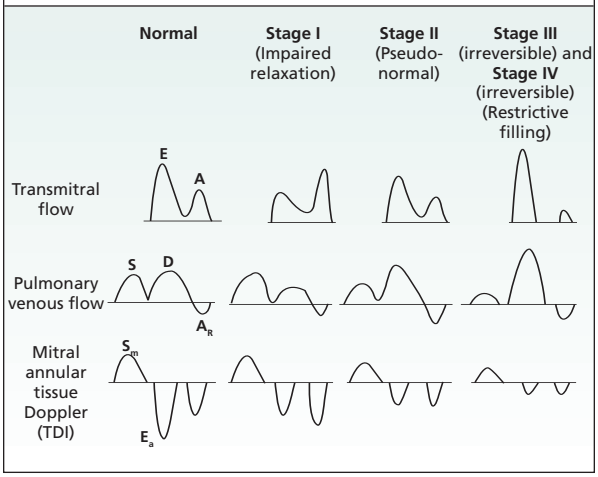
Echocardiography

While other imaging modalities, such as radionuclide angiography or magnetic resonance imaging, can be used to measure diastolic parameters, echocardiography remains the most commonly utilized diagnostic imaging modality to detect DD. There are many echocardiographic parameters available to assess diastolic function.[8,9] Transmitral Doppler tracings remain the basis of the initial physiologic evaluation of diastolic function. Pulmonary venous flow variables and mitral annular tissue Doppler imaging (TDI) provide important incremental and supportive information to aid in grading DD (Figure 2). Normal inflow velocities across the mitral valve are greatest early in diastole and are reflected by tall E waves. The A wave represents LV filling by atrial contraction and, normally, has a smaller role in overall LV filling, resulting in a ratio of E waves to A waves (E/A ratio) >1.

- In mild DD (*Stage I*-impaired relaxation), the E/A ratio is <1 (E/A reversal), with tall A waves resulting from a significant contribution of atrial contraction to LV filling. Deceleration time is prolonged (>250 ms) due to the relaxation abnormality. At this stage, pulmonary venous flow occurs predominantly in systole, while early diastolic myocardial velocities by TDI (E_a) are mildly diminished.
- *Stage II* DD is characterized by reduced LV compliance, resulting in increased left atrial pressure. The transmitral inflow pattern appears normal, but E/A reversal can be unmasked with the Valsalva maneuver that reduces LV preload (pseudonormal). At this stage, pulmonary venous flow occurs predominantly in diastole (D), and systolic flow (S) is blunted, while early E_a are moderately diminished.
- With progression to *Stage III*, there is a severe reduction in LV compliance with further increases in left atrial pressure, resulting in a very high E wave, a low A wave (E/A ratio >2), and a short deceleration time (<150 ms; restrictive filling). Systolic blunting of pulmonary venous flow is marked, and tissue Doppler velocities are severely reduced.[8,9]
- If this pattern remains fixed with the Valsalva maneuver, DD is categorized as *Stage IV* (Figure 2).

Various echocardiographic methods for estimating LV filling pressures have been developed. As LV filling pressures rise, the mitral E wave increases from the impaired relaxation pattern to pseudonormal and, finally, to a restrictive pattern. Concomitantly, the E_a at the mitral annulus progressively diminishes. Thus, the ratio of mitral E to TDI E_a (E/E_a ratio) increases as LV filling pressures rise

Figure 2: Doppler echocardiographic grading of diastolic dysfunction



(E=mitral E wave, A=mitral A wave, S=systolic pulmonary venous flow, D=diastolic pulmonary venous flow, A_R=pulmonary venous atrial reversal, S_m=Tissue Doppler systolic wave, E_a=Tissue Doppler early diastolic wave

and the severity of DD worsens. Several studies have demonstrated that the E/E_a ratio correlates with left atrial (LA) pressures by pulmonary artery catheter measurements.[10,11] An E/E_a ratio >15 is consistent with an elevated LA pressure, whereas an E/E_a ratio <8 is sensitive for normal LA pressures. While the utility of the E/E_a ratio to detect elevated LA pressures has been demonstrated in patients with DHF, sensitivity and specificity tend to be higher in the setting of SHF.[12]

Similar to studies in SHF, the severity of DD by echo-Doppler provides prognostic information in DHF. In the echocardiographic substudy of CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) – CHARM-Preserved – moderate and severe DD (found in less than one-half of the patients) were important predictors of adverse outcome.[13] The results demonstrated the prognostic significance and potential importance of assessing the severity of DD in patients with DHF.

In summary, while the need for the assessment of DD in the diagnosis of DHF has been questioned, echocardiography continues to have an important role in the evaluation of patients with DHF. It allows for the exclusion of reduced LVEF and significant valvular abnormalities, provides a noninvasive estimation of right ventricular systolic pressure, and helps elucidate the underlying cause of DD. In addition, echocardiography aids in the diagnosis of DHF and provides important prognostic information on the severity of DD.

Biomarkers

The cardiac natriuretic peptides, particularly B-type natriuretic peptide (BNP), have become useful biomarkers in HF. Several studies have demonstrated that the BNP level is more accurate than clinical or other laboratory findings in identifying HF as the cause of dyspnea. Thus, a potentially useful application of BNP would be the diagnosis of HF in patients with preserved systolic function. It has been demonstrated that BNP levels are elevated in patients with HF or DD based on Doppler filling characteristics.[14] However, the classification of diastolic function using BNP in comparison to echo-Doppler parameters has been debated.[15] A community-based study by Redfield et al found that the optimal sensitivity and specificity of BNP to detect moderate-to-severe diastolic dysfunction was only 75% and 69%, respectively.[16]

The utility of BNP measurement in the treatment of DHF is less well known. The ongoing European study, BATTLE-SCARRED (BNP Assisted TreaTment to LEssen Serial CARdiac REadmissions and Death), may provide insights into using BNP levels to treat HF across a broad spectrum of LVEF. Finally, although BNP levels in DHF tend to be lower than those found in patients with SHF,[17] BNP levels by themselves cannot be used to differentiate between the two entities. Therefore, for now, the BNP level must be considered as an adjunct to clinical evaluation and echocardiography in the setting of DHF.

Diastolic dysfunction versus diastolic heart failure

DD is primarily an *echocardiographic* diagnosis, not a clinical one. The clinical significance of DD has recently been studied. Redfield and colleagues performed a population-based study using echocardiography to assess diastolic function in 2,042 patients aged >45 years.[18] In their study, the prevalence of DD was 28% in those without symptomatic HF. DD on echocardiography was found to be an independent predictor of mortality, even after accounting for other clinical variables. These results demonstrate the potential clinical significance of DD, even in the absence of symptomatic HF.

In contrast, DHF is a *clinical* syndrome, defined by the American College of Cardiology/American Heart Association (ACC/AHA) as the "presence of clinical HF in the presence of normal LVEF and no significant valvular abnormalities." It is important to note that the ACC/AHA criteria for DHF do *not* require an echocardiographic diagnosis of DD. It has been argued that, since the echocardiographic characteristics of DD are potentially difficult to interpret and user-dependent, the simple syndrome of HF with preserved LVEF should be sufficient to establish the diagnosis of DHF.[19]

Natural history and outcomes of patients with DHF

It was originally thought that patients with DHF had a relatively benign prognosis compared to those with SHF; ie, the estimated annual mortality in patients with DHF was between 5%-8%. In later studies of patients admitted with HF, the mortality for DHF was higher, anywhere from 13% to 21% annually, but still less than the annual mortality for patients with SHF.[20] In an analysis of the Digitalis

Figure 3: Kaplan-Meier survival curves for patients with DHF (black) and SHF (green) over the year after first hospital admission for HF[21]

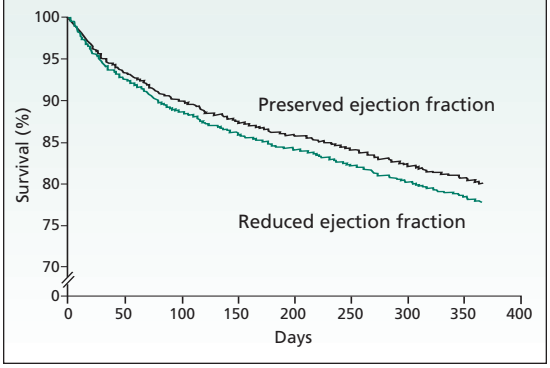
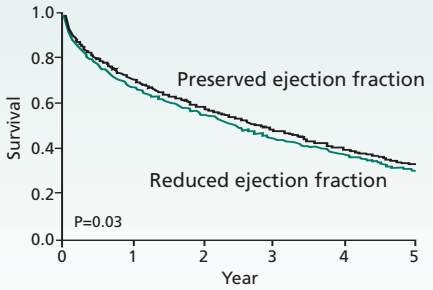


Figure 4: Kaplan-Meier survival curves for patients with DHF (black) and SHF (green) over 5 years[22]



No. at risk						
Reduced ejection fraction	2424	1637	1350	1049	813	604
Preserved ejection fraction	2166	1537	1270	1001	758	574

Investigative Group (DIG) trial, for example, the mortality of patients with SHF was 35% at 1 year, versus patients with DHF whose mortality was 23%. More recently, analyses of the Danish Investigation of Arrhythmia and Mortality on Dofetilide – Congestive Heart Failure (DIAMOND-CHF) study, the Management to Improve Survival in Congestive Heart Failure (MISCHF) study, and the Euro Heart Survey, all found lower mortality rates for patients with DHF compared with those with SHF. The overall mortality for DHF was estimated to be between 10% and 17%. Many of these studies, however, had no standard definitions for HF, used ambulatory populations, and patients were not assessed during their first admission for HF; therefore, the results may be representative of patients at different timepoints in their disease state.

More recently, 2 large, population-based studies were published that cast the previous ideas on the natural history of DHF into question. The first, by Bhatia and colleagues, was a study carried out in hospitals across Ontario, Canada.[21] This study examined patients admitted to hospital with a first episode of HF. Of the 2,802 patients in the study, one-third had DHF and two-thirds were women. The patients with DHF were significantly older, with a mean age of 75 years versus 72 years for patients with SHF. Patients admitted with DHF were found to have similar 30-day and 1-year mortality as those with SHF (5.3% versus 7.1%, p=0.08 at 30 days and 22.2% versus 25.5%, p=0.07 at 1 year; Figure 3). On multivariate analysis, the hazard ratio for DHF versus SHF was 1.13 (p=0.18). Thus, for both unadjusted and adjusted mortality, there was no significant difference between SHF and DHF.

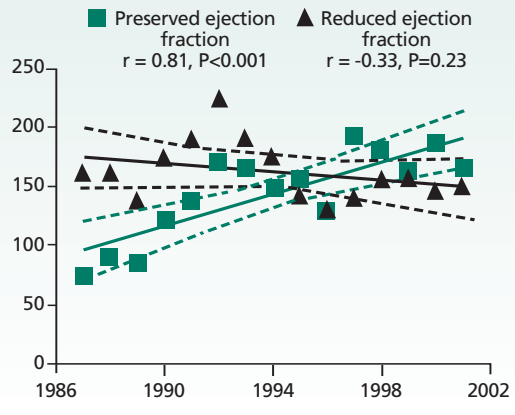
The second population-based study of DHF was carried out at the Mayo Clinic in Rochester, Minnesota, by Owan and colleagues.[22] Over a period of 15 years, they examined 6,076 patients admitted to hospital with HF for the first time. They found that the incidence of DHF rose over that time and the mortality rate in DHF patients was only slightly lower than the rate in SHF patients (Figure 4). More interestingly, over the 15-year study period, the mortality rate in patients with SHF actually *decreased*, whereas the mortality for those with DHF remained unchanged (Figure 5). This finding likely relates to advances in evidence-based medical therapies for SHF during that period and underscores the lack of proven medical therapies for DHF.

Therapy for DHF

Although therapies have proven effective in reducing mortality from SHF, mortality from HF with preserved LVEF remains unchanged. Thus far, no therapies have been proven to correct the abnormalities seen in DHF, halt the progression, or reduce mortality.

Currently, the AHA/ACC guidelines for treating DHF suggest 4 major tenets of therapy. They recommend:

Figure 5: Trends in the number of admissions for DHF (green) compared to SHF (black). Dashed lines indicate 95% confidence intervals[22]



- controlling symptoms with diuretics
- aggressively managing concomitant hypertension
- treating ischemic symptoms
- appropriately and aggressively managing arrhythmias, particularly atrial fibrillation, which is poorly tolerated in the presence of DD and DHF.

Since the last review of DHF in *Cardiology Rounds* (February 2003), a number of clinical trials assessing medical therapies for DHF have been completed. The CHARM program consisted of parallel, randomized, double-blind, controlled, clinical trials of 7,601 patients comparing candesartan (target dose, 32 mg once daily) with placebo in 3 distinct HF populations.[23] The CHARM-Preserved study arm enrolled 3,023 patients with HF and LVEF >45%.[24] There was no difference in cardiovascular death between treatment groups, but fewer patients in the candesartan group than in the placebo group were admitted to hospital for HF. It has been argued, however, that the patient population in CHARM-Preserved may not be representative of the typical DHF population, with younger (mean age 67 years), predominantly male patients.

The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study randomized HF patients (aged ≥70 years), whose echocardiograms suggested diastolic dysfunction and excluded substantial LV systolic dysfunction or valvular disease, to placebo or perindopril, 4 mg/day.[25] The primary endpoint was a composite of all-cause mortality and unplanned HF-related hospitalization, with a minimum follow-up of 1 year. Unfortunately, enrollment and event rates were lower than anticipated, drastically reducing the power of the study. Thus, despite an enrollment goal of 850 patients, only 207 of the randomized patients reached the minimum follow-up. By 1 year, there was no difference in the primary outcome between treatment groups; however, hospitalizations for HF were significantly reduced (HR 0.628; 95% CI, 0.408-0.966; p = 0.033), and functional class and 6-min walk distance had improved in those assigned to perindopril.

The MCC-135-GO1 study[26] is a phase II, randomized, double-blind trial with a parallel group design comparing 3 oral dose regimens of MCC-135 (a modulator of calcium homeostasis at the level of the sarcoplasmic reticulum and cellular membrane) to placebo in 511 patients with mild-to-moderate heart failure, a subset of whom had an EF >40%. Patient recruitment is complete, and follow-up is ongoing.

The ongoing Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) study[27] plans to randomize 4,100 subjects with DHF (aged ≥60 years, EF ≥45%) to 300 mg irbesartan or placebo, with a primary endpoint of mortality and cardiovascular hospitalizations. Follow-up will continue until 1,440 patients experience a primary endpoint. Thus, I-PRESERVE would potentially be the largest therapeutic trial in DHF and will likely provide important information on the characteristics and course of DHF, as well as the efficacy of the angiotensin receptor blocker, irbesartan.

Given the potential impact on cardiovascular medicine and the recent evidence suggesting that DHF has a similar prevalence, morbidity, and mortality as SHF, there remains an urgent need to determine the underlying pathophysiology of this clinical entity and to develop appropriate, effective, and safe therapeutic strategies.

Conclusions

DHF is a condition that continues to confound clinicians and remains a source of great debate. It is now recognized as a common condition, representing one-third of all HF admissions. Recent evidence reveals that the natural history for DHF is not as benign as traditionally thought. While angiotensin converting enzyme inhibitors and angiotensin receptor blockers may reduce HF hospitalizations in the setting of DHF, there are still no proven therapies to reduce mortality in patients with DHF. In the meantime, research continues into the pathophysiology of DHF and the development of strategies to treat this increasingly recognized and challenging medical condition.

Dr. Bhatia is a cardiology trainee at St. Michael's Hospital, Toronto.

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Abstract of Interest

Diastolic dysfunction in heart failure with preserved systolic function: need for objective evidence: results from the CHARM Echocardiographic Substudy-CHARMES.

PERSSON H, LONN E, EDNER M, BARUCH L, LANG CC, MORTON JJ, OSTERGREN J, MCKELVIE RS; INVESTIGATORS OF THE CHARM ECHOCARDIOGRAPHIC SUBSTUDY-CHARMES.

OBJECTIVES: We tested the hypothesis that diastolic dysfunction (DD) was an important predictor of cardiovascular (CV) death or heart failure (HF) hospitalization in a subset of patients (ejection fraction [EF] >40%) in the CHARM-Preserved study.

BACKGROUND: More than 40% of hospitalized patients with HF have preserved systolic function (HF-PSF), suggesting that DD may be responsible for the clinical manifestations of HF.

METHODS: Patients underwent Doppler echocardiographic examination that included assessment of pulmonary venous flow or determination of plasma NT-pro-brain natriuretic peptide > or months after randomization to candesartan or placebo. The patients were classified into 1 of 4 diastolic function groups: normal, relaxation abnormality (mild dysfunction), pseudonormal (moderate dysfunction), and restrictive (severe dysfunction).

RESULTS: There were 312 patients in the study, mean age was 66 ± 11 years, EF was 50 ± 10%, and 34% were women. The median follow-up was 18.7 months. Diastolic dysfunction was found in 67% of classified patients (n = 293), and moderate and severe DD were identified in 44%. Moderate and severe DD had a poor outcome compared with normal and mild DD (18% vs. 5%, $p < 0.01$). Diastolic dysfunction, age, diabetes, previous HF, and atrial fibrillation were univariate predictors of outcome. In multivariate analysis, moderate (hazard ratio [HR] 3.7, 95% confidence interval [CI] 1.2 to 11.1) and severe DD (HR 5.7, 95% CI 1.4 to 24.0) remained the only independent predictors ($p = 0.003$).

CONCLUSIONS: Objective evidence of DD was found in two-thirds of HF-PSF patients. Moderate and severe DD, which were found in less than one-half of the patients, were important predictors of adverse outcome. The results demonstrate the prognostic significance and need for objective evidence of DD in HF-PSF patients.

J Am Coll Cardiol 2007;49:687-94.

Upcoming meetings

24-27 March 2007
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5-9 May 2007
American Association for Thoracic Surgery (AATS) 87th Annual Meeting
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Contact: Tel.: 978-927-8330
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Disclosure Statement: *Dr. Bhatia and Dr. Leong-Poi have no disclosures to announce in association with the contents of this issue.*

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