Journal of Intensive Care Medicine
00(0) 1-9

DOI: 10.1177/0885066612453131
http://jicm.sagepub.com
SAGE

# Diastolic Heart Failure: The Current Understanding and Approach for Management With Focus on Intensive Care Unit Patients

**Wassef Karrowni, MD[1] and Kanu Chatterjee, MB, FRCP (Lond), FRCP (Edin)[1]**

**Abstract**

Multiple recent epidemiologic studies have highlighted the importance of diastolic heart failure (DHF) as a public health problem. Approximately half of patients presenting with symptomatic heart failure (HF) have DHF and they suffer from morbidity and mortality comparable to those with systolic HF. Our understanding of the pathophysiology of DHF has evolved rapidly over the last decade, and the associated echo-Doppler findings that assist with its diagnosis are greatly refined. Recently, there has been increased recognition of the role of diastolic dysfunction and DHF in the care of critically ill patients, including those admitted to noncardiac units. The purpose of this review is to provide an up-to-date summary of the concepts of the pathophysiology of DHF. In addition, we provide an overview of the diagnostic approaches, prognostic identifiers, and associated comorbidities that make DHF more resistant to manage with a focus of the patients admitted to the intensive care unit. The current approach to managing patients with DHF is also reviewed.

**Keywords**

diastolic heart failure, heart failure preserved ejection fraction, intensive care unit, biomarkers, prognosis

Received February 15, 2012, and in revised form April 26, 2012. Accepted for publication May 7, 2012.

## Introduction

During the last decade, there has been an increasing interest in the understanding of diastolic heart failure (DHF). DHF is also known as "heart failure (HF) with preserved systolic function" or "HF with normal ejection fraction (EF)."[1,2] At this point, it constitutes roughly half the total HF population.[3] In addition, its prevalence is expected to increase steadily with the change in patients' demographics and/or increasing recognition among physicians of the syndrome, to make it the most prevalent form of HF in the near future.[4] Recent data indicate that morbidity and mortality in patients with advanced DHF is as poor as in patients with systolic HF.[4-6] However, the patients with DHF are less likely to receive primary care from a cardiologist and have a cardiology consultation than those with reduced EF.[6] The purpose of this article is to provide an overview of the pathophysiology, clinical profile, and management of patients with diastolic HF, with focus on the care of patients admitted in the intensive care unit (ICU).

## Components of Normal Left Ventricular Diastolic Function at Rest and Stress

One of the essential components of effective ventricular pumping action is the ability of the ventricle to fill adequately during diastole. Diastole is energy dependent as systole and is composed of 3 phases: early rapid filling, diastasis, and late atrial filling. Under normal conditions, the myofiber architecture arrangement promotes torsion during systole with clockwise rotation of the base and counterclockwise rotation of the apex.[7] In early diastole, the ventricle "untwists," rapidly recoiling and creating left atrial (LA) to left ventricular (LV) gradient that promote filling.[8,9] This "suction" effect and myocardial relaxation are the main factors in normal LV filling during diastole (Figure 1). The LA pressure plays less important role in normal conditions. The diastasis phase has minimal contribution to the filling of the LV, as the pressures in the LA and LV are nearly equal. Atrial contraction normally contributes to only 10% to 20% of LV filling at rest and normal heart rate (HR).

[1] Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA, USA

**Corresponding Author:**
Wassef Karrowni, Division of Cardiovascular Diseases, University of Iowa Hospitals and Clinics, 200 Hawkins Dr., Int. Med. E-316-1 GH, Iowa City, IA 52242, USA
Email: wassef@hotmail.com

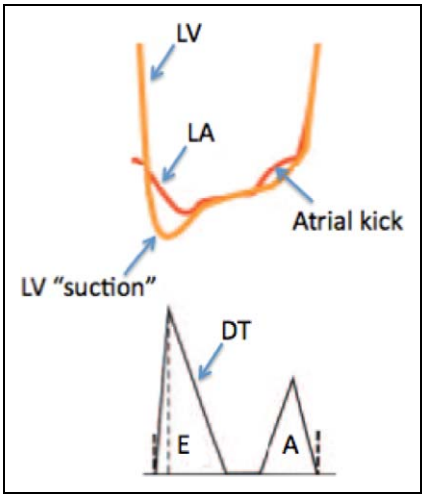


**Figure 1.** Demonstration of the simultaneous left ventricular (LV) pressure tracing and left atrial (LA) pressure tracing during diastole. The pressure gradient between LA and LV is the main determinant of LV filling; E Doppler velocity represents the early mitral inflow filling, and the A velocity represents the atrial contractile component. DT indicates deceleration time.

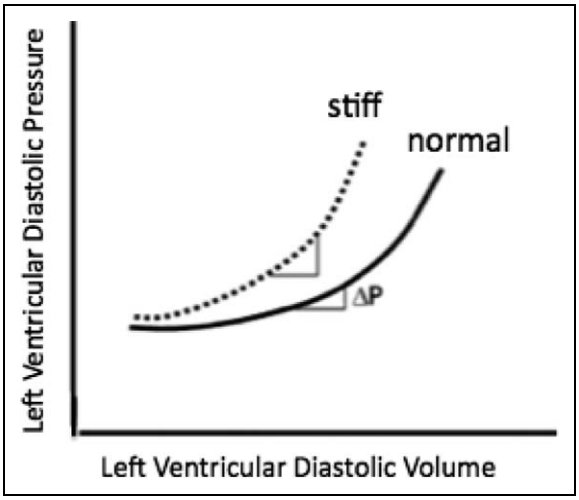


**Figure 2.** The changes in left ventricular diastolic pressure (y-axis) in relation to left ventricular diastolic volume (x-axis) in patients with diastolic heart failure (stiff ventricle) and normal controls. In stiff ventricle, there is more increase in pressure ($\Delta P$) for same increase in volume.

**Table 1.** Adaptive Response of Diastolic Function to Stress

| |
|---|
| Enhanced elastic recoil and suction effect |
| Increased relaxation rate |
| Shortened diastasis |
| Increased atrial kick contribution |
| Normal distensibility of the left ventricle |

During bodily stress (eg, exercise or sepsis), the cardiovascular system responds by enhancing cardiac output (around 3 times normal with strenuous exercise). This demand of increasing cardiac output must be met by the ability of the LV to handle increased filling volumes during shorter periods with the increased HR. There are multiple physiologic reserve mechanisms that permit normal diastolic function and adequate LV filling during stress (Table 1). Early diastolic elastic recoil and suction effect are enhanced as a result of the increased force of systolic contraction with greater shortening.[7] There is also accelerated myocardial relaxation secondary to the β-adrenergic stimulation during stress resulting in an increased rate of calcium uptake by the sarcoplasmic reticulum.[7] The increase in HR during stress leads to shorter diastolic filling period and less time to accomplish the increased filling. However, the diastolic duration shortening is mostly at the expense of the diastasis phase, which is not a major contributor to LV filling. The atrial kick contribution to LV filling is increased with tachycardia and might reach up to 40%. Finally, the normal distensibility of the LV allows an increase in end-diastolic volume with minimal change in filling pressures, as manifested by a downward shift of the LV diastolic pressure–volume curve.[10,11]

## Definition and Mechanisms of Diastolic HF

Diastolic dysfunction refers to a condition in which the ventricular chamber is unable to accept an adequate volume of blood during diastole at normal diastolic pressures and/or at volumes sufficient to maintain an appropriate stroke volume.[12] This is due to abnormalities in the mechanical function of the LV during diastole, either at rest or during stress.[12] Diastolic HF is a clinical syndrome characterized by abnormal diastolic function, preserved ejection fraction, and the symptoms and signs of HF.[12]

There are 2 components of abnormal LV diastolic function: impaired relaxation and increased passive stiffness (decreased compliance).[13] As a result, there is a substantially greater increase in diastolic pressure for any increase in volume (Figure 2).[14,15] Myocardial relaxation is an active energy-requiring process that restores the myocardium to its resting force and length.[16-18] Impaired relaxation has its most impact on the early filling phase of diastole (decreased suction effect). Relaxation can be impaired by multiple factors including ischemia or hypoxia, increased arterial impedance or coronary turgor, and asynchrony between contraction and relaxation events (eg, intraventricular conduction defect) resulting in dissipation of myocardial energy.

Ventricular compliance is a passive process that has impact on all 3 filling phases of diastole. It is altered by either intrinsic or extrinsic components. Intrinsic components include myocardial stiffness resulting from diffuse extracellular matrix fibrosis (eg, prolonged hypertension, amyloidosis, and hemachromatosis) and chamber stiffness resulting from increase in the thickness of wall. The extrinsic components include the structures that surround the LV such as the pericardium (eg, constrictive pericarditis and pericardial tamponade), right ventricular (RV) interaction with septal deviation (eg, acute RV infarct and

**Table 2.** Expected Isolated or Combined Findings on Echocardiography in Patients With DHF

| |
|---|
| Normal left ventricle (LV) systolic function, end-systolic volume, and end-diastolic volume |
| Enlarged LA chamber volume-based size: reflects the chronicity of elevation in LV filling pressure |
| Concentric LV hypertrophy and increased LV mass |
| Abnormal Doppler filling pattern: ranges from grade I to grade IV depending on the severity of diastolic dysfunction and loading conditions |
| Decreased $e'$ (tissue Doppler): predicts decreased longitudinal motion and suction |
| Increased $E/E'$: predicts elevated filling pressures |
| Increased right ventricular (RV)/right atrial pressure gradient: indicates elevated pulmonary artery systolic pressure and pulmonary hypertension |
| Enlarged RV chamber size and decreased RV systolic function: secondary to long-term pulmonary hypertension |
| Tricuspid regurgitation: secondary to dilated right ventricle |
| Dilated inferior vena cava with decreased compressibility: predicts elevated central venous pressure |

massive pulomary embolism), and the mediastinal or pleural pressure (eg, positive pressure ventilation).[19]

In addition to ventricular stiffening, there is increase in vascular stiffening in patients with DHF.[4,20] This combined ventricular–arterial stiffening creates a "high gain" system which leads to greater blood pressure lability, with amplified blood pressure changes for any alteration in preload or afterload.[21] Thus, patients with DHF develop much more dramatic shifts in blood pressure with vasodilation or vasoconstriction which makes them more prone to hypotension with aggressive diuresis or vasodilation and to develop hypertensive crisis and/or acute pulmonary edema with dietary or medication nonadherence.[22,23]

The clinical manifestations of diastolic dysfunction are the consequence of the elevation of the diastolic pressure, which causes a passive increase in LA and pulmonary venous pressures, and the symptoms of pulmonary venous congestion.[24] When severe and/or over prolonged period of time, passive increase in pulmonary artery pressure leads to postcapillary pulmonary hypertension. Consequently, this leads to secondary RV failure associated with increased RV diastolic and right atrial pressure and signs and symptoms of systemic venous hypertension. With marked restriction in ventricular filling, stroke volume may decline due to decreased preload associated with secondary signs and symptoms of low cardiac output.[24]

## Morphologic, Hemodynamic, and Serologic Changes

For the diagnosis of either systolic or diastolic HF, it is necessary to establish the presence of HF, which is a clinical diagnosis, based on an analysis of the symptoms and signs. In clinical practice, Framingham or Boston criteria can be applied.[25,26] However, DHF cannot be diagnosed "at the bedside" as differentiation from systolic HF cannot be made on the basis of history or physical examination.[12] For example, in a considerable proportion of patients with DHF, S3 gallop can be recognized.[27] Radiologic findings of chamber enlargement and pulmonary venous hypertension cannot be used to distinguish between systolic and diastolic HF and there are no specific electrocardiographic findings that are characteristic of systolic or diastolic HF.[28,29]

The echocardiogram is a powerful tool that allows clinicians to gain insight into the morphologic and physiologic parameters of the failing heart. Table 2 summarizes the changes we look for on echocardiography in patients with DHF. The 2-dimensional images often provide the first diagnostic clues to the presence of DHF based on normal LV EF and characteristic structural changes.[20] Patients with DHF generally exhibit a normal ventricular chamber size, with increased wall thickness, greater ratio of wall thickness to chamber dimension, and increased ratio of ventricular mass to chamber volume compared in patients with systolic HF and healthy controls.[30] However, it should be recognized that not all patients who meet the criteria for diastolic HF exhibit these gross structural changes.[31] Some are with little or no evidence of LV hypertrophy (LVH) or concentric remodeling.[31] In a large echocardiographic substudy in patients with DHF, as part of the Irbesartan in Heart Failure With Preserved Ejection Fraction (I-PRESERVE) trial, only 54% to 59% of patients had LVH or LV concentric remodeling.[32]

The volume-based measure of the LA size is an important part of the evaluation of LV diastolic function. It reflects cumulative effect of filling pressure over time, as prolonged exposure to elevated filling pressure results in structural remodeling of the left atrium leading to its enlargement. In the absence of secondary causes of atrial remodeling (atrial arrhythmias or mitral valve disease), the degree of LA volume enlargement correlate with the duration and severity of diastolic dysfunction and thus may be considered to be the "morphophysiologic" expression of LV diastolic function.[33] And more importantly, the volume-based measure of LA size characterizes the global cardiovascular risk.[34] In the I-PRESERVE imaging substudy, LA area was increased in 66% of the patients and of those, the LA enlargement was mild in 51% and moderate to severe in 15%.[32]

Because invasive hemodynamic studies are not convenient to perform, noninvasive measurements are routinely used to characterize diastolic function utilizing Doppler echocardiography.[12] In contrast to enlarged LA, which reflects chronicity of LV filling pressure elevation, Doppler-derived LV filling dynamics reflect acuity and can vacillate moment to moment.[35] The mitral inflow velocity profile is the initial step in evaluating LV filling dynamics. Its components are the E velocity ($E$) which represents the early mitral inflow filling, the A velocity ($A$) represents the atrial contractile component, and the deceleration time of the $E$ velocity (the interval from peak $E$ to a point of intersection of the deceleration of flow with the baseline; Figure 1).[35] These 3 parameters are integrated together to classify diastolic function as normal, delayed relaxation, or restrictive (Figure 3).

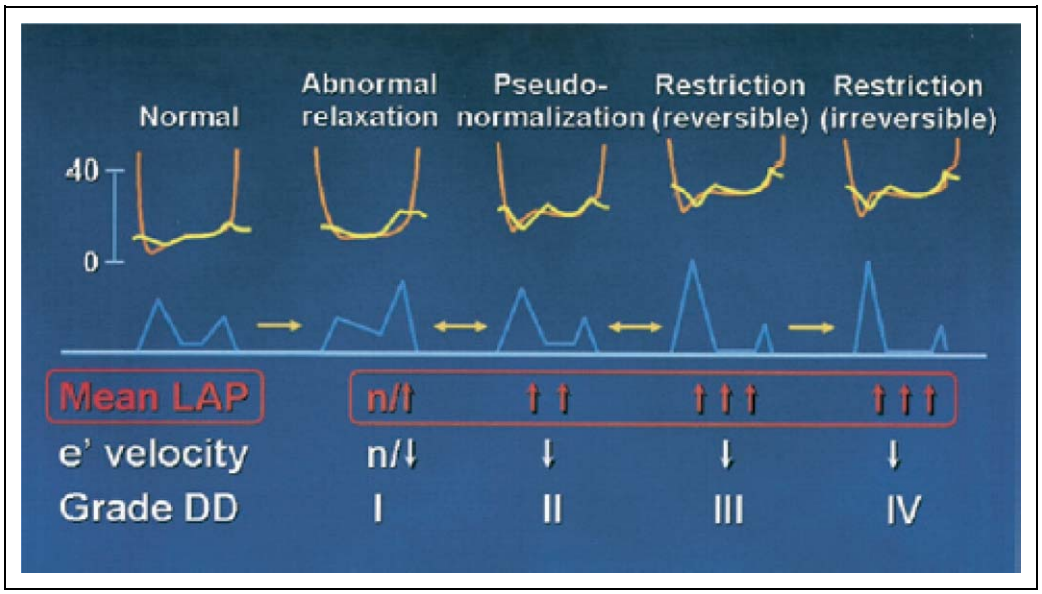


**Figure 3.** The natural history of diastolic function and LV filling. DD indicates diastolic function; e′, early diastolic mitral annular velocity; LAP, left atrial pressure; LV, left ventricular. Adapted with permission from Lester et al.[35]

Tissue Doppler imaging is another modality that add valuable information to the assessment of diastolic function. Tissue Doppler is used to measure $e'$, which is the early diastolic mitral annular longitudinal motion. The reduction in early LV relaxation (suction effect) is reflected through decrease in the $e'$ velocity (<10 cm/s).[35] A combination of reduced $e'$ velocity and increased $E/e'$ ratio predict elevated filling pressures and can be used to discriminate an individual with normal versus grade II (pseudonormal) diastolic dysfunction (Figure 3).[37,38] Other Doppler-derived parameters can be used to fully characterize diastolic function including pulmonary vein flow, isovolumic relaxation time, and mitral inflow propagation velocity (Vp), which are beyond the scope of the current review. The reader is referred to an excellent review that highlights the developments in echo-Doppler in the understanding of diastology.[35]

Data from the I-PRESERVE imaging substudy indicated that 31% of the patients with chronic compensated DHF have normal diastolic function indices, 29% have mild (grade I) diastolic dysfunction, 36% have moderate (grade II) diastolic dysfunction, and 4% have (severe grade III or IV) diastolic dysfunction.[32] Taken together, the I-PRESERVE imaging substudy showed that all the patients with chronic compensated DHF had at least one of the following findings: LVH, concentric remodeling, LA enlargement, or diastolic dysfunction.[32] It suggests that the absence of any evidence of structural remodeling or abnormal diastolic function would place the diagnosis of DHF in doubt.[32]

Finally, serologic biomarkers have been used to support the diagnosis of DHF. Of these, brain natriuretic peptide (BNP and NT-proBNP) has emerged as valuable noninvasive surrogates of elevated filling pressures.[39] However, it is necessary to recognize that natriuretic peptides are not useful to distinguish between systolic and diastolic HF, as they are elevated in both.[40] They are generally elevated to a greater extent in systolic HF and this is not surprising because the stimulus for myocardial BNP release is wall stress, which varies directly with filling pressures and chamber size (elevated in systolic but normal in DEF).[41]

## Clinical Profile of Patients With DHF

The majority of patients with DHF have a history of hypertension.[20,42,43] Abundant data suggest that DHF develops as a progression from asymptomatic hypertensive heart disease and this is supported by the fact that the cardiac structural changes seen in DHF are similar to those observed with chronic pressure overload due to arterial hypertension.[20,44,45] However, hypertension is an uncommon solitary cause of DHF.[3,46] Other risk factors associated with DHF are female sex, older age, obesity, and diabetes.[3,5,36] The clinical profile of patients with DHF differs in a number of ways from those with systolic HF with the most robust being the predominance of female sex (weighted average, 63% vs 38% respectively).[47] This is possibly related to enhanced concentric remodeling, more prominent age-related vascular stiffening, and less coronary artery disease in women.[47,48] Patients with DHF are also older than systolic HF (weighted average, 74 vs 70 years).[3] The predominance of ischemic heart disease is not as prominent in patients with DHF compared with systolic HF (weighted average, 46% vs 58%).[3,4,6,43] Finally, it is important to note that there is ethnic difference in the clinical profile of patients with DHF. In African Americans, diabetes and obesity appear to be more important associations than in Caucasians.[49]

Hypertrophic, restrictive, or infiltrative cardiomyopathy should be suspected when younger patients present with DHF, particularly in the absence of a history of hypertension.[50] These patients tend to be very difficult to treat.[23] There are multiple

**Table 3.** Conditions Associated With Difficult to Treat DHF

| Cardiac | Noncardiac |
|---|---|
| Atrial fibrillation | Obstructive sleep apnea |
| Myocardial ischemia | Renal artery stenosis |
| Valvular heart disease | End-stage renal disease |
| Pericardial disease | Anemia |

Abbreviation: DHF, diastolic heart failure.

**Table 4.** Predictors of Morbidity and Mortality in Patients With DHF

| |
|---|
| Elevated natriuretic peptide levels |
| Pulmonary hypertension |
| Increased left atrial volume |
| Increased left ventricular mass |
| BMI <23.5 or BMI 35 kg/m2 |
| Anemia |

Abbreviations: DHF, diastolic heart failure; BMI, body mass index.

other conditions that could be associated with DHF and make it more challenging to manage (Table 3).

## Morbidity and Mortality

The morbidity and mortality is as poor in HFpEF as in heart failure with reduced EF.[4-6] The mode of death in patients with compensated DHF enrolled in I-PRESERVE trial was cardiovascular in 60% (including 26% sudden, 14% HF, 5% myocardial infarction, and 9% stroke), noncardiovascular in 30%, and unknown in 10%.[51] Multiple clinical factors are known as bad prognostic factors in DHF (Table 4).

Pulmonary hypertension is present in around 80% of patients with DHF, and its presence and severity predict increased morbidity and mortality.[52-54] It is important to note that elderly patients diagnosed with pulmonary hypertension by echo are more frequently found to display elevated LV filling pressures at catheterization, suggesting that many of these patients in fact have DHF.[55] Elevated natriuretic peptide levels predict increased risk of HF morbidity and mortality.[56] In the I-PRESERVE trial, NT-proBNP above the median of 339 pg/mL was independently associated with worse outcome.[57] A high body mass index (BMI) appears to be paradoxically associated with better outcomes in patients with systolic HF. However, there is a U-shaped relationship between BMI and DHF outcomes, with the greatest rate of adverse outcomes in the lowest and highest BMI categories.[58]

Anemia is a common comorbidity in patients with HF and is equally prevalent in patients with diastolic (27%) and systolic (25%) HF.[59] It is associated with an increased risk of mortality in both forms of HF.[60] The underlying mechanisms regarding the causes of anemia and the associated increased mortality are not well understood. Multiple other prognostic markers were derived from the I-PRESERVE trial including age, diabetes mellitus, hospitalization for HF within 6 months preceding randomization, chronic lung disease, log neutrophil count, and ejection fraction.[27] The LV mass and LA size were also independently associated with an increased risk of morbidity and mortality in the I-PRESERVE echo substudy.[32]

## Prevention and Treatment

It is important to realize that early diagnosis of patients with DHF is beneficial as the degree of the underlying cardiovascular remodeling and dysfunction is less severe and potentially still amenable to treatment.[3] However, this is challenging because exertional intolerance, which is a common early symptom, may be ascribed to deconditioning, obesity, pulmonary disease, or pulmonary vascular disease. Recent studies have shown that patients with early-stage DHF may display hemodynamic abnormalities (elevated filling pressures) exclusively during the stress of exercise (despite normal examination, BNP, echocardiography, and resting hemodynamics).[3,61] Thus, invasive exercise hemodynamic testing or noninvasive exercise pulmonary artery pressure should be considered in patients with excertional intolerance or dyspnea of unknown etiology.[61]

Despite that considerable advances have been made in the treatment of systolic HF over the last 3 decades with subsequent substantial improvements in prognosis, no such therapeutic advances have been made in the management of DHF. This is reflected in the fact that mortality from DHF has remained the same.[4] Most of the time, the management of patients with DHF is not guided by clinical trials. The relative paucity of data could be secondary to multiple reasons including limited appreciation of the scope of the DHF epidemic, difficulty with accurate diagnosis, the multiple comorbidities of these patients causing exclusion from trials, and the frequent noncardiac complications which importantly drive rehospitalization rates and overall mortality.[23,62,63]

Many trials have tested the effectiveness of angiotensin-converting enzyme inhibitor, angiotensin II receptor blockers, β-blockers, digitalis, and calcium channel blockers in patients with DHF. For the most part, these trials have been small or have produced inconclusive results.[64-69] Nevertheless, because of the frequent presence of comorbid conditions (ie, atrial fibrillation, hypertension, diabetes mellitus, and coronary artery disease), many patients with DHF are treated with these drugs.[64] The current management of these patients are not disease-specific and targets symptoms reduction, principally by reducing cardiac filling pressures at rest and during exertion, and pursue control of physiological factors (blood pressure, HR, blood volume, and myocardial ischemia) that are known to exert negative effects on ventricular relaxation and stiffness.[64]

The echo-Doppler findings are helpful in guiding the symptomatic management of patients with DHF. For individuals with grades I and II diastolic dysfunction, the prominent abnormality is delayed relaxation. Thus, most of the filling of the LV is delayed to mid to late diastole and the duration of diastole is critical (Figure 3).[35] The HR slowing medications (β-blockers or rate slowing calcium-channel blockers) prolong the diastole time and provide a favorable symptomatic relief at

**Table 5.** Therapeutic Approaches Directed Toward the Myocardial Abnormality and the Elevated Filling Pressures

| | |
|---|---|
| Relieve Congestion | Diuretics; Nitrates |
| Decrease heart rate and improve filling | β-Blockers, or heart rate-regulating CCB; most helpful with grades I and II diastolic dysfunction; cautious use with grades III and IV diastolic dysfunction |
| Improve myocardial relaxation | Phosphodiesterase-5 inhibitors; ACE inhibitors; AT1 blockers |
| Decrease left ventricular hypertrophy and mass | ACE inhibitors; AT1 blockers; β-blockers; CCB; any drug effective for adequate control of hypertension |
| Decrease myocardial fibrosis and collagen content | ACE inhibitors; AT1 blockers; aldosterone antagonists |
| Prevent and treat pulmonary hypertension (WHO group II) | Relieve congestion; phosphodiesterase-5 inhibitors |

Abbreviations: CCB, calcium channel blockers; ACE, angiotensin-converting enzyme; AT1 blockers, angiotensin II subtype 1 receptor-blocking agents; WHO, World Health Organization.

**Table 6.** Therapeutic Approaches Directed Toward Associated Comorbid Conditions

| | |
|---|---|
| Atrial fibrillation | Sinus rhythm maintaining strategy is favorable (eg, amiodarone); if failed, rate control (β-blockers, CCB, and digitalis) and anticoagulation as necessary |
| Coronary artery disease | Improve myocardial perfusion via revascularization; decrease myocardial oxygen demand (β-blockers, CCB, and nitrates) |
| Hypertension | Adequate control and close monitoring of blood pressure |
| Diabetes/metabolic syndrome | Adequate control of blood sugar; lifestyle modifications |
| Obesity | Weight loss; lifestyle modification |
| Obstructive sleep apnea | CPAP or BiPAP |
| Renal artery stenosis | Revascularization |
| Advanced kidney disease | Initiate renal replacement therapy |

Abbreviations: CCB, calcium channel blockers; CPAP, continuous positive airway pressure; BiPAP, bi-level positive airway pressure.

rest or with exercise.[35] In contrast, patients with grade III or IV diastolic dysfunction have a fixed stroke volume as LV filling may be complete by mid-diastole (Figure 3). Thus, empirically slowing the HR into the 50s and 60s may worsen patients' symptoms secondary to further reduction in cardiac output.[35] Therefore, in these patients, the initiation of HR slowing therapy should be done in small increments and monitored closely.[35] Otherwise, the therapeutic approaches toward DHF are classified into those directed toward the primary myocardial abnormality and the consequent elevated filling pressures and those directed toward the associated comorbid conditions. The summary of these approaches is provided in Tables 5 and 6. Unfortunately, most of these approaches are not supported by strong evidence and are based on opinions. However, there are multiple ongoing trials that in the near future will, at least partly, provide evidence-based approach for the management of patients with DHF. Recently, a small randomized study showed promise in the role of the pulmonary-specific vasodilators in the management of patients with DHF.[70] Patients randomized to the phosphodiesterase-5 inhibitor (sildenafil) showed improvement in pulmonary pressure and vasomotility, RV function and dimension, LV relaxation and distensibility, and lung interstitial water metabolism compared with the control group.[70]

## Diastolic Dysfunction and DHF in the ICU

Cardiogenic shock and HF encountered in the ICU frequently result from depressed LV systolic function. However, a similar clinical and hemodynamic profile can occur in patients with preserved systolic function. DHF is only one of the long list of conditions that can lead to HF with preserved ejection fraction in the ICU setting (summarized in Table 7 and discussed extensively elsewhere[19]).

**Table 7.** The Causes of Heart Failure and Cardiogenic Shock in Patients With Preserved Ejection Fraction

| |
|---|
| Primary diastolic heart failure—normal left ventricular ejection fraction |
| Cardiac tamponade |
| Acute massive pulmonary embolism |
| Acute right ventricular infarction |
| Acute severe primary valvular regurgitation (aortic, mitral, or tricuspid) |
| Chronic valvular heart disease (eg, aortic stenosis) |
| Pericardial disease—constrictive pericarditis |
| Pulmonary arterial hypertension |
| Myocardial disease—restrictive or hypertrophic cardiomyopathy |

Evaluation of diastolic function in critical illness might be challenging from the technical standpoint and also likely to be confounded by the hemodynamic shift variables in this setting. Nevertheless, patients in ICU are frequently elderly and with multiple comorbid conditions (hypertension, diabetes, chronic kidney disease, valvular heart disease, and coronary artery disease). Thus, some degree of diastolic dysfunction is likely to commonly coexist in these patients (whether previously diagnosed or not).

There is emerging evidence that diastolic dysfunction is an independent predictor of mortality in critically ill patients.[71-73]

**Table 8.** Conditions Frequently Encountered in the Intensive Care Unit and Implicated in Precipitated/Worsening Diastolic Dysfunction

| Pathophsiologic Condition | Comments |
|---|---|
| Acute hemodynamic shifts (fluctuations in blood pressure, heart rate, or volume status) | Precipitated by excessive fluid resuscitation, intubation, infusion of inotropes and vasopressors, pain, anxiety, fever, and so on. |
| Sepsis and septic shock | Affects both systolic and diastolic function; complex mechanisms—likely related to nitration of contractile proteins |
| Hypoxia | Direct effects on myocardial function and indirect effects via hemodynamic changes |
| Mechanical ventilation | Mostly related to excessive positive pressure ventilation |
| Myocardial ischemia | Frequently related to increased myocardial demand |
| Atrial fibrillation | Precipitated by the acute illness |
| Withdrawal of medications | Especially β-blockers, diuretics, anti-hypertension drugs |
| Acute renal failure | Precipitates volume overload and metabolic derangements |
| Anesthetic agents | No strong evidence; agent specific; propofol associated with decreased left ventricular compliance |
| Extrinsic compression of the cardiac chambers | High levels of positive end-expiratory pressure, distended abdomen (ascites, obesity, and bowel obstruction), pleural/pericardial effusion |

Also, there is evidence linking the presence of diastolic dysfunction to difficulty weaning mechanical ventilation in the critically ill and to prolonged ICU stay.[74,75]

There are a multiple conditions that can induce or aggravate diastolic dysfunction and are commonly encountered in the ICU. These pathophysiologic conditions are summarized in Table 8. Management of DHF in critically ill patients is challenging with a scarce of supporting data available. At this point, management should focus on avoiding contributing or aggravating factors and maintaining a delicate hemodynamic balance. Whether monitoring diastolic function in the ICU and using it to guide management would provide any benefit remains to be answered.

## Conclusion

DHF is a common disease with a steadily increasing prevalence and significant morbidity and mortality. With the lack of disease-specific therapies, the current therapeutic approach is mostly symptomatic. The impact of diastolic dysfunction and DHF on the care of critically ill patients has been of a recent interest and is of increased recognition. Thus, it is essential that intensivists have good understanding of the concepts related to these conditions.

### Acknowledgments

The authors would like to thank Diane Kraft, MD, for her review and critique of this article.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

### References

1. Sanderson JE. Heart failure with a normal ejection fraction. *Heart*. 2007;93(2):155-158.
2. McMurray J, Pfeffer MA. New therapeutic options in congestive heart failure: Part II. *Circulation*. 2002;105(18):2223-2228.
3. Borlaug BA, Redfield MM. Diastolic and Systolic Heart Failure Are Distinct Phenotypes Within the Heart Failure Spectrum. *Circulation*. 2011;123(18):2006-2013.
4. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med.* 2006;355(3): 251-259.
5. Lee DS, Gona P, Vasan RS, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. *Circulation*. 2009;119(24): 3070-3077.
6. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med*. 2006;355(3):260-269.
7. Foster E, Lease KE. New Untwist on Diastole: What goes around comes back. *Circulation*. 2006;113(21):2477-2479.
8. Buckberg GD, Weisfeldt ML, Ballester M, et al. Left ventricular form and function: scientific priorities and strategic planning for development of new views of disease. *Circulation*. 2004;110(14): e333-e336.
9. Corno AF, Kocica MJ, Torrent-Guasp F. The helical ventricular myocardial band of Torrent-Guasp: potential implications in congenital heart defects. *Eur J Cardiothorac Surg*. 2006;29 suppl 1: S61-S68.
10. Carroll JD, Hess OM, Hirzel HO, Krayenbuehl HP. Dynamics of left ventricular filling at rest and during exercise. *Circulation*. 1983;68(1):59-67.
11. Cheng CP, Igarashi Y, Little WC. Mechanism of augmented rate of left ventricular filling during exercise. *Circ Res*. 1992;70(1):9-19.
12. Zile MR. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. *Circulation*. 2002;105(11):1387-1393.
13. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure–abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med*. 2004;350(19):1953-1959.

14. Aurigemma GP, Gaasch WH. Clinical practice. Diastolic heart failure. *N Engl J Med*. 2004;351(11):1097-1105.
15. Grossman W. Defining diastolic dysfunction. *Circulation*. 2000; 101(17):2020-2021.
16. Ramirez-Correa GA, Murphy AM. Is phospholamban or troponin I the "prima donna" in beta-adrenergic induced lusitropy? *Circ Res*. 2007;101(4):326-327.
17. Paulus WJ, Vantrimpont PJ, Shah AM. Acute effects of nitric oxide on left ventricular relaxation and diastolic distensibility in humans. Assessment by bicoronary sodium nitroprusside infusion. *Circulation*. 1994;89(5):2070-2078.
18. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J*. 2011;32(6):670-679.
19. Chatterjee K, McGlothlin D, Michaels A. Analytic reviews: cardiogenic shock with preserved systolic function: a reminder. *J Intensive Care Med*. 2008;23(6):355-366.
20. Melenovsky V, Borlaug BA, Rosen B, et al. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction. *J Am Coll Cardiol*. 2007;49(2):198-207.
21. Borlaug BA, Kass DA. Ventricular-vascular interaction in heart failure. *Heart Fail Clin*. 2008;4(1):23-36.
22. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation*. 2003;107(5):714-720.
23. From AM, Borlaug BA. Heart failure with preserved ejection fraction: pathophysiology and emerging therapies. *Cardiovasc Ther*. 2011;29(4):e6-e21.
24. Chatterjee K. Primary diastolic heart failure. *Am J Geriatr Cardiol*. 2002;11(3):178-187; quiz 188-189.
25. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med*. 1971;285(26):1441-1446.
26. Carlson KJ, Lee DC, Goroll AH, Leahy M, Johnson RA. An analysis of physicians' reasons for prescribing long-term digitalis therapy in outpatients. *J Chronic Dis*. 1985;38(9):733-739.
27. Komajda M, Carson PE, Hetzel S, et al. Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). *Circ Heart Fail*. 2011;4(1): 27-35.
28. Chatterjee K, Massie B. Systolic and diastolic heart failure: differences and similarities. *J Card Fail*. 2007;13(7):569-576.
29. McDermott MM, Feinglass J, Sy J, Gheorghiade M. Hospitalized congestive heart failure patients with preserved versus abnormal left ventricular systolic function: clinical characteristics and drug therapy. *Am J Med*. 1995;99(6):629-635.
30. Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. *JAMA*. 2002;288(17):2144-2150.
31. Aurigemma GP, Zile MR, Gaasch WH. Contractile behavior of the left ventricle in diastolic heart failure: with emphasis on regional systolic function. *Circulation*. 2006;113(2):296-304.
32. Zile MR, Gottdiener JS, Hetzel SJ, et al. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation*. 2011;124(23):2491-2501.
33. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. *Am J Cardiol*. 2002;90(12):1284-1289.
34. Douglas PS. The left atrium: a biomarker of chronic diastolic dysfunction and cardiovascular disease risk. *J Am Coll Cardiol*. 2003;42(7):1206-1207.
35. Lester SJ, Tajik AJ, Nishimura RA, Oh JK, Khandheria BK, Seward JB. Unlocking the mysteries of diastolic function. *J Am Coll Cardiol*. 2008;51(7):679-689.
36. Masoudi FA, Havranek EP, Smith G, et al. Gender, age, and heart failure with preserved left ventricular systolic function. *J Am Coll Cardiol*. 2003;41(2):217-223.
37. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol*. 1997;30(6):1527-1533.
38. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. *Circulation*. 2000; 102(15):1788-1794.
39. Tschope C, Kasner M, Westermann D, Gaub R, Poller WC, Schultheiss HP. The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements. *Eur Heart J*. 2005;26(21): 2277-2284.
40. Lee DS, Vasan RS. Novel markers for heart failure diagnosis and prognosis. *Curr Opin Cardiol*. 2005;20(3):201-210.
41. Iwanaga Y, Nishi I, Furuichi S, et al. B-type natriuretic peptide strongly reflects diastolic wall stress in patients with chronic heart failure: comparison between systolic and diastolic heart failure. *J Am Coll Cardiol*. 2006;47(4):742-748.
42. Lam CS, Roger VL, Rodeheffer RJ, et al. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. *Circulation.* 2007;115(15):1982-1990.
43. Klapholz M, Maurer M, Lowe AM, et al. Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: results of the New York Heart Failure Registry. *J Am Coll Cardiol*. 2004;43(8):1432-1438.
44. Lakatta EG. Cardiovascular regulatory mechanisms in advanced age. *Physiol Rev*. 1993;73(2):413-467.
45. Borlaug BA, Olson TP, Lam CS, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. *J Am Coll Cardiol*. 2010;56(11):845-854.
46. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med*. 2000;342(15):1077-1084.
47. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: a community-based study. *Circulation*. 2005;112(15):2254-2262.

48. Douglas PS, Katz SE, Weinberg EO, Chen MH, Bishop SP, Lorell BH. Hypertrophic remodeling: gender differences in the early response to left ventricular pressure overload. *J Am Coll Cardiol*. 1998;32(4):1118-1125.
49. Nivekananthan K QH, Dali S. Heart failure with preserved systolic function in African-Americans: the rule of diabetes mellitus and obesity. *Circulation*. 2000;102: II-781.
50. Maurer MS, King DL, El-Khoury Rumbarger L, Packer M, Burkhoff D. Left heart failure with a normal ejection fraction: identification of different pathophysiologic mechanisms. *J Card Fail*. 2005;11(3):177-187.
51. Zile MR, Gaasch WH, Anand IS, et al. Mode of death in patients with heart failure and a preserved ejection fraction: results from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-Preserve) Trial. *Circulation*. 2010;121(12):1393-1405.
52. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. *J Am Coll Cardiol*. 2009;53(13):1119-1126.
53. Kjaergaard J, Akkan D, Iversen KK, et al. Prognostic importance of pulmonary hypertension in patients with heart failure. *Am J Cardiol*. 2007;99(8):1146-1150.
54. Bursi F, McNallan SM, Redfield MM, et al. Pulmonary pressures and death in heart failure a community study. *J Am Coll Cardiol*. 2012;59(3):222-231.
55. Shapiro BP, McGoon MD, Redfield MM. Unexplained pulmonary hypertension in elderly patients. *Chest*. 2007;131(1):94-100.
56. Cleland JG, Taylor J, Tendera M. Prognosis in heart failure with a normal ejection fraction. *N Engl J Med*. 2007;357(8):829-830.
57. Anand IS, Rector TS, Cleland JG, et al. Prognostic value of baseline plasma amino-terminal pro-brain natriuretic peptide and its interactions with irbesartan treatment effects in patients with heart failure and preserved ejection fraction: findings from the I-PRESERVE trial. *Circ Heart Fail*. 2011;4(5):569-577.
58. Haass M, Kitzman DW, Anand IS, et al. Body mass index and adverse cardiovascular outcomes in heart failure patients with preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. *Circ Heart Fail*. 2011;4(3):324-331.
59. O'Meara E, Clayton T, McEntegart MB, et al. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. *Circulation*. 2006;113(7):986-994.
60. Groenveld HF, Januzzi JL, Damman K, et al. Anemia and mortality in heart failure patients a systematic review and meta-analysis. *J Am Coll Cardiol*. 2008;52(10):818-827.
61. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail*. 2010;3(5):588-595.
62. Henkel DM, Redfield MM, Weston SA, Gerber Y, Roger VL. Death in heart failure: a community perspective. *Circ Heart Fail*. 2008;1(2):91-97.
63. Shah SJ, Gheorghiade M. Heart failure with preserved ejection fraction: treat now by treating comorbidities. *JAMA*. 2008;300(4):431-433.
64. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119(14):1977-2016.
65. The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. *N Engl J Med*. 1997;336(8):525-533.
66. Setaro JF, Zaret BL, Schulman DS, Black HR, Soufer R. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. *Am J Cardiol*. 1990;66(12):981-986.
67. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. *Am J Cardiol*. 1997;80(2):207-209.
68. Aronow WS, Kronzon I. Effect of enalapril on congestive heart failure treated with diuretics in elderly patients with prior myocardial infarction and normal left ventricular ejection fraction. *Am J Cardiol*. 1993;71(7):602-604.
69. Warner JG Jr, Metzger DC, Kitzman DW, Wesley DJ, Little WC. Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise. *J Am Coll Cardiol*. 1999;33(6):1567-1572.
70. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. *Circulation*. 2011;124(2):164-174.
71. Landesberg G, Gilon D, Meroz Y, et al. Diastolic dysfunction and mortality in severe sepsis and septic shock. *Eur Heart J*. 2012;33(7):895-903.
72. Ikonomidis I, Nikolaou M, Dimopoulou I, et al. Association of left ventricular diastolic dysfunction with elevated NT-pro-BNP in general intensive care unit patients with preserved ejection fraction: a complementary role of tissue Doppler imaging parameters and NT-pro-BNP levels for adverse outcome. *Shock*. 2010;33(2):141-148.
73. Sturgess DJ, Marwick TH, Joyce C, et al. Prediction of hospital outcome in septic shock: a prospective comparison of tissue Doppler and cardiac biomarkers. *Crit Care*. 2010;14(2):R44.
74. Lamia B, Maizel J, Ochagavia A, et al. Echocardiographic diagnosis of pulmonary artery occlusion pressure elevation during weaning from mechanical ventilation. *Crit Care Med*. 2009;37(5):1696-1701.
75. Papanikolaou J, Makris D, Saranteas T, et al. New insights into weaning from mechanical ventilation: left ventricular diastolic dysfunction is a key player. *Intensive Care Med*. Oct 6 2011.