DIASTOLIC DYSFUNCTION: A REVIEW
Rajat Jain§, Kshitiz Nath§, Nutan Agarwal§, Manish Jain§, Rahul Rai§

1Assistant Professor, Department of Medicine, M.L.B. Medical College, Jhansi.
2Senior Resident, Department of Medicine, M.L.B. Medical College, Jhansi.
3Professor, Department of Medicine, M.L.B. Medical College, Jhansi.
4Associate Professor, Department of Surgery, M.L.B. Medical College, Jhansi.
5Resident, Department of Medicine, M.L.B. Medical College, Jhansi.

ABSTRACT

INTRODUCTION
Diastolic heart failure is an underestimated pathology. Epidemiological and clinical studies suggest that HF with a preserved ejection fraction will become the more common form of HF which clinicians will encounter. Symptomatic treatment focuses on the reduction in pulmonary congestion and the improvement in LV filling. Specific treatment is actually lacking, but encouraging data are emerging concerning the use of renin–angiotensin–aldosterone axis blockers, nitric oxide donors, or, very recently, new agents specifically targeting actin–myosin cross-bridges. It is generally considered to have a somewhat better prognosis than systolic HF, but frequency of hospitalizations is comparable in systolic and diastolic HF. Despite the recognition of its importance, definition and diagnostic criteria of diastolic dysfunction and diastolic HF remain controversial.

AIMS AND OBJECTIVES
This review focuses on definition, diagnosis and management of diastolic heart failure with its prognosis.

MATERIAL AND METHODS
We have studied various guidelines, articles, reviews using given keywords, along with our experience in management of diastolic heart failure in 2015. The articles and the references were reviewed keeping in mind about the simplified management offered to the patient.

KEYWORDS
Diastolic Heart Failure, Congestive Heart Failure, NT-proBNP, Color Doppler Echocardiography.


INRODUCTION: Diastolic dysfunction refers to abnormalities in left ventricular distensibility, filling or relaxation regardless of signs and symptoms of HF or left ventricular ejection fraction. Diastolic dysfunction in the absence of symptoms is common in elderly hypertensive patients. Heart failure with a preserved ejection fraction (HFpreEF), or diastolic HF, refers to the clinical syndrome of HF coupled with evidence of diastolic dysfunction and is estimated to occur in approximately 50% of patients with chronic HF. In patients older than 70 years, the adjusted mortality rate for HFpreEF is equivalent to those patients with reduced systolic function. There have been numerous attempts to develop diagnostic criteria; however there has been little consensus. In 1998 Paulus et al. developed the European Criteria for HFpreEF. This group suggested that there must be objective evidence of HF with a normal or mildly impaired systolic function (left ventricular ejection fraction (LVEF) >45%) and abnormal left ventricular (LV) relaxation. All three criteria are required for the diagnosis of HFpreEF. Plasma levels of B-natriuretic peptide (BNP) are elevated in patients with HF, independent of the aetiology of HF. An alternative and simpler definition of HFpreEF is an elevated BNP with a normal LVEF, however, there may be several limitations to this definition. Specifically elevated BNP levels have been found in patients with myocardial ischemia in the absence of congestive heart failure (CHF), renal failure, and obesity. Most widely accepted as a threshold value of LVEF is >50%. Diastolic is characterized by the upward and leftward displacement of the end-diastolic pressure-volume relationship. However, these changes may occur in patients with diminished systolic function and in the absence of overt HF, and hence by themselves do not confirm a diagnosis of HFpreEF. The need for confirming evidence of diastolic dysfunction remains controversial particularly if there is evidence of hypertrophic remodelling. The updated consensus statement from the European Society of Cardiology is summarized in Table 1. This report considers an LV wall index >122 g/m2 or an LV wall mass index >149 g/m2, in the presence of symptoms, adequate evidence for the diagnosis of diastolic HF when other modalities such as Tissue Doppler Imaging (TDI) are inconclusive in the context of elevated BNP levels.
Table 1: The European Society of Cardiology Criteria for Diastolic Heart Failure

The European consensus criteria for diastolic HF.

1. Signs and symptoms of CHF.
   - Effort dyspnoea, orthopnoea, pulmonary rales/oedema.
   - Cardiopulmonary exercise testing (VO$_{2\text{max}}$ <25ml/kg/min).

2. Normal or mildly reduced ejection fraction and normal chamber size.
   - LVEF >50% and Normal LV end diastolic volume (<97ml/m$^2$).

3. Abnormal LV relaxation, filling or diastolic distensibility or stiffness.
   - Echocardiographic: Tissue Doppler (E/Ea >15), LA volume ≥ 34 ml/m$^2$ if E/Ea between 9 and 14.
   - Cardiac catheterization: LVEDP >16mmHg.
   - Biomarkers NT-proBNP >220 pg/ml or BNP >200 pg/ml.

All three criteria are required for the diagnosis of diastolic heart failure.

**DIAGNOSIS OF DIASTOLIC HEART FAILURE:**

**Non-invasive assessment of diastolic function:**
Several non-invasive techniques have been used for assessing diastolic function in patients with coronary, valvular or myocardial heart disease. The most commonly used methods are 2D-and Doppler-echocardiography, Doppler-tissue imaging, radionuclide ventriculography, and MR myocardial tagging and MR imaging.

1. **Echocardiography:** During the last 2 decades Doppler-echocardiography has emerged as an important clinical tool providing reliable and useful data on diastolic performance. Three different approaches are routinely used in the assessment of diastolic dysfunction: measurement of trans-mitral and pulmonary venous flow as well as intra-ventricular filling patterns (Doppler flow propagation). The trans-mitral velocity pattern remains the starting point of echocardiographic assessment of LV diastolic function; since it is easy to acquire and can rapidly categorize patients with normal or abnormal diastolic function by E/A ratio (early to late filling velocity). In healthy young individuals, most diastolic filling occurs in early diastole so that the E/A ratio is >1. When relaxation is impaired, early diastolic filling decreases progressively and a vigorous compensatory atrial contraction (‘atrial kick’) occurs. The results in a reversed E/A ratio, increased deceleration time, and increased isovolumic relaxation time. With disease progression LV compliance becomes reduced and filling pressures begin to increase leading to compensatory augmentation of left atrial pressure with increase in early filling despite improved relaxation, so that filling pattern looks relatively normal (‘pseudo-normalization’ pattern= E/A > 1). Finally, in patients with severe decrease in LV compliance, left atrial pressure is markedly elevated and compensates with vigorous early diastolic filling for impaired relaxation. This ‘restrictive’ filling pattern (E/A >1) is consistent with an abnormal rise in LV pressure and an abrupt deceleration of flow with little additional filling during mid-diastole and atrial contraction. In extreme cases the LV pressure rise overshoots left atrial pressure so that diastolic mitral regurgitation in mid diastole may be seen.

Colour Doppler M-mode provides a unique window into the fluid dynamics of flow across the mitral valve. The speed of propagation is enhanced with rapid relaxation and LV suction. Clinical and experimental studies have demonstrated that the inverse correlation to t is relatively independent of left atrial pressure. Furthermore, combined evaluation of flow propagation velocity and early diastolic annular velocity can be used for estimation of filling pressure.

Doppler tissue imaging yields information on intramyocardial velocity, providing a unique insight into LV mechanics during isovolumic contraction and relaxation. In normal persons the mitral annular motion is almost a mirror image of the trans-mitral flow pattern, but in patients with pseudo normal or restrictive filling pattern, annular motion is abnormally low, implying that it is relatively independent of preload.

It has been shown that relaxation velocities in the myocardium are inversely correlated with t, so that a non-invasively calculation of the time constant of relaxation seems to be possible. Through the integrated use of Doppler echocardiography and Doppler tissue imaging, it is possible to obtain a fairly precise picture of LV diastolic function. However, atrial fibrillation or frequent ectopic beats are the major limitation of these techniques. To overcome this problem, averaging of several heart cycles with similar RR intervals has been proposed.

2. **Magnetic resonance imaging:** This technique has been shown to be of considerable use in the morphologic assessment of the heart, but functional assessment can also be obtained. However, their clinical relevance remains to be demonstrated. Additional information may be gained from newer techniques such as magnetic resonance myocardial tagging, which allows the labelling of specific myocardial regions. From these tags the rotational and translational motion of the left ventricle 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.

3. **Radionuclide angiography:** This technique may be used to study the rapid filling phase of diastole, the duration of the isovolumic relaxation phase, the relative contribution of rapid filling to total diastolic filling and the relation between regional non-uniformity of left ventricular function and global filling properties. However, radionuclide angiography does not permit
assessment of the left atrial-left ventricular pressure gradient or the simultaneous evaluation of changes in left ventricular pressure and volume during relaxation and filling. Therefore, complete clinical interpretation of abnormal left ventricular filling indexes, or changes in these indexes after interventions, is not possible. Despite the inherent limitations of non-invasive assessment of left ventricular diastolic function, radionuclide evaluation of left ventricular filling may provide clinically useful insights.39

**Invasive assessment of diastolic function:** Cardiac catheterization with simultaneous pressure and volume measurements is the ‘gold’ standard for assessing LV diastolic function. Prerequisites are high-fidelity pressure recordings with simultaneous angiography or echocardiography or the use of the conductance technique. The rate of LV relaxation, rate and timing of diastolic filling as well as myocardial and chamber stiffness can be determined.40

**PROGNOSIS:** Prognosis of diastolic HF is slightly less ominous than that of systolic HF, with an annual mortality of 5–8% in those individuals with the former and 10–15% in those with the latter.31 Presence of coronary disease, age and the LVEF cut-off value are important factors in the prognosis. When patients with ischemic heart disease are excluded, annual mortality for diastolic congestive HF falls to 2–3%. In patients with congestive HF, mortality is similar in systolic and diastolic HF.41,42

**TREATMENT:** To date, only one large scale monitored randomized clinical trial was undertaken to compare drug versus placebo administration in patients with HF and preserved systolic function (CHARM-preserved). This trial compared the efficacy of a daily 32 mg dose of candesartan versus a placebo in 3023 patients with chronic HF and LVEF >40%. After a 36.6 month mean follow up, primary combined outcome incidence (death by cardiovascular cause or admission for congestive HF) was similar in both groups. Data for cardiovascular mortality did not differ, but a moderate impact of candesartan in preventing admissions for congestive HF among patients who have HF and LVEF>40% was observed.43-44 Although the moderate benefit of candesartan should be taken into consideration, until data from randomized clinical trials provide new evidence.

Zile and Brutsaert45 propose that treatment of diastolic HF must be directed toward symptoms, aetiology and, in the future, underlying mechanisms, as outlined in table 2.

**Table 2. Diastolic heart failure: Treatment.**

**Symptoms targeted treatments.**
- Decrease pulmonary venous pressure.
  - Reduce left ventricular volume.
  - Maintain atrial contraction.
  - Prevent tachycardia.

- Improve exercise tolerance.
- Use positive inotropic agents with caution.
- Non-Pharmacological treatment.
  - Restrict sodium to prevent volume overload.
  - Restrict fluid to prevent volume overload.
  - Perform moderate aerobic exercise to improve cardiovascular conditioning, decrease heart rate, and maintain skeletal muscle function.
- Pharmacological treatment.
  - Diuretics, including loop diuretics, thiazides, spironolactone.
  - Long acting nitrates.
  - B adrenergic blockers.
  - Calcium channels blockers.
  - Renin-angiotensin-aldosterone antagonist, including ACE inhibitors, angiotensin receptor blockers, and aldosterone antagonist.

**Deseased targeted treatments.**
- Prevent/treat myocardial ischemia.
- Prevent/regress ventricular hypertrophy.

**Mechanism targeted treatments.**
- Modify myocardial and extra myocardial mechanisms.
- Modify intracellular and extracellular mechanism.

Angiotensin receptor blockers (ARBs) have proven effective in causing regression of LV hypertrophy (LIFE) and may reduce morbidity, but not mortality (CHARM). Maintenance of sinus rhythm, heart rate control (b blockers, calcium channel blockers) and anti-ischemic treatment may be indicated in view of pathophysiological aspects. Diuretics should be administered with caution in patients with symptoms of congestion; digitalis is not useful in the treatment of isolated diastolic HF. The results of ongoing trials (for example, I-Preserve) may offer new therapeutic options, and evidence based guidelines for the so far often unsatisfactory treatment of diastolic dysfunction/ HF are awaited.

Therefore, even if the rationale of their use differs, these principles suggest that drugs recommended for diastolic HF may be the ones recommended for systolic dysfunction. For example, b blockers are now recommended for the treatment of both systolic and diastolic HF. In diastolic HF, however, b blockers are used to decrease heart rate, increase the duration of diastole, and modify the hemodynamic response to exercise. In systolic HF, b blockers are used chronically to increase inotropic state and modify LV remodelling. In systolic HF, b blockers must be titrated slowly and carefully over an extended time period. This is generally not necessary in diastolic HF. Diuretics are used in the treatment of both systolic and diastolic HF. However, the doses of diuretics used to treat diastolic HF are generally smaller than the doses used in systolic HF. Some drugs are used only to treat either systolic or diastolic HF, but not both. For example, calcium channel blockers have no place in the treatment of systolic HF, but have been considered potentially useful in the treatment of diastolic HF.46
Conceptually, an ideal therapeutic agent should target the underlying mechanisms that cause diastolic HF. Therefore, a therapeutic agent might improve calcium homeostasis and energetics, blunt neurohumoral activation and decrease myocardial stiffness. Fortunately, some pharmaceutical agents that fit these design characteristics are already in existence, and many more are under development. Unfortunately, randomized, double blind, placebo controlled, multicenter trials that examine the efficacy of these agents used either singly or in combination have been slow to develop.

REFERENCES:


