

Understanding Asymptomatic Diastolic Dysfunction in Clinical Practice

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Introduction

The contemporary concept of heart failure (HF) is based on the cardiovascular continuum, which begins in the presence of risk factors, proceeds to asymptomatic changes in cardiac structure and function, and then evolves into the symptomatic forms and eventually to the final stage (refractory HF)¹. Cardiac dysfunction, either systolic or asymptomatic diastolic, has a high prevalence in the adult population older than 45 years, and is a phase during which the patient can progress to the clinical form of HF; this transition brings a five-fold increase in mortality².

Identifying patients with asymptomatic cardiac dysfunction may allow the implementation of nonpharmacological or pharmacological interventions aiming at reversing heart functional and structural abnormalities, thus delaying the onset of symptomatic HF. The concept that HF has progressive stages and is therefore a preventable condition was proposed by the American College of Cardiology (ACC) and the American Heart Association (AHA)³ and was incorporated by the Chronic HF Guidelines of the Brazilian Society of Cardiology⁴.

HF with normal ejection fraction (HFNEF) is now a new epidemic that affects elderly hypertensive patients and represents more than 50% of patients hospitalized for HF. The onset of HFNEF is preceded by diastolic abnormalities such as slowing in relaxation and alterations in the filling pressures and structure of the left ventricle (LV) – left ventricular hypertrophy (LVH), and increased left atrial volume (LAV). Thus, it is important to detect these abnormalities in a preclinical phase².

Asymptomatic systolic dysfunction is easily recognized by clinicians using a cardiac imaging method, for the presence of left ventricular ejection fraction (LVEF) < 50%. The characterization of asymptomatic diastolic dysfunction (DD) is made by a triad consisting of absence of HF symptoms, evidence of DD and LVEF ≥ 50%, and its presence is a marker for the onset of symptomatic HF and reduced life expectancy⁵. However, DD is still overlooked in daily clinical practice⁵ and its detection is a complex process that requires multiple measures for its correct identification, with the invasive method being the gold standard⁶.

Keywords

Heart failure; ventricular dysfunction; echocardiography; diagnostic imaging; heart failure diastolic; heart failure systolic.

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Currently, the invasive method for DD assessment has been replaced by modern techniques of Doppler echocardiography using tissue Doppler (TDE)⁷ and also the measurement of natriuretic peptide (NP) levels⁸. The assessment by Doppler echocardiography allows the stratification of the degree of DD, its severity and the assessment of the impact of therapeutic measures and prognosis⁷.

The objectives of this review are to show the epidemiological bases of the clinical impact of asymptomatic DD (stage B of HF), recent advances in pathophysiology and modern diagnostic methods used for its characterization.

Epidemiology and staging of heart failure

Staging of the population at risk for the development of HF allows better understanding of the prognostic impact of ventricular dysfunction and implementation of measures to prevent its onset or delay its progression to more advanced stages (Figure 1)².

Stage A

Stage A can be defined by the presence of modifiable risk factors for the development of HF without the presence of structural or functional cardiac abnormalities. Risk factors that should be considered are those well established as predictive of HF in large longitudinal studies – hypertension, diabetes, obesity and coronary artery disease¹. In our country, alcoholism and Chagas disease⁴ should also be considered.

Stage B

Stage B is characterized by the presence of structural changes (remodeling, fibrosis and valvular heart disease) and asymptomatic systolic or diastolic dysfunction, which can be identified by electrocardiographic and Doppler echocardiographic abnormalities in the absence of signs or symptoms of HF².

Currently, in order to achieve a better and objective identification of asymptomatic individuals, the patient's functional capacity should be assessed; those capable of performing activities requiring ≥ 7 METs of exercise capacity without limitations due to fatigue or dyspnea are considered asymptomatic⁹. In elderly patients with a low level of physical activity, the 6-minute walk test or exercise testing with peak oxygen consumption (VO₂ max.) may be useful to confirm the presence of asymptomatic DD⁹.

Stage C

Stage C shows the onset of symptoms or signs of HF, with the earliest signs being exertional dyspnea and fatigue (exercise capacity between 2 and 7 METs)⁹.

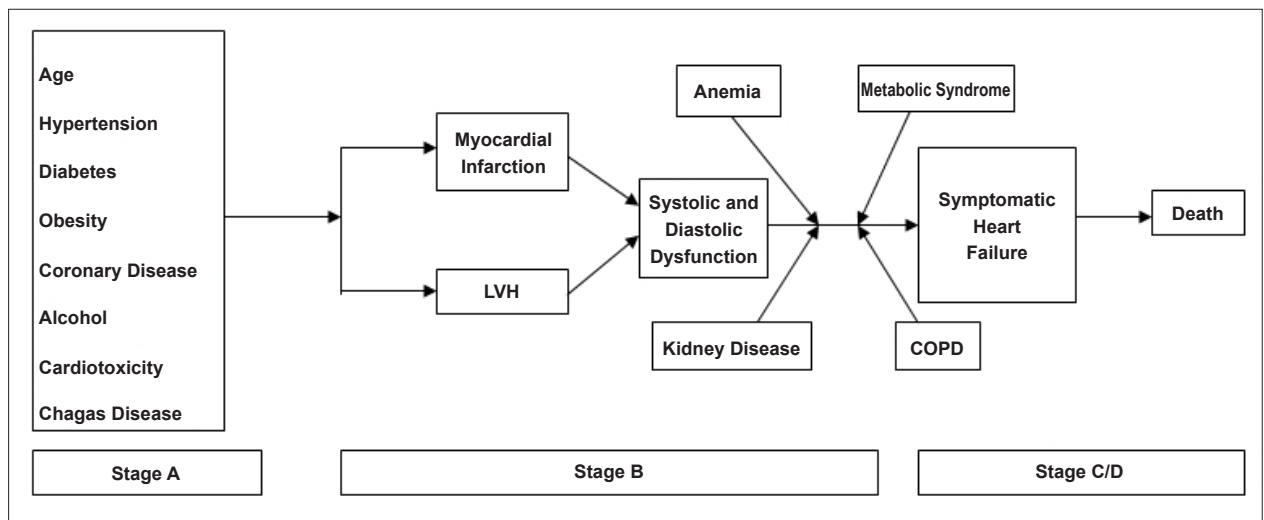


Figure 1 – HF progression and interaction of cardiac and noncardiac dysfunction. LVH - left ventricular hypertrophy, COPD - chronic obstructive pulmonary disease. Adapted from Baliga RR & Young JB; *Heart Failure Clin* 8 (2012) XI-XV.

Stage D

Stage D or the final stage consists of patients with refractory HF and severe exercise limitation (< 2 METs), in addition to multiple hospitalizations for decompensated HF⁹.

The pioneering study by Ammar et al² involving 2029 individuals randomly selected from the community (age > 45 years) tested the staging concept and showed that 32% of the patients were healthy, i.e., had no risk factors for HF (stage 0), 22% were in stage A, 34% in stage B and 12% were symptomatic (stages C and D). This study showed the association between different stages of HF and increased levels of B-type natriuretic peptides (BNPs) and five-year mortality (Figure 2)².

Risk factors and diastolic dysfunction

Different therapeutic intervention studies in HFNEF¹⁰⁻¹³ showed no effect on mortality reduction, which may mean that interventions should be targeted at the initial phases of HFNEF, as there is clinical and epidemiological evidence that intervention on the four main risk factors involved (diabetes, hypertension, obesity and coronary heart disease) can affect the cardiovascular continuum associated with HFNEF^{1,14}.

The presence of more than one of these associated factors is common in clinical practice and it is important to emphasize that aging exacerbates diastolic abnormalities in the presence of cardiovascular risk factors¹.

Diabetes

Diastolic dysfunction is observed in 40% of patients with diabetes and correlates with poor glycemic control¹⁵. Multiple mechanisms are involved in DD, such as abnormalities in the metabolism of adenosine triphosphate (ATP), impaired calcium transport, interstitial accumulation of advanced glycation end products, imbalance in collagen

synthesis and degradation, abnormal microvascular function, renin-angiotensin system activation, decreased adiponectin levels, and alterations in the metabolism of free fatty acids and glucose¹⁵.

The Framingham study was the first to demonstrate an increased risk for HF in diabetic patients. The incidence of HF in men and women was 2 to 5-fold higher in those with diabetes than in nondiabetics¹⁶. The LVDD is identified as the initial finding of diabetic cardiomyopathy. A study involving 86 young patients with type-2 diabetes (mean age of 43 years) without hypertension and with excellent glycemic control (mean glycated hemoglobin (HbA1c) of 6.5 mg/dL) showed the presence of asymptomatic DD in more than 40% of these patients¹⁷.

The Strong Heart Study¹⁸, which studied 2411 patients, found an association between type-2 diabetes and abnormal LV relaxation regardless of age, blood pressure, LV mass, and LV systolic function.

The DD findings in patients with diabetes are a strong marker for the progression to the symptomatic stages of HF and glycemic control and treatment of associated risk factors are strongly recommended in these patients⁴.

Arterial hypertension

Arterial hypertension is the most common risk factor for HF. The risk of developing HF in hypertensive patients, when compared with non-hypertensive patients, is approximately three-fold higher¹⁹.

Hypertension induces LV wall thickening in an attempt to normalize wall stress. This process results in increased LV mass, called concentric hypertrophy, which is defined by an increase in wall thickness without changes in LV shape²⁰.

Many stage-B hypertensive patients have evidence of LVH on echocardiography, causing changes in the pressure-volume curve, which decreases the atrioventricular pressure gradient

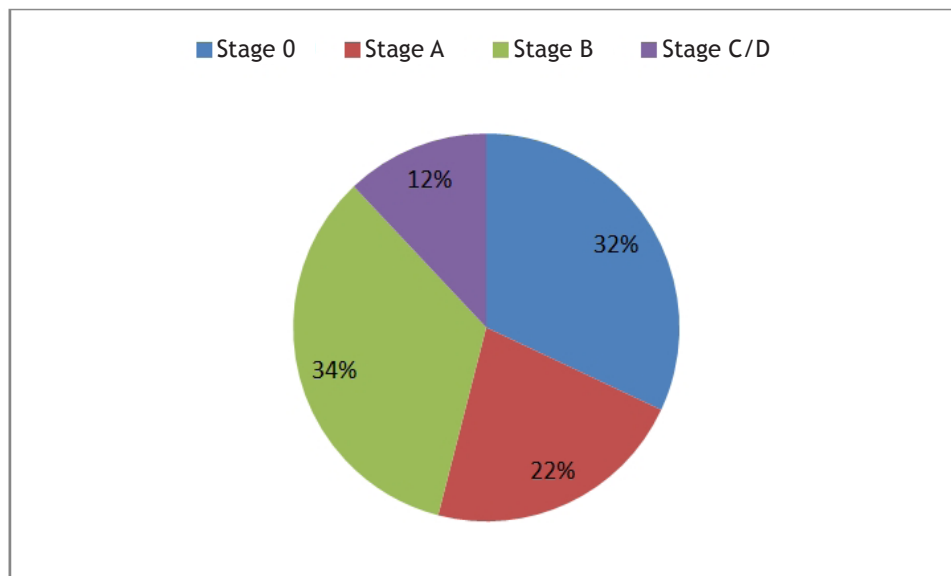


Figure 2 – Prevalence of HF stages. Adapted from Ammar KA; *Circulation*, 2007;115:1563-70.

and reduces LV filling²⁰. LVH in these patients is related to changes in the extracellular matrix and alterations in the matrix metalloproteinase (MMP) balance, with collagen accumulation in the extracellular space²¹. The pressure overload observed in these patients activates the intracardiac renin-angiotensin aldosterone system (RAAS) resulting in cardiac fibroblast growth and increased collagen, leading to reduced ventricular compliance^{22,23}.

Blood pressure control can reduce myocardial hypertrophy in hypertensive individuals and different antihypertensive medications show a greater or lesser degree of LVH reduction in patients with hypertension²⁴.

Obesity

Obesity has been considered a condition of chronic volume overload because the heart is forced to pump blood through a large deposit of fat tissue. It is also associated with a number of cardiovascular disorders mediated by neurohormonal, hemodynamic and inflammatory changes that lead to structural and functional cardiac alterations²⁵.

Visceral fat, which is metabolically active, can interfere with the increase in LV mass by secreting a variety of bioactive molecules, such as angiotensin II and inflammatory cytokines (adiponectin)²⁵. Hyperinsulinemia and increased insulin resistance, which are related to obesity, induce myocardial hypertrophy through the stimulating effect of cell growth caused by insulin and sympathetic activation.

In Mesa's study²⁵, LV mass and end-diastolic volume were positively associated with obesity in both genders after adjustment for other risk factors and it demonstrated that obesity is associated with LV concentric remodeling with no decrease in LVEF.

Obstructive sleep apnea is associated with obesity and may also contribute to the exacerbation of LVH by nocturnal hypertension, increased sympathetic tone and chronic hypoxemia²⁵.

Coronary atherosclerotic disease

Acute or chronic myocardial ischemia can lead to DD through worsening in calcium sequestration during active ventricular relaxation. Myocardial ischemia also worsens passive stiffness due to fibrosis formation²⁶.

The association between myocardial ischemia and DD is a common situation in clinical practice, and the treatment of ischemia is capable of improving the alterations in diastolic function, thus reducing the chance of development of HF in these patients².

Pathophysiology of diastolic dysfunction

LV cardiac function depends mainly on the two large myocardial layers – the fibers of the midwall, which are circumferentially oriented, and the subendocardial and epicardial fibers, which are longitudinally aligned from tip to base and have a double helix configuration (Figure 3). This distribution allows the LV twist-untwist mechanism during systole and diastole, thus leading to an interdependence between the phases of the cardiac cycle^{27,28}.

Diastole is the phase of the cardiac cycle during which the myocardium relaxes and the ventricles dilate, allowing their chambers to fill with blood with adequate filling pressures (12 mmHg at rest and up to 15 mmHg during exercise). The mechanical process of diastole can be divided into an active phase called relaxation and a passive phase called stiffness; the ventricular filling in its initial phase,

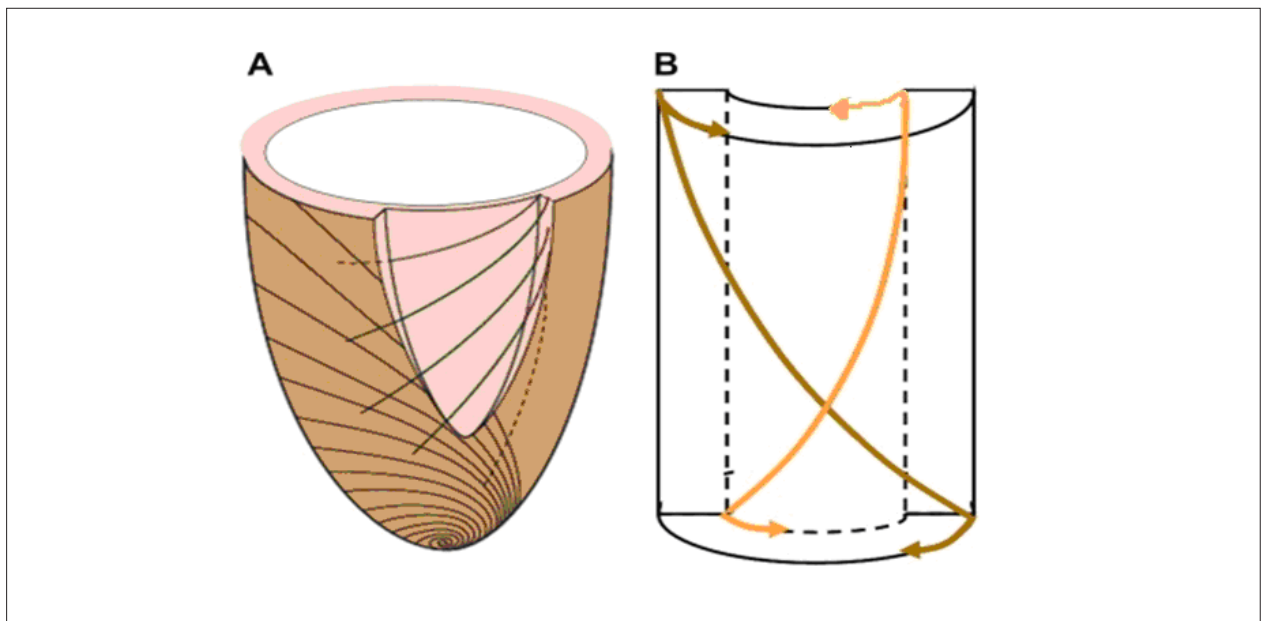


Figure 3 – Left Ventricular Architecture

Arrangement of fibers in a double helix - fiber orientation changes from the left in the subepicardium to the right in the subendocardium. The arrows represent the components that result from the force developed in each fiber of the subendocardium and subepicardium. Model proposed by Ingels et al. Adapted from Sengupta PP et al. *Heart Failure Clin* 2008;4:315-24.

which corresponds to 70% of the process, is carried out by the phenomenon of diastolic suction, which depends on relaxation²⁹.

Ventricular relaxation is a process with energy expenditure mainly regulated by the calcium pump of the sarcoplasmic reticulum (Serca). Reductions in Serca activity levels can reduce the removal of calcium from the cytosol, slowing ventricular relaxation. Myocardial ischemia is the main determinant for the slowing of relaxation by reducing ATP production¹⁵.

The increase in resting tension (F passive - passive force of cardiomyocytes at rest) is another important finding related to the presence of DD. Increase in F passive of cardiomyocytes has been attributed to the giant cytoskeletal protein called titin, which can be seen as a bi-directional spring that contracts at the beginning of relaxation and offers resistance to ventricular distension at end-diastole, thereby determining ventricular stiffness and diastolic function³⁰.

Titin is expressed as its two isoforms: N2B (more rigid form) and N2BA (more compliant), and the modulation of F passive can occur through changes in the expression of these isoforms and their phosphorylation state. Patients with HFNEF, for instance, have a lower N2BA/N2B association than that observed in patients with HF with reduced ejection fraction (HFREF); this increased expression of the N2B isoform can explain the increased ventricular stiffness (F passive) found in diastolic dysfunction³⁰.

Changes in the extracellular matrix structure promote increased LV stiffness. The changes observed in collagen regarding the quantity, geometry, distribution, formation of cross-bridges with glycation end-products and rates of

collagen types I and III lead to diastolic dysfunction^{31,32}. Changes in the levels of proteolytic enzymes such as MMPs, which control collagen degradation, also play an important role in the development of ventricular stiffness¹⁵.

DD then causes abnormalities in relaxation and/or stiffness of the ventricular chamber, which in turn will interfere with LV filling, causing the atrial contraction to have an important role in ventricular filling with the progression of DD. In more advanced forms of DD, there is an increase in the mean left atrial pressure, pulmonary venocapillary hypertension, elevated pulmonary artery systolic pressure and decreased diastolic reserve, which are caused mainly by changes in calcium regulation, cytoskeletal proteins (titin), extracellular matrix, myocyte hypertrophy and interstitial fibrosis^{33,34}.

The RAAS hyperactivation contributes to DD not only through the development of arterial hypertension, but also by impairment of ventricular relaxation, ventricular hypertrophy, fibrosis and vascular remodeling^{35,36}.

The arterial vascular function contributes significantly to diastolic abnormalities. Changes in the vascular wall associated with aging and arterial hypertension interfere with the afterload and the reflection of wave propagation on the arterial wall, increasing LV impedance, causing slowing of relaxation and myocardial hypertrophy¹⁵.

Inflammation and fibrosis play an important role in the development of cardiac structural changes that can cause the progress of HF stage A to B. In the myocardium, perivascular inflammation precedes reactive fibrosis, which is a key determinant of adverse prognosis and that has an effect on myocardial oxygen transport, on tissue

stiffness and is a risk factor for cardiac arrhythmias. The major consequence of the fibro-inflammatory response is ventricular dysfunction, which can be defined by Doppler echocardiography. However, because of the large number of individuals in stage B of HF, Doppler echocardiography becomes an expensive and difficult-to-perform procedure in daily practice. In these patients, the use of serum markers of inflammation that reflect structural and histopathological alterations in the heart is considered a new option³⁷.

Thus, the contemporary evaluation of diastolic function involves the integration of these pathophysiological concepts, with the use of measures that may reflect abnormalities of the active relaxation process (ATP consumption) and passive stiffness. This division is arbitrary because the structures and processes that change in the relaxation process can also result in stiffness abnormalities. However, the division is pragmatic and provides a rationale for the understanding of noninvasive methods that assess diastolic function¹⁴.

How to diagnose diastolic dysfunction

Clinical cardiologists often use Doppler echocardiography to assess patients with hypertension, diabetes and coronary disease, and the finding of isolated diastolic abnormalities is common in asymptomatic patients. Therefore it is essential to understand the new Doppler echocardiographic techniques such as tissue Doppler echocardiography (TDE) and Speckle Tracking, which allow a more complete quantification of diastolic function, as well as the new biomarkers that assess LV filling pressures, the presence of inflammation and fibrosis that are currently used to identify the presence of diastolic dysfunction.

Biomarkers

Biomarkers such as natriuretic peptides (NP) are important for the diagnosis and prognosis of HF as they are able to quickly assess LV dysfunction, being especially useful when there is limited access to echocardiography³⁸.

A well-established cutoff value for NP is yet to be defined for the diagnosis of DD. Ammar et al² observed, in 2029 patients, increasing BNP values with the progression of DD, but did not define the ideal point to characterize these patients in clinical practice².

A comparison of BNP levels and Doppler echocardiography data was performed in 294 patients with normal or abnormal LV diastolic function. It was observed that patients with DD had mean levels of BNP of 286 ± 31 pg/mL, whereas normal individuals had a mean of 33 ± 3 pg/mL. In this study, patients with abnormal diastolic function were subdivided into patients with impaired relaxation, pseudonormal and restrictive pattern with and without symptoms of HF, and it was demonstrated that BNP levels were very accurate to predict the restrictive pattern with an area under the ROC curve of 0.98 (95% CI: 0.95 to 0.97, $p < 0.001$). Patients with symptoms of HF had higher levels of BNP than asymptomatic patients³⁹.

In another study with 135 asymptomatic patients with hypertension, BNP levels were compared with Doppler echocardiographic DD indexes that included indexed LV mass, E/A ratio and isovolumetric relaxation time. In this study, the ROC curve showed an area under the curve (AUC) of 0.904 ($p < 0.01$), using a cutoff value > 40 pg / mL with specificity of 92% and sensitivity of 79% for BNP to diagnose LV diastolic pressure increase⁴⁰.

Biomarkers of fibrosis and inflammation bring new expectations for the assessment of the risk of developing HFNEF, as well as for its diagnosis. A recent study showed that HFNEF may be associated with increased levels of biomarkers of inflammation, such as interleukin 6 (IL - 6), interleukin 8 (IL-8) and monocyte chemoattractant protein 1 (MCP1), and of collagen metabolism such as type I collagen carboxyterminal telopeptide (ICTP), matrix metalloproteinase 2 (MMP2) and matrix metalloproteinase 9 (MMP9)⁴¹. In another study, a cutoff value of 1585 ng / mL of MMP2 showed sensitivity of 91% and specificity of 76% for predicting HFNEF⁴².

The finding of increased left atrial volume by Doppler echocardiography is an important piece of information in the evaluation of these patients, as it is related to the presence of LV diastolic dysfunction; the association between MMP9 and tissue inhibitor of matrix metalloproteinase-1 (TIMP1) was able to identify patients with increased left atrial volume, leading to the conclusion that biomarkers related to fibrosis may reflect chronic LV concentric remodeling⁴¹.

Echocardiography

Doppler echocardiography is the most widely used method for the assessment of diastolic dysfunction, but there are limitations caused by aging and technical aspects related to the test performance. Recently, the American and European Societies of Echocardiography developed a guideline for the evaluation of ventricular diastolic function⁷. In this document, the normal values of echocardiographic parameters are related to the age range (Table 1), giving emphasis to the new TDE techniques and diastolic stress for the correct characterization of DD⁷.

Doppler echocardiography is a method that can identify such early structural and functional cardiac alterations in patients at risk for the development of HF. Although the echocardiographic parameters used to assess diastolic function and LVEF are influenced by changes in preload and afterload, these indexes are widely used for the assessment of systolic and diastolic function⁴³.

Other parameters used in clinical practice to evaluate and characterize DD ventricular remodeling are indexed LV mass and indexed LAV⁴⁴.

The hemodynamic variables that help classify diastolic function can be obtained by Doppler echocardiography and TDE and include the measurement of transmitral flow (E/A ratio), isovolumetric relaxation time (IVRT), pulmonary vein flow, E-wave deceleration time (DT), pulmonary artery systolic pressure and the ratio between transmitral flow in early diastole with mitral annular velocity during early diastole (E/E' ratio) which, when

Table 1 – Normal values of diastolic parameters obtained by echocardiography

Measurement	16 – 20 yrs.	21 – 40 yrs.	41 – 60 yrs.	60 yrs.
IVRT (ms)	50 ± 9	67 ± 8	74 ± 7	87 ± 7
E/A ratio	1.88 ± 0.45	1.53 ± 0.40	1.28 ± 0.25	0.96 ± 0.18
DT (ms)	142 ± 19	166 ± 14	181 ± 19	200 ± 29
A (ms)	113 ± 17	127 ± 13	133 ± 13	138 ± 19
Septal E' (cm/s)	14.9 ± 2.4	15.5 ± 2.7	12.2 ± 2.3	10.4 ± 2.1
Lateral E' (cm/s)	20.6 ± 3.8	19.8 ± 2.9	16.1 ± 2.3	12.9 ± 3.5
Ar PV (cm/s)	16 ± 10	21 ± 8	23 ± 3	25 ± 9

IVRT : isovolumetric relaxation time; E : mitral flow peak at early diastole; A : mitral flow peak at the end diastole (atrial contraction); DT : deceleration time of E wave; E' : mitral annular velocity at early diastole; Ar : A-wave reversal velocity; PV : pulmonary vein.
Adapted from Nagueh SF et al.; JASE, 2009; 22;107-33.

> 15, have high specificity to characterize elevations of LV diastolic pressures.

DD can be classified into grades 1-4, and the main criteria to classify diastolic function by Doppler echocardiography and TDE are listed in Table 2.

Stress echocardiography

Many patients with DD are asymptomatic at rest and become dyspneic only on exertion, when LV filling pressures are elevated. Stress echocardiography is therefore a valuable tool with the potential to identify patients with impaired functional capacity and increased LV filling pressures⁴⁵⁻⁴⁷.

Stress Doppler echocardiography with the use of a supine cycle ergometer is technically feasible to demonstrate the changes in E/E' and variations of systolic pulmonary artery pressure with exercise; it also allows continuous imaging of the heart and provides LV filling measurements immediately in the recovery phase, which is important for the interpretation of alterations in diastolic function⁴⁷.

Elderly patients or patients with arterial hypertension show evidence of impaired diastolic function on Doppler echocardiography, but no symptoms at rest. Similarly, patients with HF in NYHA functional class I may be asymptomatic at rest, but will develop symptoms with exercise.

The E/E' ratio obtained at rest might not be sufficiently sensitive to identify patients with diastolic dysfunction in its initial phase, in which the filling pressures only increase with

exertion. Furthermore, exercise intolerance with increased E/E' at rest might not be specific enough, as dyspnea may be an angina equivalent and, in these cases, the use of stress echocardiography may help clarify the diagnosis⁴⁸⁻⁵².

Conclusion

Asymptomatic diastolic dysfunction is a common finding in ambulatory practice mainly in adults and particularly in association with risk factors, such as hypertension, diabetes, obesity and coronary heart disease, which increases the risk for the development of HF. However, its characterization in these patients is a complex process that requires, on the part of the clinical cardiologist, knowledge of new techniques for the systematic assessment of diastolic function with the use of Doppler echocardiography and biomarkers, both at rest and during exercise, as well as the clinical impact of DD on patient prognosis.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

Table 2 – Diastolic dysfunction classification (echocardiography)

	E/A ratio	Deceleration Time	E/E' ratio
Normal diastolic function	Between 0.75 and 1.50	> 140 ms	< 8
Diastolic Dysfunction grade I (relaxation impairment)	≤ 0.75	> 140 ms	< 8
Diastolic Dysfunction grade II (pseudonormal)	Between 0.75 and 1.50	> 140 ms	Between 8 and 15
Diastolic Dysfunction grade III (restrictive pattern)	> 1.50	< 140 ms	> 15

Adapted from Nagueh SF et al.; JASE, 2009; 22; 107-33.

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