Echocardiographic Assessment of Diastolic Heart Failure

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Abstract

A normal ejection fraction (EF) is present in >50% of patients with clinical features of heart failure (HF). This entity has been referred to as HF with normal EF (HFNEF), or diastolic HF. The underlying pathophysiology of HFNEF is still under debate and this is reflected in the unsatisfactory results of pharmacological treatment and in the high mortality and morbidity rates, which are similar to those for systolic HF. By providing evidence of left ventricular (LV) diastolic dysfunction in patients with clinical features of HF and normal LVEF, echocardiography, the most practical and widely available diagnostic modality, can offer two of the three current diagnostic criteria for HFNEF. Moreover, abnormalities in LV myocardial deformation and torsional dynamics at rest and during exercise were recently demonstrated in HFNEF patients by echocardiography. Newer echocardiographic parameters may improve the understanding of this complex entity, but further studies are needed before using them in clinical practice for the diagnostic and therapeutic approach of patients with HFNEF. This article discusses the current echocardiographic approach to the diagnosis of diastolic HF, as well as the potential role of newer echo indices and modalities.

Keywords

Echocardiography, heart failure, preserved ejection fraction, diastolic dysfunction

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Chronic heart failure (CHF) is a major cause of morbidity and mortality in the general population with a prevalence of 1–2% in developed countries, where it accounts for 1–2% of total healthcare resources. Therefore, the economic burden of HF may become unmanageable, indicating the need for cost-effective preventative strategies and treatments.[1] It has been acknowledged that about 50% of patients with clinical features of HF have a normal or near normal left ventricular ejection fraction (LVEF) or fractional shortening.[2,3] These patients are typically older and more likely to be women, with a higher likelihood of hypertension, LV hypertrophy, obesity, renal failure, anaemia and atrial fibrillation.[2,4] The pathophysiology underlying this entity, currently referred to as HF with normal EF (HFNEF), is under debate and the increasing interest in its diagnostic evaluation is related to the ominous prognosis of these patients, similar to that of patients with HF with reduced LVEF.[5,6] Uncertainty in this area is also reflected in the unsatisfactory results of pharmacological treatment. The high variability of criteria used for patient recruitment in HFNEF trials is one reason for the lack of evidence-based treatment for reducing cardiovascular mortality and morbidity in HFNEF compared with HF with reduced LVEF.[7]

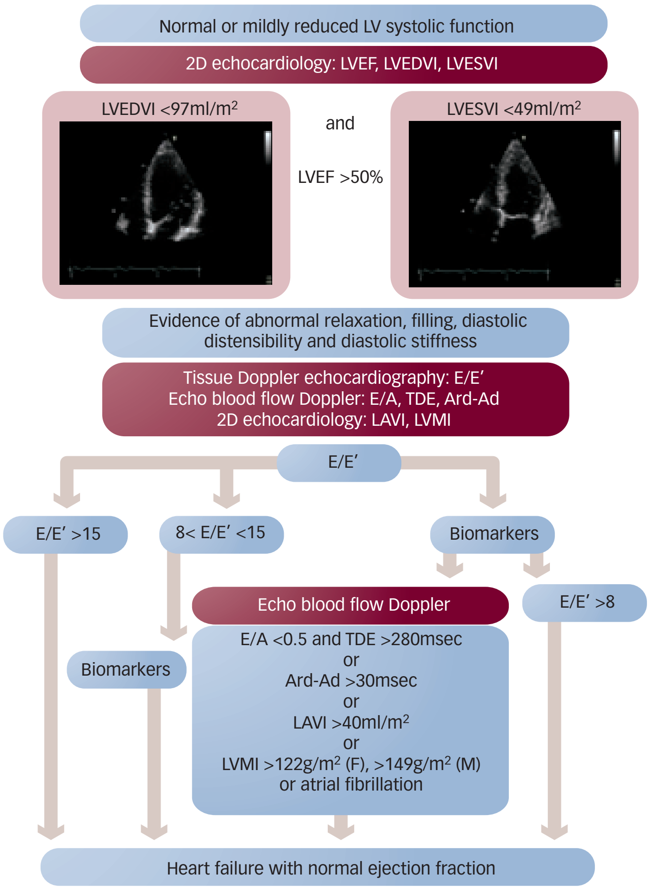
As initial studies in patients with HFNEF demonstrated abnormalities of active relaxation and passive stiffness leading to impaired diastolic filling in conjunction with normal global LV systolic function, HFNEF was originally referred to as diastolic HF. However, further studies showed that although LVEF is preserved, HFNEF patients have reduced mitral annular velocities[8,9] and depressed LV longitudinal and radial deformation.[10] These initial concepts underestimate the intimate link between systole and diastole and the impact of the previous systole on early diastolic filling.[11] Moreover, other abnormalities were emphasised in this setting: altered ventriculovascular coupling, chronotropic incompetence, left atrial (LA) dilation, volume overload and pulmonary arterial hypertension.[12–17]

In the recently updated European Society of Cardiology (ESC) guidelines,[18] the term 'HF with preserved left ventricular EF' was chosen to replace the term 'diastolic HF', and three obligatory conditions are proposed for the diagnosis of HFNEF: presence of signs or symptoms of congestive HF, presence of normal or mildly abnormal LV systolic function and evidence of diastolic LV dysfunction. By demonstrating intrinsic diastolic dysfunction in patients with clinical features of HF and normal LVEF, echocardiography, the most practical, available and reproducible diagnostic modality, can provide two out of the three diagnostic criteria for HFNEF. The role of echocardiography in the diagnostic algorithm of HFNEF, according to the most recent recommendations of the ESC, can be seen in *Figure 1*.

Echocardiographic Evidence of Normal or Mildly Reduced Left Ventricular Systolic Function

As an obligatory criterion, the diagnosis of HFNEF requires the presence of normal LVEF. However, the cut-off value for 'normal' LVEF

Figure 1: The Role of Echocardiography in the Diagnostic Algorhythm of Heart Failure with Normal Ejection Fraction[18]



A = late filling velocity; Ad = Awave duration; Ar = pulmonary vein reversed flow; biomarkers = N-terminal prohormone brain natriuretic peptide (NT-proBNP) >220pg/ml or BNP >200pg/ml; E = peak early filling velocity of transmitral flow; E′ = tissue Doppler early diastolic velocity; EDT = E wave deceleration time; F = female; LAVI = left atrial volume indexed to body surface area (BSA); LVEDVI = left ventricle end-diastolic indexed to BSA; LVEF = left ventricular ejection fraction; LVESVI = left ventricle end-systolic indexed to BSA; LVMI = left ventricular mass indexed to BSA; M = male.

Table 1: Echocardiographic Parameters Used to Assess Left Ventricle Relaxation, Compliance and Filling Pressure

LV Relaxation	LV Compliance	LV Filling Pressure in Patients with Normal LVEF
E	A wave duration	E/E′ ratio
E/A ratio	Ar duration	A-Ar duration
EDT	E/E′ ratio	E/A ratio change during Valsalva
IVRT	LA volume	A velocity change during Valsalva
Vp		E/Vp ratio
E′		LA volume
SE′		IVRT/TE-E′
SRE′		

A = late filling velocity; Ar = pulmonary vein reversed flow; E = peak early filling velocity of transmitral flow; E′ = tissue Doppler early diastolic velocity; EDT = E wave deceleration time; IVRT = isovolumetric relaxation time; LA = left atrium; SE′ = peak early diastolic strain; SRE′ = peak early diastolic strain rate; TE-E′ = time delay between onset of mitral E and onset of annular E′; Vp = flow propagation velocity.

changed along with the four sets of guidelines so far published for the diagnosis of HFNEF from 45% (used in the first set of guidelines provided by the Working Group on Myocardial Function of the ESC in 1998) to 50% (arbitrarily chosen in the last set of guidelines published by the Heart Failure and Echocardiography Associations of the ESC in 2007).[18–21] Another shortcoming of using LVEF as a measure of LV systolic function is the considerable load dependence in the predominantly elderly HFNEF population. Therefore, exclusion of significant LV enlargement (LV end-diastolic volume index <97ml/m^2 and LV end-systolic volume index <49ml/m^2) is also currently required to define 'normal or mildly reduced LV systolic function'. Both LVEF and LV volumes can be measured by echocardiography in accordance to the recent recommendations for cardiac chamber quantification issued by the American Society of Echocardiography and the European Association of Echocardiography.[22]

Nonetheless, the traditional view that systolic function is entirely normal in HFNEF patients has recently been challenged in studies using newer echocardiographic techniques, such as tissue Doppler imaging (TDI). While some investigators[23] have not found abnormal cardiac function in comparison with a control group, other studies[8,9,24–26] demonstrated that both peak annular systolic and peak early-diastolic velocities and the respective excursions that are measures of LV long-axis function were lower in patients with HFNEF than in age-matched controls. However, mitral annular and myocardial systolic velocities are influenced by tethering, translation and loading conditions, which must be considered when these measurements are used to assess cardiac systolic function.

Myocardial deformation measurements are not affected by tethering and translation, although they may still be affected by loading conditions. One recent study using 2D speckle tracking echocardiography demonstrated that in patients with diastolic heart failure (DHF), LV longitudinal and radial deformation are reduced compared with normal controls, while circumferential deformation is preserved.[27] Moreover, LV twist was assessed and was not significantly different in HFNEF patients from that in normal controls, but was significantly higher than that in systolic HF patients. Therefore, the authors suggested that preserved LV twist and circumferential strain may contribute to the normal LVEF in patients with HFNEF.

Evidence of Abnormal Left Ventricular Relaxation, Filling, Diastolic Distensibility and Diastolic Stiffness

Cardiac catheterisation using LV pressure–volume relations is considered to be the 'gold standard' for obtaining objective evidence of diastolic dysfunction, and throughout the previous three sets of guidelines[19–21] this was required to provide definite evidence of HFNEF. Nonetheless, invasive assessment of LV diastolic function (LVDF) as a routine procedure in patients with HF syndrome and normal LVEF is impractical, and different studies have found contradictory results in terms of the presence of increased stiffness and impaired relaxation in this setting.[28–31]

In the most recent set of recommendations, the diagnostic evidence of diastolic LV dysfunction can be obtained either invasively (LV end-diastolic pressure [LVEDP] >16mmHg or mean pulmonary capillary wedge pressure [PCWP] >12mmHg) or non-invasively by tissue Doppler echocardiography complemented in special situations with data from 2D or blood flow Doppler echocardiography and/or plasma levels of natriuretic peptides.[18] Comprehensive 2D and Doppler echocardiography remains the most widely available non-invasive clinical tool able to assess abnormal LV relaxation, changes in compliance or stiffness and the level of LV filling pressure (LVFP), thus providing a clinically relevant assessment of diastolic function (see *Table 1*).[32,33]

Blood-flow Doppler Echocardiography

Because of their load dependence, conventional Doppler parameters derived from mitral inflow and pulmonary venous flow have clear limitations in terms of the assessment of LVDF. Therefore, these indices are no longer recommended as a first-line diagnostic approach for LV diastolic dysfunction assessment and need to be used in combination with other methods.

Mitral inflow Doppler has been used most frequently for the assessment of LVDF because it is easy to acquire, feasible and reproducible. Isovolumic LV relaxation time (IVRT), the ratio of peak early (E) to peak atrial (A) Doppler mitral flow velocity (E/A) and deceleration time of early mitral valve flow velocity (EDT) were originally used to characterise LVDF and LVFP. Deceleration time of the E-wave is a very good predictor of elevated PCWP in patients with poor LV systolic function in both sinus rhythm and in atrial fibrillation.[34,35] The best cut-off for EDT in this setting was 120msec in both studies; however, when LVEF is normal, there is no correlation between EDT and LVFP.[36]

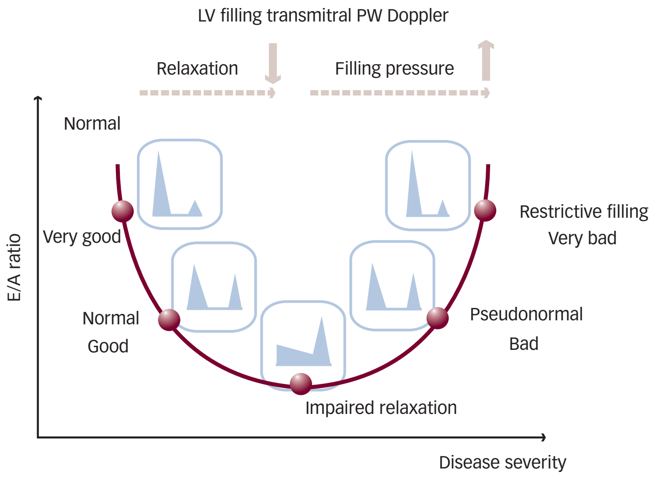
The opposing effects of impaired relaxation and increased filling pressure on mitral flow pattern (E/A) confound its interpretation. Mitral inflow has a parabolic distribution during progression from normal function to severe diastolic dysfunction, describing a U-shaped curve (see *Figure 2*).

Identifying whether a patient is on the left ('good') side or on the right ('bad') side of the curve is sometimes not possible unless another method is used in addition. The temporary decrease in venous return during the Valsalva manoeuvre allows the unmasking of an impaired relaxation pattern in patients with pseudonormalisation. The initial study concentrated on the E/A ratio behaviour during Valsalva showing that reversal of the E/A ratio from >1 to <1 identifies patients with increased LVFP.[37] Although it is generally assumed that an E/A ratio <1 implies normal LVFP this is not always the case and one can have elevated LVFP even with an E/A ratio <1. This can be unmasked by assessing the change in A-wave velocity during a standardised Valsalva manoeuvre.[38]

Pulmonary vein flow parameters are more difficult to record than mitral flow parameters and have the same drawback of load dependence. Forward flow occurs during ventricular systole (S-wave) and diastole (D-wave), and retrograde flow may occur with atrial systole (Ar-wave). Measurements of pulmonary venous flow waveforms include peak systolic (S) velocity, peak diastolic (D) velocity, the S/D ratio, systolic filling fraction and the peak velocity and duration of the Ar-wave in late diastole.

It was demonstrated that a systolic fraction of <40% reliably predicts a PCWP >18mmHg in patients with LV systolic dysfunction.[39–41] However, the correlation is much weaker in patients with normal LVEF. With atrial contraction blood flows forwards in the LV and backwards in the pulmonary veins. As LVEDP increases, the duration of the Ar-wave increases. Thus, the time difference between Ar duration measured at pulmonary vein flow and A-wave duration measured at mitral inflow has a direct correlation with LVEDP. When this time difference is >30msec it accurately predicts an increased LVEDP.[42] The correlation is independent of LVEF and is also age independent.

Figure 2: Changes in Doppler Left Ventricular Filling Pattern with Progression of Diastolic Dysfunction



A = late filling velocity; E = peak early-filling velocity of transmitral flow; LV = left ventricle; PW = pulsed-wave Doppler echocardiography.

The velocity of flow propagation into the LV (Vp), assessed by colour M-mode echocardiography has a significant inverse correlation with the time constant of LV relaxation (τ) and therefore represents an index of LV relaxation.[43] Several studies have shown that Vp is not significantly affected by pre-load alterations and LV relaxation rate seems to represent its main determinant. As mitral E-wave has a direct relation with LVFP and an inverse one with τ, while Vp is inversely related to τ and not significantly influenced by LVFP, combining these two parameters would give a ratio (E/Vp) directly related to LVFP. This hypothesis was tested and validated by Garcia et al., who found a significant correlation between the E/Vp ratio and PCWP.[44] However, Vp can be falsely high in small ventricles and has a somewhat lower accuracy in patients with normal LVEF. Moreover, Vp is sometimes difficult to measure (curvilinear slope) and the interobserver variability is high (especially when Vp is high).

For all the above-mentioned limitations, a diagnosis of HFNEF based on Doppler echocardiography alone is not recommended in the current guidelines.[18]

Tissue Doppler Echocardiography

Currently, the most sensitive and widely available echocardiographic technique for the assessment of LVDF is TDI. Tissue Doppler parameters have given a better insight into the mechanics of HFNEF and a non-invasive method for assessing both LV relaxation and LVFPs.

The early and late diastolic mitral annular velocities (E', A'), the E'/A' ratio, the mitral inflow E velocity to tissue Doppler E' (E/E') ratio and the time interval between the onset of QRS complex and the onset of mitral E velocity subtracted from the time interval between the onset of QRS and E' onset (TE-E') can be measured/calculated for the assessment of LVDF by TDI.

Kasner et al.[45] compared various conventional and tissue Doppler echocardiographic indices with pressure–volume loop analysis to assess their accuracy in detecting LV diastolic dysfunction in patients with HFNEF in whom the diagnosis of diastolic dysfunction was confirmed by conductance catheter data. Of all echocardiographic parameters investigated, the E/E′ ratio (with E′ measured at the lateral mitral annulus) was identified as the best index to detect diastolic dysfunction in this setting.

Whereas the E/A ratio of the mitral inflow exhibits a U-shaped relationship with the increase in LVFP, tissue Doppler-derived mitral annulus velocities continuously decline with the progression of LV diastolic dysfunction. As a consequence, E′ decreases and the E/E′ ratio increases linearly in a monotonous fashion with worsening of LV diastolic dysfunction.[46]

Nonetheless, it should be noted that the correlation between E/E′ (with E′ measured at the medial mitral annulus) and LVFP described by Ommen et al.[47] in HF patients, was higher for patients with depressed LVEF (<50%, r = 0.60) than for those with preserved LVEF (>50%, r=0.47). However, all patients with an E/E′ ratio >15 had a mean diastolic LV pressure >12mmHg and the ratio E/E′ is therefore considered diagnostic evidence of LV diastolic dysfunction if E/E′ >15, and diagnostic evidence of absence of HFNEF if E/E′<8 in a patient with typical symptoms and signs of HF and LVEF >50%. The proposed E/E′ cut-off values are based on pulsed Doppler measurements and on averaged velocities of lateral and septal mitral annulus.[18]

However, an E/E′ ratio in the 'grey zone' between eight and 15 was associated with a very wide range of mean LV diastolic pressures;[47] therefore, in a patient with suspected HFNEF and an E/E′ ratio between eight and 15 the following should also be evaluated in order to confirm HFNEF: the combined change in E/A ratio with Valsalva manoeuvre (decrease by >50%) and DT (duration >280ms), the duration of the atrial reversal signal in pulmonary venous flow (duration >30msec longer that mitral A), LV mass index (LVMI) (>122g/m^2 for women and 149g/m^2 for men), left atrial volume index (LAVI) (>40ml/m^2).

LAVI represents a relatively independent pre-load index of chronically increased LVFP.[48] Moreover, LA size emerged as an independent outcome predictor in patients with symptomatic stable CHF and preserved LVEF.[49,50]

Therefore, in the absence of significant mitral valve disease or atrial fibrillation, an elevated LAVI is a reliable marker for the diagnosis of HFNEF in patients with suspected history of HF but preserved LVEF. Currently, a LAVI >40ml/m^2 is sufficient to provide evidence of LV diastolic dysfunction when E/E′ is inconclusive[8–15] while LAVI <29ml/m^2 is a pre-requisite to exclude HFNEF.[18] The two cut-off values represent the lower values for mildly and severely enlarged LAV, according to the recent recommendations for cardiac chamber quantification.[22]

LV hypertrophy is a common feature in patients with HFNEF and the most recent consensus document considers an LVMI >122g/m^2 (women) or an LV mass index >149g/m^2 (men) sufficient evidence for the diagnosis of HFNEF when TDI yields inconclusive results or when plasma levels of natriuretic peptides are elevated.

In a study comparing echocardiographic features of patients with hypertension and HFNEF with hypertensives without HF, Melenovski et al.[51] found that the product of LV mass index and left atrial volume had the highest accuracy for the prediction of HFNEF. Therefore, the presence of LV hypertrophy (LVH) and an increased LAVI in a breathless patient strongly increases the likelihood of HFNEF.

The presence of atrial fibrillation or increased values of cardiac natriuretic peptides (plasma N-terminal prohormone brain natriuretic peptide [NT-proBNP] >220pg/ml or BNP >200pg/ml) are also arguments for HFNEF in patients with HF symptoms and E/E′ ratio between eight and 15.

Newer Indices

In the presence of impaired LV relaxation and irrespective of LA pressure, the E′ velocity is reduced and delayed. On the other hand, mitral E velocity occurs earlier with increased LVFP. Accordingly, the time interval between the onset of E and that of E′ is prolonged with diastolic dysfunction. The ratio between IVRT and the time delay (TE-E′) between onset of mitral E and onset of annular E′ (IVRT/TE-E′ ratio) was proposed for the assessment of LVFP in special situations and has good accuracy for detecting LV diastolic dysfunction in patients with normal EF and equivocal values of E/E′ (IVRT/TE-E′ ratio <2).[52]

Reduced early diastolic strain rate (SR) is observed in patients with hypertension and diastolic dysfunction. As global longitudinal SR during IVRT (GSRIVR) can be easily assessed by speckle-tracking echocardiography, a new index was derived: the ratio of mitral E velocity to GSRIVR (E/GSRIVR).[53] The new index effectively predicts LVFP and has the advantages of myocardial deformation over velocity measurements. It is most useful when the E/E′ ratio is inconclusive and is more accurate than E/E′ in patients with normal EF and those with regional LV dysfunction.

Apart from different technical requirements, a major disadvantage of the new indices is the longer time needed for analysis compared with E′, which limits their clinical use. However, they can be used and provide useful information in special situations.

New Insights into the Pathophysiology of Heart Failure with Normal Ejection Fraction

Left Ventricular Torsional Dynamics

LV torsion generates energy during systole, which is released during early diastole. Diastolic LV recoil determines a negative intraventricular pressure gradient or suction important to maintain LV filling at normal pressures. With the development of speckle-tracking echocardiography, the assessment of LV rotation and torsion becomes widely accessible beyond the research field. With systolic dysfunction, twist is reduced and recoil is delayed and reduced, which adversely affects LV filling. Few studies have been published on LV torsional dynamics in patients with normal EF. The LV untwisting rate was reduced and delayed in 49 patients with LV hypertrophy and normal EF and was worst in patients with the most extensive hypertrophy.[54] However, another study with speckle tracking noted that the untwisting rate is increased with early-stage diastolic dysfunction and becomes normal with more advanced disease, except in patients with cardiac amyloidosis, in whom it was significantly reduced.[55]

Stress Testing

Assessment of LV function during exercise seems to be intuitive in HFNEF patients as their symptoms occur mainly with exertion. Patients with HFNEF have limitations in increasing their LV stroke work to meet the metabolic demand at exercise due to dynamic impairment of LV active relaxation and contraction. An increase of LVFP with exertion is needed to maintain adequate LV filling and stroke volume.

Recent studies[56] have shown a variety of abnormalities of systolic and diastolic function on exercise in patients with HFNEF: reduced myocardial systolic strain, reduced ventricular systolic apical rotation at rest (which fails to increase normally on exercise), reduced mitral annular motion in systole and diastole and delayed ventricular untwisting associated with reduced LV suction. Mean mitral annular systolic and diastolic velocities, systolic LV rotation and early diastolic untwist on exercise correlated with peak VO_2 max. Impaired atrial function on exercise may also contribute to breathlessness.

Ventricular–Arterial Coupling

It has been suggested that combined ventricular–arterial stiffening contributes to the syndrome of HFNEF, and several studies demonstrated that both effective arterial elastance (Ea) and LV end-systolic elastance (Es) increase, and the Ea/Es ratio was similar in HFNEF patients compared with hypertensive patients without HF.[29] Therefore, the consensus from the published literature supports the notion that abnormal ventricular-arterial coupling at rest is not the culprit for developing DHF. However, as one study noted a reduced vasodilator reserve with exercise, further studies are needed during effort for reliable conclusions. If and how echocardiography can find a place in this scenario remains to be seen.[57,58]

Conclusion

In summary, in patients with clinical features of HF, a normal LVEF on echocardiography can suggest the presence of HFNEF. Furthermore, echocardiographic evidence of LV hypertrophy, left atrial dilation, abnormal LV relaxation, filling, diastolic distensibility and diastolic stiffness can confirm the diagnosis, give an insight into the pathophysiology of specific cases, monitor the response to treatment and assess prognosis. Newer echocardiographic parameters may improve the understanding of this complex entity, but further studies are needed before using them in clinical practice for the diagnostic and therapeutic approach of patients with HFNEF. ■

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