

How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology

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Received 28 November 2006; accepted 23 February 2007; online publish-ahead-of-print 11 April 2007

See page 2421 for the editorial comment on this article (doi:10.1093/eurheartj/ehm412)

KEYWORDS

Heart failure;
Diastole;
Tissue doppler;
Natriuretic peptides;
Ejection fraction

Diastolic heart failure (DHF) currently accounts for more than 50% of all heart failure patients. DHF is also referred to as heart failure with normal left ventricular (LV) ejection fraction (HFNEF) to indicate that HFNEF could be a precursor of heart failure with reduced LVEF. Because of improved cardiac imaging and because of widespread clinical use of plasma levels of natriuretic peptides, diagnostic criteria for HFNEF needed to be updated. The diagnosis of HFNEF requires the following conditions to be satisfied: (i) signs or symptoms of heart failure; (ii) normal or mildly abnormal systolic LV function; (iii) evidence of diastolic LV dysfunction. Normal or mildly abnormal systolic LV function implies both an LVEF > 50% and an LV end-diastolic volume index (LVEDVI) < 97 mL/m². Diagnostic evidence of diastolic LV dysfunction can be obtained invasively (LV end-diastolic pressure > 16 mmHg or mean pulmonary capillary wedge pressure > 12 mmHg) or non-invasively by tissue Doppler (TD) ($E/E' > 15$). If TD yields an E/E' ratio suggestive of diastolic LV dysfunction ($15 > E/E' > 8$), additional non-invasive investigations are required for diagnostic evidence of diastolic LV dysfunction. These can consist of blood flow Doppler of mitral valve or pulmonary veins, echo measures of LV mass index or left atrial volume index, electrocardiographic evidence of atrial fibrillation, or plasma levels of natriuretic peptides. If plasma levels of natriuretic peptides are elevated, diagnostic evidence of diastolic LV dysfunction also requires additional non-invasive investigations such as TD, blood flow Doppler of mitral valve or pulmonary veins, echo measures of LV mass index or left atrial volume index, or electrocardiographic evidence of atrial fibrillation. A similar strategy with focus on a high negative predictive value of successive investigations is proposed for the exclusion of HFNEF in patients with breathlessness and no signs of congestion.

The updated strategies for the diagnosis and exclusion of HFNEF are useful not only for individual patient management but also for patient recruitment in future clinical trials exploring therapies for HFNEF.

Introduction

In 1998, the European Study Group on Diastolic Heart Failure published a set of criteria for the diagnosis of diastolic heart

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failure (DHF).¹ At that time, DHF was presumed to account for approximately one-third of all patients with heart failure and its natural history was considered to be more benign than systolic heart failure (SHF) with a lower mortality and morbidity rate.²⁻⁷ Over the last two decades, these perspectives have changed substantially with an increase in the prevalence of DHF from 38 to 54% of all heart failure cases.^{8,9} Moreover, the prognosis of patients suffering from DHF is as ominous as the prognosis of patients suffering of SHF.¹⁰⁻¹⁵ Predisposing conditions for DHF are older age, female gender, diabetes and obesity, arterial hypertension, and left ventricular (LV) hypertrophy.^{16,17} Even following a myocardial infarction, many elderly patients still present with DHF.¹⁸

Because of this epidemiological evolution towards a predominance of DHF in western populations, a re-appraisal of the original set of criteria for the diagnosis of DHF is required. This re-appraisal should address the critiques, which have been phrased concerning the original set of criteria, and should accommodate new pathophysiological insights, modern cardiac imaging technology, and the widespread clinical use of heart failure biomarkers.

Heart failure with normal left ventricular ejection fraction or diastolic heart failure

Heart failure with normal LV ejection fraction (HFNEF) is frequently referred to as DHF because of the presence of diastolic LV dysfunction evident from slow LV relaxation and increased LV stiffness.¹⁹ Diastolic LV dysfunction, however, is not unique to patients with DHF but also occurs in heart failure patients with SHF, and in this last group, it even correlates better with symptoms than LVEF.^{20,21} Furthermore, although global LV systolic performance is preserved,²² HFNEF patients have reduced myocardial tissue Doppler (TD) velocities²³⁻²⁸ and abnormal ventriculo-arterial coupling.^{29,30} On the basis of these observations, the distinction between DHF and SHF is challenged,^{31,32} and heart failure is considered to be a single syndrome characterized by a progressive decline in systolic performance appreciated better by TD velocities than by LVEF (Figure 1). The concept of a single syndrome is reinforced by the unimodal distribution of LVEF in large heart failure trials that recruited both patients with reduced and normal LVEF.³³ According to the single syndrome hypothesis, diastolic LV dysfunction is of similar origin in all heart failure patients and consists primarily of increased interstitial deposition of collagen and modified matricellular proteins.^{34,35} In the absence of a discriminatory role for diastolic LV dysfunction, patients presenting with heart failure without depressed LVEF are better characterized by the term 'HFNEF'³⁶ or the term 'heart failure with preserved left ventricular ejection fraction',³⁷ than by the term 'DHF'.

In the single syndrome hypothesis, the major difference between the two ends of the spectrum [HFNEF and heart failure with reduced LVEF (HFREF)] is the degree of LV ventricular dilatation and shape change or LV remodelling.³⁶ Thus, it is postulated that there is an evolution or progression from HFNEF to HFREF with the onset of LV remodelling. LV volumes measured by three-dimensional echocardiography are indeed already increased in HFNEF patients compared with normal subjects after matching for

age, gender, and body size suggesting that early stages of remodelling are already occurring in HFNEF.³⁸ Such an evolution has also been observed in hypertensive heart disease,³⁹⁻⁴² especially in African⁴³⁻⁴⁵ and Asian^{46,47} populations. In many of these studies, interval clinical events, such as myocardial infarction, were, however, not reported or significantly higher³⁹ in the patients, who subsequently developed a depressed LVEF. An occasional (3.5%) evolution to eccentric LV remodelling is also observed in patients with hypertrophic cardiomyopathy,⁴⁸ a disease characterized in its initial stages by concentric LV remodelling and prominent diastolic LV dysfunction. A small, serial echocardiographic study of HFNEF patients observed in one-fifth of the patients a decline in LVEF below 45% after a 3-month follow-up period.⁴⁹ Larger follow-up studies, preferably with sequential coronary angiograms, are required to investigate whether HFNEF is indeed a precursor stage to HFREF and to identify patient characteristics, such as female gender,⁵⁰ regular aerobic exercise,⁵¹ chronic alcohol ingestion,⁵² genetic background,⁵³ and comorbidities, such as diabetes,^{54,55} that may prevent or retard the evolution from HFNEF to HFREF.

Structural, functional, and molecular biological arguments support the theory that clinical heart failure presents and evolves not as a single syndrome but as two syndromes, one with depressed LVEF and other with normal LVEF and specific mechanisms responsible for diastolic LV dysfunction (Figure 1). Patients with SHF have eccentric LV hypertrophy in contrast to patients with DHF, who have concentric LV hypertrophy^{56,57} as evident from the numerous studies, which reported a high LV wall mass-volume ratio in DHF and a low LV wall mass-volume ratio in SHF.⁵⁸⁻⁶¹ Differences between DHF and SHF have also been reported at the ultrastructural level:⁶¹ patients with DHF have a 50% larger cardiomyocyte diameter than patients with SHF and myofibrillar density is also higher in the myocardium of patients with DHF. Cardiomyocytes isolated from biopsies of DHF and SHF patients also differ functionally. *In vitro* cardiomyocyte resting tension is higher in DHF,⁶² and together with collagen volume fraction, this higher cardiomyocyte resting tension significantly contributes to *in vivo* myocardial stiffness. The cytoskeletal protein titin⁶³ likely accounts for this higher resting tension. Titin functions as a bidirectional spring responsible for early diastolic LV recoil⁶⁴ and late diastolic resistance to stretch.^{65,66} Isoform expression of titin differs in patients with SHF and DHF: in patients with SHF, titin isoform expression shifts towards the more compliant isoform,⁶⁷⁻⁶⁹ whereas in patients with DHF the shift is towards the less compliant isoform.⁶¹ Apart from distinct isoforms of cytoskeletal proteins in the LV myocardium of patients with SHF and DHF, expression patterns of matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs) also differ. In the myocardium of hypertensive patients with DHF⁷⁰ and in aortic stenosis,⁷¹ there is a decreased matrix degradation because of downregulation of MMPs and upregulation of TIMPs, whereas in dilated cardiomyopathy, there is an increased matrix degradation because of upregulation of MMPs.⁷² In patients with aortic stenosis, who develop a depressed LVEF, this balance between proteolysis and antiproteolysis shifts⁷³ and important cardiomyocyte degeneration occurs.⁷⁴ Furthermore, in trabeculae of explanted human hearts, alterations of calcium handling have been observed which selectively

Heart failure presents and evolves as a single syndrome with HFNEF preceding HFREF	Heart failure presents and evolves as two syndromes: one with concentric LV remodelling and mainly diastolic LV dysfunction (DHF) and other with eccentric LV remodelling and combined systolo-diastolic dysfunction (SHF)
<p>Arguments</p> <p>Unimodal distribution of LVEF in HF trials³³ Continuous decline of TD LV long axis shortening velocity (S) from HFNEF to HFREF^{23–28} Progression to eccentric LV remodeling in hypertensive heart disease,^{39–42} especially in African^{43–45} and Asian populations,^{46,47} Progression to eccentric LV remodelling in end-stage hypertrophic cardiomyopathy⁴⁸</p>	<p>Arguments</p> <p>Presence of concentric LV remodelling in DHF and eccentric LV remodeling in SHF^{56–61} Distinct myocardial ultrastructure with prominent cardiomyocyte hypertrophy in DHF and reduced myofilamentary density in SHF⁶¹ Higher <i>in vitro</i> cardiomyocyte resting tension in DHF⁶² Distinct isoform shifts of the cytoskeletal protein titin^{61,67–69} Distinct expression pattern of matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases^{70–72} Prognostic improvement under current heart failure therapy in SHF but not in DHF^{8,82}</p>

Figure 1 Heart failure: a single or two syndromes? Listing of arguments favouring heart failure to be a single or two distinct syndromes.

disturb relaxation and diastole.^{75–81} These alterations may also be more prominent in DHF. Finally, in clinical outcome trials with pharmacological intervention, patients with DHF have not responded as convincingly as patients with SHF,^{8,82} which suggests that different pathophysiological mechanisms may be operative.

For clarity, the terms HFNEF and HFREF will be used throughout the remaining part of this manuscript and, respectively, replace the terms DHF and SHF. This use of HFNEF and HFREF does not imply that the issue of heart failure presenting as one or two syndromes is resolved.

Three obligatory conditions for heart failure with normal left ventricular ejection fraction

Three obligatory conditions need to be satisfied for the diagnosis of HFNEF (*Figure 2*): (i) presence of signs or symptoms of congestive heart failure; (ii) presence of normal or mildly abnormal LV systolic function, and (iii) evidence of diastolic LV dysfunction.

Signs or symptoms of congestive heart failure

Signs or symptoms of congestive heart failure include lung crepitations, pulmonary oedema, ankle swelling, hepatomegaly, dyspnoea on exertion, and fatigue. Different modes of presentation of dyspnea (i.e. effort related or nocturnal) need to be distinguished.⁸³ In HFNEF, breathlessness is frequently the earliest symptom due to pulmonary congestion,⁸⁴ whereas muscle fatigue is more prominent in HFREF due to reduced cardiac output, impairment of vasodilator capacity, and abnormalities of skeletal muscle metabolism. Breathlessness is especially difficult to interpret in elderly and in obese, who represent a large proportion of the HFNEF population. Objective evidence of reduced exercise performance can be provided by metabolic exercise testing with measurement of peak exercise oxygen consumption (VO_{2max})^{85–89} (reduced $VO_{2max} < 25$ mL/kg/min; low $VO_{2max} < 14$ mL/kg/min) or by the 6 min walking test^{90–92} (marked limitation < 300 m). In the hospital setting, signs and symptoms of congestive heart failure are usually simultaneously present as many patients are

hospitalized for decompensated heart failure or episodes of pulmonary oedema. In the outpatient setting, however, complaints of breathlessness are frequently reported without detectable signs of congestion. 'Presence of signs or symptoms of congestive heart failure' as the first criterion for the diagnosis of HFNEF is therefore preferable to 'presence of signs and symptoms of congestive heart failure'. The latter criterion is used by the National Heart, Lung, and Blood Institute's Framingham Heart Study.⁹³

Normal or mildly abnormal systolic left ventricular function

The presence of normal or mildly abnormal systolic LV function constitutes the second criterion for the diagnosis of HFNEF. Since LVEF of heart failure patients presents as a unimodal distribution, the choice of a specific cut-off value remains arbitrary.³³ The National Heart, Lung, and Blood Institute's Framingham Heart Study⁹³ used an LVEF $> 50\%$ as cut-off for normal or mildly abnormal systolic LV function and this cut-off value has meanwhile been used or proposed by other investigators.^{60,94} In the present consensus document, an LVEF $> 50\%$ is also considered consistent with the presence of normal or mildly abnormal systolic LV function. LVEF needs to be assessed in accordance to the recent recommendations for cardiac chamber quantification of the American Society of Echocardiography and the European Association of Echocardiography.⁹⁵ It is of importance to note that in HFNEF reduced long-axis shortening is frequently compensated for by increased short-axis shortening.

As already demonstrated by Frank, Starling, and Wiggers and later re-appraised,⁹⁶ LV relaxation depends on end-systolic load and volume.^{97–101} The criterion of 'presence of normal or mildly abnormal LV function' therefore needs to be implemented with measures of LV volumes. To exclude significant LV enlargement,⁹⁵ LVEDVI and LV end-systolic volume index cannot exceed 97 mL/m² and 49 mL/m², respectively.

Another concern related to establishing normal or mildly abnormal LV function deals with the time elapsed between the clinical heart failure episode and the procurement of

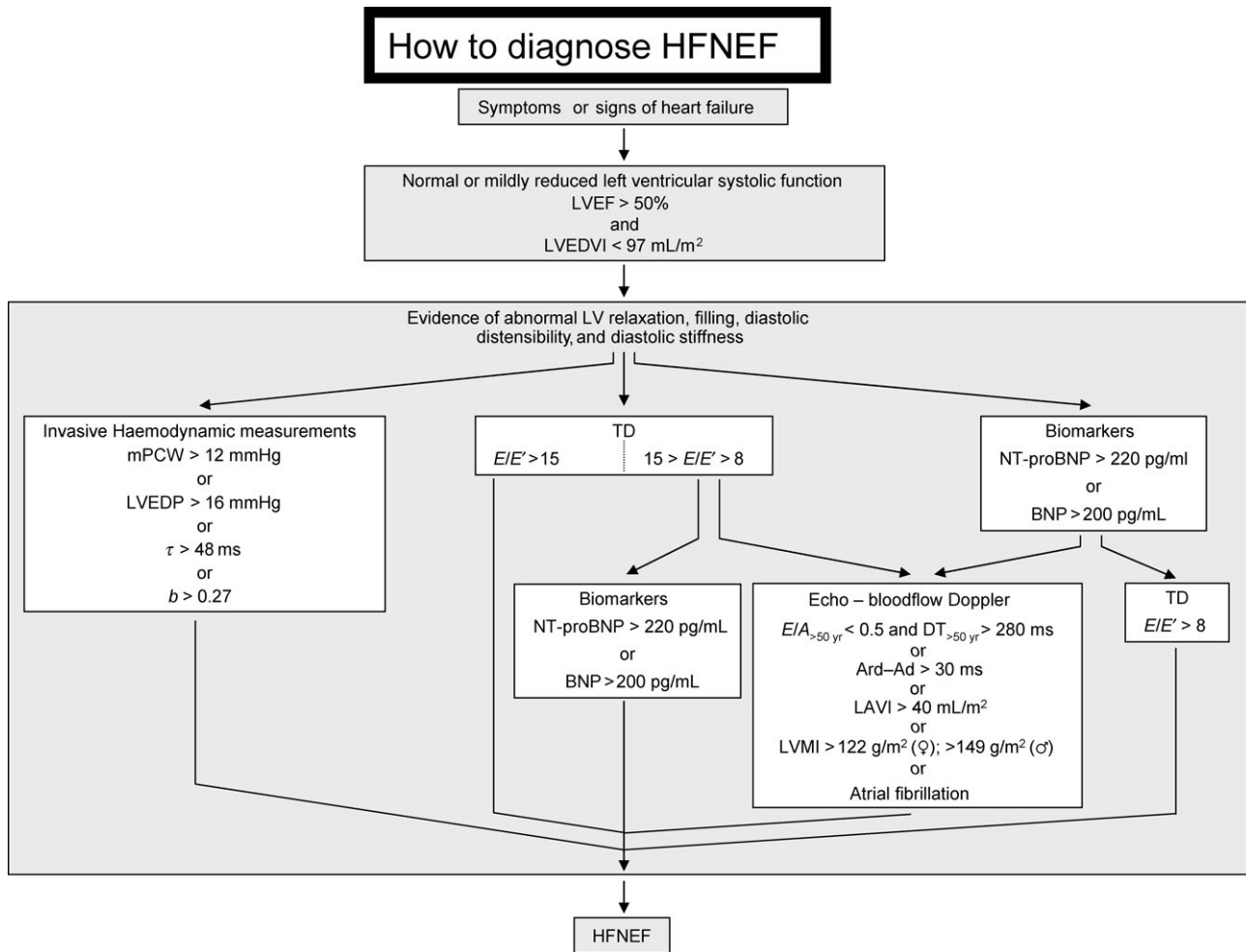


Figure 2 Diagnostic flowchart on 'How to diagnose HFNEF' in a patient suspected of HFNEF. LVEDVI, left ventricular end-diastolic volume index; mPCW, mean pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; τ , time constant of left ventricular relaxation; b , constant of left ventricular chamber stiffness; TD, tissue Doppler; E , early mitral valve flow velocity; E' , early TD lengthening velocity; NT-proBNP, N-terminal-pro brain natriuretic peptide; BNP, brain natriuretic peptide; E/A , ratio of early (E) to late (A) mitral valve flow velocity; DT, deceleration time; LVMI, left ventricular mass index; LAVI, left atrial volume index; Ard, duration of reverse pulmonary vein atrial systole flow; Ad, duration of mitral valve atrial wave flow.

the LV systolic function data. According to the criteria of the National Heart, Lung, and Blood Institute's Framingham Heart Study, a definite or probable diagnosis of HFNEF requires the information on LV systolic function to be obtained within 72 h following the heart failure episode.⁹³ This requirement may be obsolete because Doppler echocardiographic examinations of patients with hypertensive pulmonary oedema performed sequentially at the time of hospital admission and following stabilization revealed identical LVEF and LV end-diastolic volume without evidence of improvement of LV systolic function in the days following hospital admission.¹⁰²

Evidence of abnormal left ventricular relaxation, filling, diastolic distensibility, and diastolic stiffness

Do we need evidence of left ventricular dysfunction during relaxation or diastole?

The need to obtain positive evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness, as proposed in the original guidelines of the European Study Group,¹ has been challenged.⁶⁰ Recognizing the

difficulties in the assessment of diastolic LV dysfunction, the hypothesis that measurement of diastolic LV dysfunction was not required to make the diagnosis of HFNEF was tested.⁶⁰ Ninety-two per cent of patients with a history of heart failure, an LVEF > 50%, and evidence of LV concentric remodelling had an elevated LV end-diastolic pressure and all of them had at least one haemodynamic or Doppler echocardiographic index of abnormal LV relaxation, filling, or diastolic stiffness. In this group of patients, acquisition of data on diastolic LV dysfunction therefore provided no additional diagnostic information and was therefore only of confirmatory significance. As this study looked at patients with a well-established history of heart failure, these results cannot be extrapolated to patients presenting solely with symptoms of breathlessness without a history or physical signs suggestive of congestive heart failure. Nevertheless, this study among others,^{19,58-61} clearly demonstrates that evidence of concentric LV remodelling has important implications for the diagnosis of HFNEF and is a potential surrogate for direct evidence of diastolic LV dysfunction.⁹⁴ The present consensus document (Figure 2) therefore considers an LV wall mass index >122 g/m² (♀) or an LV wall mass

index $>149 \text{ g/m}^2$ (σ) sufficient evidence⁹⁵ for the diagnosis of HFNEF when TD yields non-conclusive results or when plasma levels of natriuretic peptides are elevated.

Invasive assessment of left ventricular dysfunction during relaxation or diastole

Evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness can be acquired invasively during cardiac catheterization. Invasively acquired evidence of diastolic LV dysfunction continues to be considered as providing definite evidence of HFNEF.^{1,19,93,94} Such evidence consists of a time constant of LV relaxation (τ) $>48 \text{ ms}$, an LV end-diastolic pressure $>16 \text{ mmHg}$ or a mean pulmonary capillary wedge pressure $>12 \text{ mmHg}$ ¹⁰³⁻¹⁰⁶ (Figure 2). The mathematics involved in deriving the time constant of LV relaxation is explained in the appendix (Supplementary material online). When LV end-diastolic pressure or pulmonary capillary wedge pressure is elevated in the presence of a normal LVEDVI, LV end-diastolic distensibility is considered to be reduced. LV diastolic distensibility refers to the position on a pressure–volume plot of the LV diastolic pressure–volume relation¹⁰⁷ in contrast to LV stiffness, which refers to a change in diastolic LV pressure relative to diastolic LV volume (dP/dV) and equals the slope of the diastolic LV pressure–volume relation. A diastolic LV stiffness modulus >0.27 also provides diagnostic evidence of diastolic LV dysfunction (see Supplementary material online, Appendix). The inverse of LV stiffness is LV compliance (dV/dP). Muscle stiffness (E) is the slope of the myocardial stress–strain relation and represents the resistance to stretch when the myocardium is subjected to stress. Calculation of stress (σ) requires a geometric model of the LV and calculation of strain (ϵ) an assumption of an unstressed LV dimension. Although muscle stiffness is generally considered to reflect the material properties of the myocardium and therefore be insensitive to acute neurohumoral changes, recent clinical and experimental studies provided clear evidence for altered muscle stiffness following administration of nitric oxide,¹⁰⁸ endothelin-1,¹⁰⁹ or angiotensin II.¹¹⁰ The mathematics involved in deriving an LV or myocardial stiffness modulus is outlined in the appendix (Supplementary material online).

Blood flow Doppler assessment of left ventricular dysfunction during relaxation or diastole

Isovolumic LV relaxation time (IVRT), ratio of peak early (E) to peak atrial (A) Doppler mitral valve flow velocity, deceleration time (DT) of early Doppler mitral valve flow velocity, and ratio of pulmonary vein systolic (S) and diastolic (D) flow velocities were originally considered to be indicative of diastolic LV dysfunction if they exceeded specific cut-off values indexed for age groups.¹ These blood flow Doppler-derived indices of diastolic LV dysfunction were subject of immediate critique¹¹¹ and subsequently more carefully scrutinized in numerous studies.¹¹²⁻¹¹⁷ These studies are summarized in the appendix (Supplementary material online) and showed a variable outcome of blood flow Doppler-derived indices in terms of their predictive value for HFNEF.

When combining mitral valve blood flow Doppler with pulmonary vein blood flow Doppler,¹¹⁸ 93% of patients suspected of HFNEF showed evidence of diastolic LV dysfunction.¹¹⁹ The strength of a combined use of mitral flow

velocity and pulmonary vein flow velocity is also supported by observations in hypertensives, in which the combined use of these variables provided a semiquantitative estimate of LV end-diastolic pressure.¹²⁰ Both studies measured duration of reversed pulmonary vein atrial systole flow (Ard) and duration of mitral A wave flow (Ad) and used their difference ($\text{Ard} - \text{Ad} > 30 \text{ ms}$) to diagnose diastolic LV dysfunction.¹²¹⁻¹³²

Because of the absence of pseudonormalization on TD lengthening velocity measurements, the use of blood flow Doppler measures of diastolic LV function is no longer recommended as a first-line diagnostic approach to diastolic LV dysfunction. Only when TD lengthening velocities are suggestive but non-diagnostic or when plasma levels of natriuretic peptides are elevated does the simultaneous presence of a low E/A ratio and a prolonged DT or a prolonged $\text{Ard} - \text{Ad}$ index provide diagnostic evidence of diastolic LV dysfunction (Figure 2).

Tissue Doppler assessment of left ventricular dysfunction during relaxation or diastole

TD measures tissue velocity relative to the transducer with high spatial (mm) and temporal resolution ($>>100 \text{ s}^{-1}$). The most frequently used modality of TD is measurement of LV basal ('annular'), longitudinal myocardial shortening, or lengthening velocity. Measurements can be obtained either at the septal or at the lateral side of the mitral annulus. As explained in the appendix (Supplementary material online), the peak systolic (S) shortening velocity and the early diastolic (E') lengthening velocities are considered to be sensitive measures of LV systolic or diastolic function.

Especially, the ratio of early mitral valve flow velocity (E) divided by E' correlates closely with LV filling pressures. E depends on left atrial driving pressure, LV relaxation kinetics, and age but E' depends mostly on LV relaxation kinetics and age. Hence, in the ratio E/E' , effects of LV relaxation kinetics and age are eliminated and the ratio becomes a measure of left atrial driving pressure or LV filling pressure. E' can also be conceptualized as the amount of blood entering the LV during early filling, whereas E represents the gradient necessary to make this blood enter the LV. A high E/E' thus represents a high gradient for a low shift in volume. Information on LV filling pressures can also be derived from the time interval between the onset of E and the onset of E' ($T_{E-E'}$).^{133,134}

When the ratio E/E' exceeds 15, LV filling pressures are elevated and when the ratio is lower than 8, LV filling pressures are low.¹³⁵ E/E' is a powerful predictor of survival after myocardial infarction and $E/E' > 15$ is superior as predictor of prognosis than clinical or other echocardiographic variables.¹³⁶ The close correlation between E/E' and LV filling pressures has been confirmed in heart failure patients with depressed ($<50\%$) or preserved LV ejection fraction¹³⁷ and in patients with slow relaxation or pseudonormal early mitral valve flow velocity filling patterns.¹³⁸ In the diagnostic flow charts shown in Figures 2 and 3, the ratio E/E' is therefore considered diagnostic evidence of presence of diastolic LV dysfunction if $E/E' > 15$, and diagnostic evidence of absence of HFNEF if $E/E' < 8$. An E/E' ratio ranging from 8 to 15 is considered suggestive but non-diagnostic evidence of diastolic LV dysfunction and needs to be implemented with other non-invasive investigations

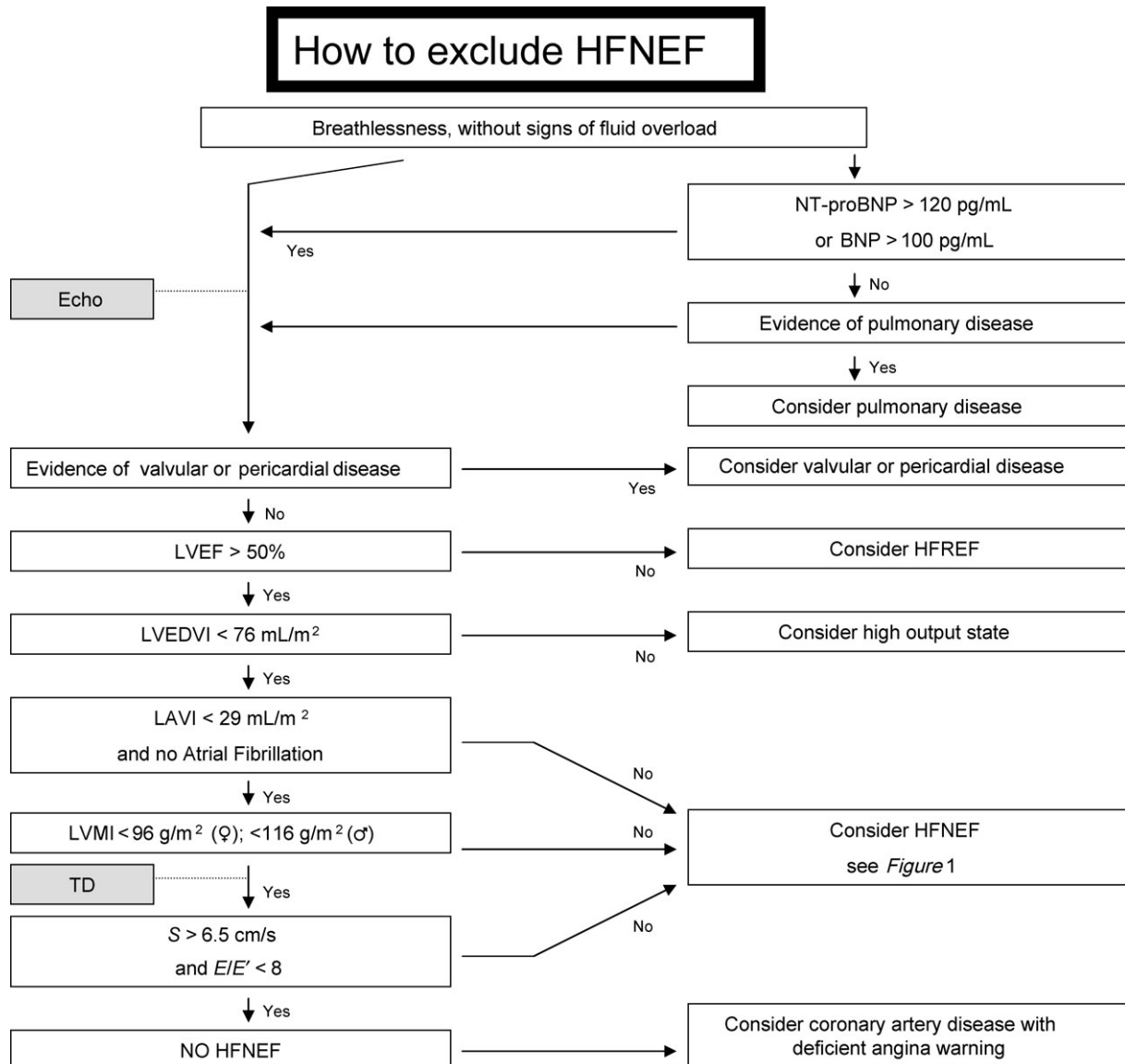


Figure 3 Diagnostic flow chart on 'How to exclude HFNEF' in a patient presenting with breathlessness and no signs of fluid overload. S, TD shortening velocity.

to confirm the diagnosis of HFNEF (Figure 2). The proposed E/E' cut-off values are based on pulsed Doppler measurements and on averaged velocities of lateral and septal mitral annulus.

Strain and strain rate imaging

TD-derived strain rate and strain measurements are new quantitative indices of regional intrinsic cardiac deformation¹³⁹ and are presumed to be independent of translational motion in contrast to myocardial velocities. Assessment of regional deformation obviously implies that all myocardial segments are to be investigated to rule out diastolic LV dysfunction. In contrast, TD E/E' interrogates global LV performance and is therefore preferred over strain and strain rate measurements in the diagnostic flow-charts of HFNEF (Figures 2 and 3). Potential future use of strain and strain rate imaging for the assessment of diastolic LV dysfunction is further highlighted in the appendix (Supplementary material online).

Left atrial volume measurements

A left atrial volume indexed to body surface area (= left atrial volume index) >32 mL/m² was first recognized in the elderly as a strong predictor ($P = 0.003$) of a cardiovascular event with a higher predictive value than other echocardiographically derived indices such as LV mass index ($P = 0.014$) or LV diastolic dysfunction ($P = 0.029$).¹⁴⁰ In a population-based study, left atrial volume index was also strongly associated with the severity and duration of diastolic LV dysfunction: the left atrial volume index progressively increased from a value of 23 ± 6 mL/m² in normals to 25 ± 8 mL/m² in mild diastolic LV dysfunction, to 31 ± 8 mL/m² in moderate diastolic LV dysfunction, and finally to 48 ± 12 mL/m² in severe diastolic LV dysfunction.¹⁴¹ Left atrial volume index was therefore proposed as a biomarker of both diastolic LV dysfunction and cardiovascular risk.^{142,143} A raised left atrial volume index (>26 mL/m²) has recently been recognized as a relatively load-independent marker of LV filling pressures and of LV diastolic dysfunction in patients with suspected heart failure and normal LVEF.¹¹⁶ In these patients, left

atrial volume index is a more robust marker than left atrial area or left atrial diameter.^{144,145} For these reasons, the present consensus document considers a left atrial volume index $>40 \text{ mL/m}^2$ to provide sufficient evidence of diastolic LV dysfunction when the E/E' ratio is non-conclusive (i.e. $15 > E/E' > 8$) or when plasma levels of natriuretic peptides are elevated (Figure 2). Similarly, a left atrial volume index $<29 \text{ mL/m}^2$ is proposed as a prerequisite to exclude HFNEF (Figure 3). Left atrial volume index values of 29 and 40 mL/m^2 correspond, respectively, to the lower cut-off values of mildly abnormal and severely abnormal LA size in the recent recommendations for cardiac chamber quantification of the American Society of Echocardiography and the European Association of Echocardiography.⁹⁵ The conduit, reservoir, and pump functions of the left atrium in normal and pathophysiological conditions are further explained in the appendix (Supplementary material online).

Heart failure biomarkers: the natriuretic peptides

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are produced by atrial and ventricular myocardium in response to an increase of atrial or ventricular diastolic stretch and their secretion results in natriuresis, vasodilation, and improved LV relaxation. Cardiac myocytes produce pro-BNP, which is subsequently cleaved in the blood into NT-proBNP and BNP.

In patients with HFNEF,^{146,147} NT-proBNP values correlate with early diastolic LV relaxation indices, such as the time constant of LV relaxation (τ), late diastolic LV relaxation indices, such as LV end-diastolic pressure, and the LV stiffness modulus. BNP and NT-proBNP values also vary with the degree of LV diastolic dysfunction: progressively higher values were observed in patients with a mitral valve flow velocity pattern of impaired LV relaxation, pseudonormalization, or restriction.^{117,148} The area under the receiver operating characteristics (ROC) curve of NT-proBNP (0.83) equalled the area observed for LV end-diastolic pressure (0.84) and exceeded the area observed for an abnormal TD E'/A' ratio (0.81).¹⁴⁶ Combining NT-proBNP with the E/E' ratio increased the area under the ROC curve from 83 to 95%.¹⁴⁶ In contrast to its usefulness in symptomatic isolated diastolic LV dysfunction, natriuretic peptides were a suboptimal screening test for preclinical diastolic LV dysfunction.¹⁴⁹

In normal individuals, the concentration of NT-proBNP rises with age and is higher in women than in men.¹⁵⁰ BNP and NT-proBNP levels can be influenced by comorbidities such as sepsis,¹⁵¹ liver failure,¹⁵² or kidney failure.^{153,154} Plasma levels of BNP rise independently of LV filling pressures once glomerular filtration rate falls below 60 mL/min . Furthermore, BNP and NT-proBNP plasma levels do not exclusively reflect left atrial distension but can also rise as a result of right atrial distension. The latter is especially important when pulmonary hypertension occurs as a result of chronic obstructive pulmonary disease,¹⁵⁵ pulmonary embolism,¹⁵⁶ or mechanical ventilation.¹⁵⁷ Finally, obesity lowers BNP levels^{158,159} and lower cut-off values have to be used once body mass index exceeds 35 kg/m^2 .

The flowcharts for the diagnosis or exclusion of HFNEF (Figures 2 and 3) do not consider an elevated BNP or NT-proBNP to provide sufficient evidence for diastolic LV dysfunction and require additional non-invasive examinations. For the diagnosis of HFNEF (Figure 2), a high positive

predictive value was aimed for when choosing the cut-off values of NT-proBNP (220 pg/mL ; Roche Diagnostics) and of BNP (200 pg/mL ; Triage Biosite). For the exclusion of HFNEF (Figure 3), a high negative predictive value was aimed for and the respective cut-off values of NT-proBNP (120 pg/mL) and of BNP (100 pg/mL) were adjusted accordingly. NT-proBNP values of 120 and 220 pg/mL yielded, respectively, a negative predictive value of 93% and a positive predictive value of 80%.¹⁴⁶ BNP values of 100 and 200 pg/mL yielded, respectively, a negative predictive value of 96% and a positive predictive value of 83%.¹⁶⁰ Cut-off values of NT-proBNP were derived from ROC analysis performed in HFNEF patients presenting with exertional dyspnoea.¹⁴⁶ An ROC analysis for BNP in HFNEF patients presenting with exertional dyspnoea has not been reported. Cut-off values of BNP were therefore derived from ROC analysis performed in HFNEF patients presenting in the emergency room with acute heart failure.¹⁶⁰ As cut-off values of NT-proBNP and BNP were derived from different HFNEF subgroups, their respective magnitudes and ranges cannot be compared. To achieve satisfactory positive predictive values, the diagnostic cut-offs of NT-proBNP and BNP had to be raised to a level, at which sensitivity drops below 80%. This results from the overlap of NT-proBNP and BNP values between controls and HFNEF patients, especially when the HFNEF patients present with exertional dyspnoea.¹¹⁷ Natriuretic peptides are therefore recommended mainly for exclusion of HFNEF and not for diagnosis of HFNEF. Furthermore, when used for diagnostic purposes, natriuretic peptides do not provide diagnostic stand-alone evidence of HFNEF and always need to be implemented with other non-invasive investigations.

Cardiac magnetic resonance

The specific advantage of cardiac magnetic resonance (CMR) over echocardiography is the possibility to acquire images in any selected plane or along any selected axis. This makes CMR the gold standard for LV volume, LA volume, and LV mass measurements.^{161,162} A routine CMR exam in the setting of heart failure will acquire the following images: cine images (same slice over the cardiac cycle) with a set of contiguous short-axis slices, covering the entire heart from base to apex and a set of long-axis slices (two, three, and four chamber). CMR can provide a whole range of LV filling parameters which are identical or nearly identical to those obtained with echocardiography. As such, CMR is a valid alternative for those patients who do not have an adequate echocardiographic image quality to reliably obtain these parameters. Moreover, CMR constitutes not only a valid alternative to echocardiography but could also be the first-choice technique if small changes in LA or LV volumes and in LV mass are expected (e.g. when evaluating progression of disease or reaction to therapy). Finally, several morphological and functional parameters such as tissue characterization or LV diastolic untwisting can only be assessed by CMR. These parameters contain important novel information for the identification of ischaemic, inflammatory, or infiltrative myocardial disease and for the evaluation of diastolic LV dysfunction. Further details on the use of CMR are available in the appendix (Supplementary material online).

Because of limited availability of CMR facilities, CMR is currently considered to be a research tool and therefore

not included in the diagnostic flowcharts of HFNEF. As the clinical use of CMR is expanding and starting to address diastolic LV dysfunction,¹⁶³ indices of diastolic LV dysfunction derived from CMR will probably have to be included in future diagnostic strategies of HFNEF.

How to diagnose heart failure with normal left ventricular ejection fraction

This consensus statement on 'How to diagnose DHF?' retains a diagnostic strategy of three requirements that need to be satisfied to diagnose HFNEF (Figure 2). These requirements are: (i) signs or symptoms of congestive heart failure; (ii) normal or mildly abnormal systolic LV function, and (iii) evidence of diastolic LV dysfunction. Since many patients with HFNEF present with breathlessness and no signs of fluid overload, symptoms are considered sufficient clinical evidence to suggest the presence of congestive heart failure. A LVEF of 50% is proposed as cut-off value of mildly abnormal LV systolic function and an LVEDVI of 97 mL/m² as cut-off value of the absence of significant LV enlargement. Invasive diagnostic evidence of diastolic LV dysfunction can be obtained by measuring the time constant of LV relaxation, LV end-diastolic pressure, pulmonary capillary wedge pressure, or the LV stiffness modulus. Non-invasive diagnostic evidence of diastolic LV dysfunction is preferably derived from myocardial TD ($E/E' > 15$). If myocardial TD yields values suggestive but non-diagnostic for diastolic LV dysfunction ($15 > E/E' > 8$), TD needs to be implemented with other non-invasive investigations to provide diagnostic evidence of diastolic LV dysfunction. These non-invasive investigations can consist of: (i) a blood flow Doppler of mitral valve flow velocity (E/A ratio and DT combined), or of pulmonary vein flow velocity (Ard–Ad index); (ii) an echocardiographic measure of LV mass index or of left atrial volume index; (iii) an electrocardiogram with evidence of atrial fibrillation; and (iv) a determination of plasma BNP or NT-proBNP. If plasma NT-proBNP > 220 pg/mL or BNP > 200 pg/mL, diagnostic evidence of diastolic LV dysfunction also requires additional non-invasive investigations, which can consist of: (i) TD (E/E' ratio); (ii) a blood flow Doppler (E/A ratio and DT combined; Ard–Ad index); (iii) echo measures of LV mass index or left atrial volume index; and (iv) electrocardiographic evidence of atrial fibrillation. The proposed use of different echocardiographic techniques, which includes measures derived from mitral valve flow velocity (E/A , DT), pulmonary vein flow velocity (Ard–Ad), and TD (E'), allows for a comprehensive non-invasive assessment of LV relaxation, LV diastolic stiffness, and LV filling pressures.¹⁶⁴

How to exclude heart failure with normal left ventricular ejection fraction

HFNEF is frequently a difficult differential diagnosis in a work-up for breathlessness in the absence of signs of fluid overload. A strategy is therefore proposed to exclude HFNEF (Figure 3). If a patient with breathlessness and no signs of fluid overload has a NT-proBNP < 120 pg/mL or a BNP < 100 pg/mL, any form of heart failure is virtually ruled out because of the high negative predictive value of the natriuretic peptides,^{146,160} and pulmonary disease

becomes the most likely cause of breathlessness. If an echocardiogram confirms the absence of valvular or pericardial disease, LV volumes and LVEF should be measured in accordance to the recent recommendations of the American Society of Echocardiography and the European Association of Echocardiography.⁹⁵ If LVEF exceeds 50%, if LVEDVI is < 76 mL/m², and if the patient has no atrial fibrillation, atrial dilatation, LV hypertrophy, low TD S or high TD E/E' , the diagnosis of HFNEF is ruled out.

Conclusions

As HFNEF currently accounts for more than 50% of all heart failure patients and as the prevalence of HFNEF in the heart failure population rises by $\sim 1\%$ a year,⁸ an updated set of diagnostic criteria for HFNEF is required. The diagnostic flowcharts on HFNEF proposed in this consensus statement provide a strategy on 'How to diagnose HFNEF' (Figure 2) and on 'How to exclude HFNEF' (Figure 3). The diagnostic strategy on 'How to diagnose HFNEF' is specifically intended for patients suspected of having HFNEF and is primarily based on the positive predictive value of successive examinations. The diagnostic strategy on 'How to exclude HFNEF' is proposed for patients presenting with breathlessness and no physical signs of fluid overload and is mainly based on the negative predictive value of successive examinations. These updated strategies for the diagnosis of HFNEF should be helpful not only for individual patient management but also for patient selection of future clinical trials looking at treatments for HFNEF.

Supplementary material

Supplementary material is available at European Heart Journal online.

Acknowledgement

The authors gratefully acknowledge the thoughtful comments of the members of the board of the Heart Failure and Echocardiography Associations of the European Society of Cardiology.

Conflict of interest: none declared.

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