Heart Failure with Normal Ejection Fraction – New Diagnostic Criteria and Pathophysiological Advances

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Summary

Heart failure (HF) is a highly prevalent complex cardiovascular syndrome, and its clinical presentation is usually associated with ventricular dilatation, decreased contractility and reduced left ventricular ejection fraction (EF). However, in the past two decades studies have demonstrated that many patients with signs and symptoms of HF have normal EF (higher than 50%). The great challenge for doctors lies in the identification of patients presenting heart failure with normal ejection fraction (HFNEF) and this challenge seems to be mainly related to the high complexity of the syndrome and to the lack of a standardized method to confirm or exclude the diagnosis that could be used in the daily clinical practice. Unlike in heart failure with reduced ejection fraction (HFREF) in which one single parameter – EF lower than 50%, is sufficient to confirm the diagnosis of the syndrome, in HFNEF different diastolic indexes have been used to characterize the presence or absence of diastolic dysfunction (DD). The purpose of this review is to show new concepts related to the diastolic function that will help understand the cardiovascular pathophysiology of HFNEF, and to discuss the new guideline of the European Society of Cardiology for the diagnosis and exclusion of HFNEF based on cardiac function indices obtained using tissue Doppler imaging (TDI) and natriuretic peptide determination.

Introduction

Assessment of the overall cardiac performance using left ventricular (LV) ejection fraction measurement has raised heated debates and controversies regarding nomenclature, definition and diagnosis of HFNEF[1].

HFNEF is frequently referred to as diastolic heart failure (DHF) because of the presence of diastolic dysfunction (DD) characterized by reduced relaxation and increased ventricular stiffness[2-4]. However, the utilization of the term DHF may not be appropriate since the diastolic dysfunction does not occur only in these patients, but also in those with HF with systolic dysfunction. Thus, in the absence of a differentiated role for diastolic dysfunction, patients presenting with HF without EF

Key Words

heart failure; diastole; systole; echocardiography, Doppler; stroke volume.

reduction would be better defined by the term HFNEF than by DHF[5].

The differentiation between HFNEF and HFREF is based on the EF measurement by Doppler echocardiography, and this gives the impression that patients with HFNEF have only diastolic function changes with preserved systolic function. However, new techniques to evaluate cardiac function with measurement of the long axis velocity using tissue Doppler imaging have proven to be a more sensitive index for the assessment of systolic function than EF[4]. Thus, HFNEF would be the result of the systolic dysfunction of the ventricular muscular pump in the presence of a preserved performance of the hemodynamic pump[6], that is, when the EF is analyzed separately from the left ventricle, the identification of myocardial contractility abnormalities may be missed[4,6].

Despite its unfavorable prognosis, HFNEF is currently a poorly valued clinical syndrome in comparison with other non-cardiac conditions such as cancer and diabetes, and heart diseases such as myocardial infarction.[1] The little importance given to the diagnosis of HFNEF may be mainly related to the high complexity of the syndrome, poor approval by the medical establishment due to the difficulty in identifying a standardized method to quantify the diagnosis that could be used in the clinical practice, and also due to controversies involving the definition of diastolic dysfunction, as well as of criteria for the diagnosis of HFNEF[1].

Recently, the European Society of Cardiology published a new guideline on how to diagnose HFNEF using two algorithms to exclude or confirm the syndrome with emphasis on the findings of TDI and natriuretic peptides[5].

Epidemiology

Different authors have demonstrated that HFNEF is currently the most common form of presentation of HF, with a prognosis similar to that of HFREF[7,8]. Epidemiological studies show that the prevalence of HFNEF is higher than 50% among patients with HF[7,8]. In a recent article published in *Arquivos Brasileiros de Cardiologia*, Moutinho et al observed a HFNEF prevalence of 64.2% in a population of patients seen in the *Programa Médico de Família* (Family Medical Program) in the city of Niterói, State of Rio de Janeiro, with signs and symptoms of HF[9].

It is important to point out that the demographics and comorbidities of patients with HF vary according to EF (Table 1)[8]. When patients with HFNEF are compared with those with HFREF, we can observe the first ones are older, more obese and most of them are females. Patients with HFNEF have a history of hypertension, diabetes and atrial fibrillation[8].

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Table 1 – **Epidemiology of heart failure stratified by EF**

Characteristics	HFNEF n = 2167	HFREF n = 2429	p
Mean age	74.4 years	71.7 years	< 0.001
Male gender	44.3%	65.4%	< 0.001
BMI > 30	41.4%	35.5%	0.002
Hypertension	62.7%	48.0%	<0.001
CAD	52.9%	63.7%	<0.001
Diabetes	33.1%	34.3%	0.61
Atrial fibrillation	41.3%	28.5%	<0.001

BMI – Body Mass Index; CAD – Coronary Artery Disease; EF – ejection fraction; Adapted from Owan et al[8]

Although patients with HFNEF have a better prognosis than those with HFREF, they present significant morbidity and mortality, and the prognosis after hospitalization for HF is poor[7,8,10], with a mortality rate of approximately 20% in one year[9]. Although strategies based on recent evidences for the treatment of HF have favorably modified the outcomes for patients with HFREF, studies have shown increased prevalence rates of HFNEF without change in mortality over the past 20 years[8].

HFNEF and HFREF – a single syndrome or not?

There is no consensus as to whether HF should be considered a single syndrome or whether HFNEF and HFREF are two different clinical forms[11].

If HF were characterized as a single syndrome[12], it would be defined by a progressive decline in the systolic performance that can be better evaluated by the analysis of velocities or measurements involving the long axis shortening using TDI than by using the EF measurement alone[13].

The theory that HF is not a single syndrome but rather two diseases is supported by structural, functional and molecular changes associated with the diastolic function as well as by clinical studies with pharmacological intervention showing that patients with HFNEF do not have the same response as patients with HFREF, thus suggesting the existence of different pathophysiological mechanisms[11].

We emphasize that it is totally artificial to split the two phases of the cardiac cycle (systole and diastole), but some authors[11] have argued that in HFNEF the systolic function is completely normal, and that this clinical condition is due to DD alone. Hence, HFNEF and HFREF should be considered different clinical entities[11]. These studies are based on global measurements derived from the LV volume pressure curve that do not take into consideration regional changes of the long axis function[4], which are compensated by an increase in contractility of the LV short axis. The pressure/volume curve may thus remain normal despite significant changes in the ventricular architecture and shape[1].

Systolic Activation - Early relaxation delay

Modulation of duration of systole
- Heterometric autoregulation - pressure or volume, hypertrophy I
- Homeometric autoregulation - neurohormones, heart rate
- Endothelial autoregulation - NO, BNP, cytokines

Modulation of relaxation velocity
- secondary to changes in duration of systole
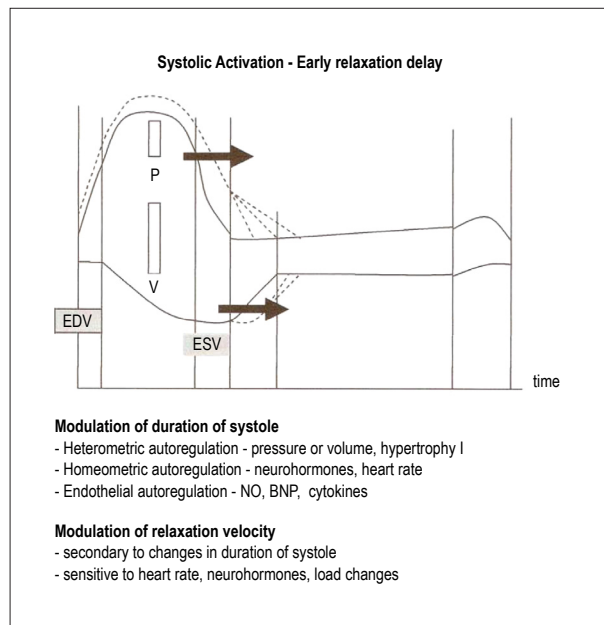- sensitive to heart rate, neurohormones, load changes

Figure 1 – Early relaxation delay (or prolonged contraction is – together with peak and increased contraction velocity – the typical characteristic of the Systolic Activation Phase of the muscular heart pump. Changes in relaxation velocity are merely an effect secondary to the delayed modulation of systole. Usually early relaxation delay does not lead to increased end-diastolic pressure/volume. P – LV pressure; V – LV volume; EDV – end diastolic volume; ESV – end systolic volume; NO – nitric oxide; BNP – B-type natriuretic peptide (reproduction authorized by Dirk L. Brutsaert [1]).

Key elements of the pathophysiology of cardiac dysfunction

The normal diastolic function allows the heart to have adequate filling both at rest and during exercise, without the occurrence of increased diastolic pressures. However, changes in cardiac relaxation, the presence of myocardial hypertrophy, and remodeling are key defects that change the ventricular stiffness and filling pressures, thus leading to exercise intolerance, which would be the first symptom of HFNEF and the first determinant of reduced quality of life[14].

In the heart with diastolic dysfunction, EF remains normal for quite a while. Maintenance of the cardiac performance is due to a compensatory period composed of two phases – the systolic activation phase, and the systolic dysfunction phase of the muscular pump[1].

The systolic activation phase (Figure 1) is characterized by increased pressure, volume and ventricular flow, which is reversible and reflects the activation of all the adaptive mechanisms of the heart as a muscular and hemodynamic pump[1].

If cardiac stress is maintained, the systolic activation may progress to the systolic dysfunction phase (Figure 2)[1].

Therefore, the complete understanding of the systolic dysfunction of the muscular pump in the presence of a preserved performance of the hemodynamic pump, that is, normal EF, would undoubtedly be a key pathway to the understanding of the initial stage of the HF syndrome, which we call HFNEF[1,4].
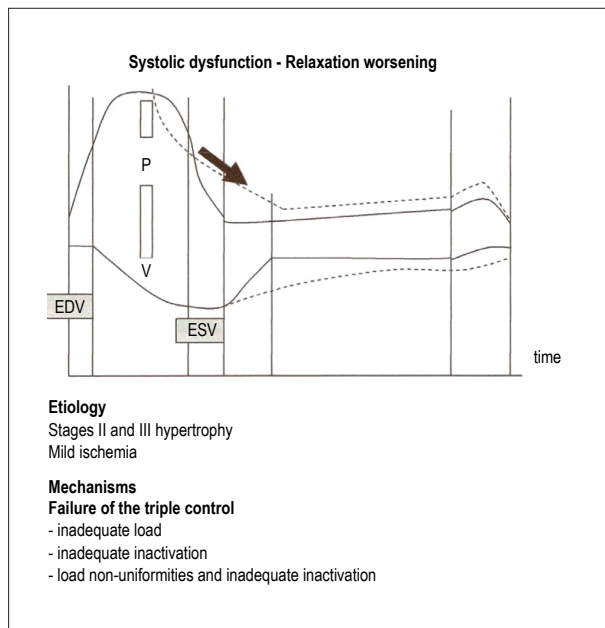
Figure 2 – *The early systolic dysfunction stage is characterized by worsened relaxation, which is slow or incomplete, with progressive loss of capacity to modulate the early relaxation. Worsened relaxation may result in increased end diastolic volume/pressure. The grey vertical bar right before peak P and peak ESV shows the transition between intracellular contraction and the relaxation process. P – LV pressure; V – LV volume; EDV – end diastolic volume; EDV – end diastolic volume (reproduction authorized by Dirk L. Brutsaert[1]).*

Abnormal relaxation

Abnormal relaxation (DD) is a functional alteration of the heart and one of the three mandatory criteria for the diagnosis of HFNEF, and should not be mistaken for or used as synonymous with HFNEF[15].

The best way to demonstrate that patients with HFNEF have abnormal relaxation is to show whether the end-diastolic pressure/volume ratio (EDPVR) is higher when compared to its normal value. Certain conditions such as hypertrophy (hypertensive heart disease, hypertrophic cardiomyopathy and/or aortic stenosis) and myocardial ischemia affect relaxation making it slower and incomplete, thus leading to increased EDV[15]. The P/EDV-R allows for the demonstration that not only is the intraventricular diastolic pressure elevated but also that this elevation is seen in ventricles presenting decreased filling volume[11].

Demonstration of increased EDPVR is important because in the absence of this alteration, the EDV may be increased because of an increase in preload, such as can be observed in patients with aortic and mitral regurgitation with no contractility impairment and no significant change in the relaxation properties, andbecause a surgical correction of the alteration also corrects the overload[16].

Cardiac hypertrophy

Ventricular hypertrophy is considered an adaptive mechanism of the heart in face of an increased load. Through intracellular mechanisms this overload may elicit different responses that can or not be associated with functional myocardial impairment[17].

The concept of hypertrophy is based on the identification of increased heart weight which is mainly determined by the increase in cardiomyocyte size.[17] We should not forget that cardiac muscle cells comprise the least percentage of all myocardial cells; however, given that they are the largest cells, variation in their size will determine a significant impact on the final heart weight[17].

The hypertrophic response may be triggered by natural overload mechanisms such as those determined by growth, pregnancy, and those induced by physical activity, or also by pathological mechanisms such as hypertension, heart valve stenosis and regurgitation, cardiomyopathy, and myocardial infarction.

Pathological hypertrophy is accompanied by loss of contractility. The analysis of the fibers of the LV long axis on TDI shows decreased contraction in hypertrophic hearts[4] due to hypertension in comparison with normal hearts or athletes' hearts with physiological hypertrophy[17].

Ventricular remodeling

The main pathophysiological difference between HFNEF and HFREF is the increased ventricular volume and the change in the ventricular shape because of the remodeling process[2]. Myocardial infarction is a powerful stimulus to the remodeling process, leading to enlargement of the LV and reduction of EF, whereas in the hypertensive heart disease the remodeling is a slow process, with LV hypertrophy leading to LV systolic and diastolic dysfunction, in which the compensatory increase in radial contraction tends to normalize the EF. However, in late stages, remodeling will occur with LV volume increase and the patient will go from HFNEF to HFREF[1].

Currently, the use of medications that act on remodeling have proven to be efficient in the treatment of HF, and signs of reverse remodeling are a powerful predictor of clinical improvement[2].

Diagnosing HFNEF in the clinical practice

The first step in the assessment of HF is to establish its diagnosis by the presence of signs and symptoms and, when available, with BNP determination. Next, a heart imaging method should be used to objectively assess LV function and determine the main etiology and its mechanisms (HFNEF, HFREF, pericardial diseases and heart valve diseases). The third step is to determine whether remodeling is already present (increased ventricular volume), and finally, to look for the presence of additional deleterious factors such as dyssynchrony, arrhythmias, and metabolic and electrolyte changes[2].

The ESC guideline[5] presents an algorithm model (Figures 3 and 4) on how to diagnose and how to exclude HFNEF using the new concepts of cardiac function and TDI measurements. It establishes three mandatory stages to diagnose HFNEF, which are: presence of signs or symptoms for the diagnosis of HF, presence of greater than 50% EF, and evidences of diastolic dysfunction (relaxation, filling and stiffness)[5].

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Signs and symptoms of HF

The signs and symptoms of HF include peripheral edema, hepatomegaly, lung crepitations, pulmonary edema, fatigue and breathlessness. Breathlessness is the most common symptom and also leads to a greater difficulty in the differential diagnosis[5]. This difficulty is more frequently seen in elderly and obese patients, who represent the largest proportion of patients with HFNEF[7]. Unlike hospitalized patients who are admitted with a classical presentation of HF which usually leaves no doubt as to the diagnosis, outpatients frequently complain of breathlessness with no detectable signs of congestion, which leads to the need for tests to confirm the diagnosis[5].

Normal or mildly abnormal systolic left ventricular function

The choice of a cut-off point to the EF value to discriminate HFNEF from HFREF remains arbitrary[5]. The ESC guideline established the value of EF≥50% as necessary for the assessment according to recent recommendations of the American Society of Echocardiography and of the European Association of Echocardiography[5].

Criteria for the presence of normal EF need to be implemented with measures of ventricular volume. Thus EDV, which must be indexed to body surface, should not exceed 97 ml/m² for the diagnosis of HFNEF[5].

Evidences of abnormal LV relaxation

The first question is whether it is necessary to evaluate relaxation changes in all patients with suspected HFNEF[5].

Considering this possibility, Zile et al[18] tested the hypothesis that measurements of diastolic function are not always necessary to establish the diagnosis of HFNEF. The authors evaluated patients with HF who had EF >50% and evidences of concentric remodeling and demonstrated that 92% of these patients had high end-diastolic pressure and all had at least one abnormal relaxation index, abnormal filling or stiffness. In this group of patients, the DD parameters obtained did not add data for the diagnosis, but only confirmed DD[18]. We should keep in mind that this study evaluated patients with history of established HF and, therefore, these data cannot be extrapolated to patients presenting only symptoms of breathlessness[19].

An important finding of this study is that the evidence of concentric remodeling has implications for the diagnosis of HFNEF and is a potential substitute for the characterization of diastolic dysfunction[18,20]. The study shows that a LV wall mass index > 122g/m² for women and > 149 g/m² for men is sufficient evidence for the diagnosis of HFNEF when TDI is not conclusive or when plasma BNP is elevated[18].

Assessment of the left ventricular function using TDI

TDI has a fundamental role in the assessment of this process since the clinical presentation of HFNEF is indistinguishable from that of HFREF and the EF measurement is certainly not relevant. Thus, assessments of systolic and diastolic dysfunction using measurements of the long axis and strain velocity in early diastole (E') with TDI are more important[5,14,21].

The development of new TDI techniques[13] has provided greater accuracy in the assessment of the ventricular function. In a recent study, Wang et al[20] showed that the measurement of strain velocity in early diastole (E') is a strong predictor of mortality in comparison with clinical data and standard echocardiography. This measurement is easy to be taken and adds significant value to the clinical management of patients with HF[20,22].

E' has proven to be a strong predictor of the prognosis of HF, since this measurement reflects both the LV systolic and diastolic function. Additionally, the subendocardial fibers, which are responsible for contraction of the long axis, may be more susceptible to the effect of fibrosis, hypertrophy and ischemia due to their position, and this would explain why E' is a good marker of the disease[5].

Another frequently used echocardiographic parameter is the measurement of the early mitral valve flow velocity (E), which can be obtained either at the septal or at the lateral side of the mitral annulus[5].

TDI has, therefore, permitted the quantitative assessment of the LV systolic and diastolic function[12]. Recent studies[22-24] investigated the prognostic role of TDI in several heart diseases such as HF, acute myocardial infarction and hypertension.

E/E' ratio

The E/E' ratio correlates closely with LV filling pressures. E depends on the left atrial pressure, LV relaxation, and age, whereas E' depends mostly on the LV relaxation and age[13].

Therefore, in the E/E' ratio, effects of LV relaxation and age are eliminated and the ratio becomes a measurement of the left atrial pressure or LV filling pressure[13]. The E/E' ratio can thus be conceptualized as the amount of blood entering the LV during the fast filling phase, where E represents the gradient necessary to make this blood enter the LV. Thus, an increase in E/E' means a high gradient to a low shift in volume[13].

When E/E' is higher than 15, LV filling pressures are elevated and when the ratio is lower than 8 these pressures are low[5].

The E/E' ratio is therefore considered diagnostic evidence of the presence of HFNEF if greater than 15, and evidence of absence of HFNEF if lower than 8[5,25]. E/E' values between 8 and 15 are considered suggestive, but not diagnostic and needs to be evaluated with other non-invasive data to confirm HFNEF[5].

Left atrial volume index

Increased left ventricular diastolic pressures lead to left atrial remodeling with increased LA volume. Therefore, the left atrial volume index (LAV-I) may be seen as a morphologic expression of the left ventricular diastolic dysfunction[21].

Increased LAV-I (>29 mL/m²) would be a load-independent marker of LV filling pressure in patients with suspected HFNEF[14]. LAV-I could then be considered the barometer of the heart[21].

When E/E' is not conclusive (15 < E/E' > 8) for the diagnosis of HFNEF, the presence of LAV-I > 40 ml/m² provides sufficient evidence to confirm the diagnosis[5,25]. Similarly, a LAV-I < 26 ml/m² is proposed as a prerequisite for the exclusion of HFNEF[5].

Natriuretic peptides

BNP is produced in the myocardium in response to an increase in ventricular diastolic stretch, and its secretion

results in natriuresis, vasodilatation, and improved ventricular relaxation[21]. In patients with HFNEF, BNP values correlate with indices that evaluate the early and late LV diastolic relaxation. High values have been observed in patients with late or abnormal relaxation[1].

Since BNP levels may be influenced by different conditions (sepsis, liver failure, kidney failure, COPD, obesity), high BNP values do not provide sufficient evidence for the diagnosis of diastolic dysfunction, requiring additional tests[5]. For the diagnosis of HFNEF, a high positive predictive value was determined when the BNP cut-off point was chosen (200 pg/ml). For the exclusion of HFNEF, a high negative predictive value was determined for the choice of the BNP cut-off point (<100 pg/ml)[5].

Therefore, natriuretic peptides are mainly recommended for exclusion, and not for diagnosis, of HFNEF. Since BNP alone does not provide evidence for the diagnosis of HFNEF, it should always be used with other non-invasive tests[5,25].

How to confirm and exclude HFNEF

Diagnosing HFNEF (Figure 3) is as important as excluding this diagnosis in patients with breathlessness and no signs of congestion (Figure 4), since the differential diagnosis of HFNEF is very difficult, especially in these patients[5].

We can exclude HFNEF in patients with breathlessness who present lower than 100 pg/ml BNP values because of its high negative predictive value[5,25].

If echocardiography rules out the presence of heart valve or pericardial disease, if the EF is higher than 50% and the EDV index is lower than 76 ml/m², if there is no atrial fibrillation, atrial dilatation or left ventricular hypertrophy, and if the E/E′ ratio is lower than 8, the diagnosis of HFNEF can be ruled out[5].

Conclusion

The ECS guideline which established criteria for diagnostic confirmation and exclusion of HFNEF should be increasingly more frequently used by cardiologists and echocardiographers in the assessment of patients with suspected HFNEF.

Although EF is an important index to assess the hemodynamic heart pump, it should not be used as the main criterion for the diagnosis and/or exclusion of HF, since the assessment of EF alone may not identify myocardial contraction abnormalities.
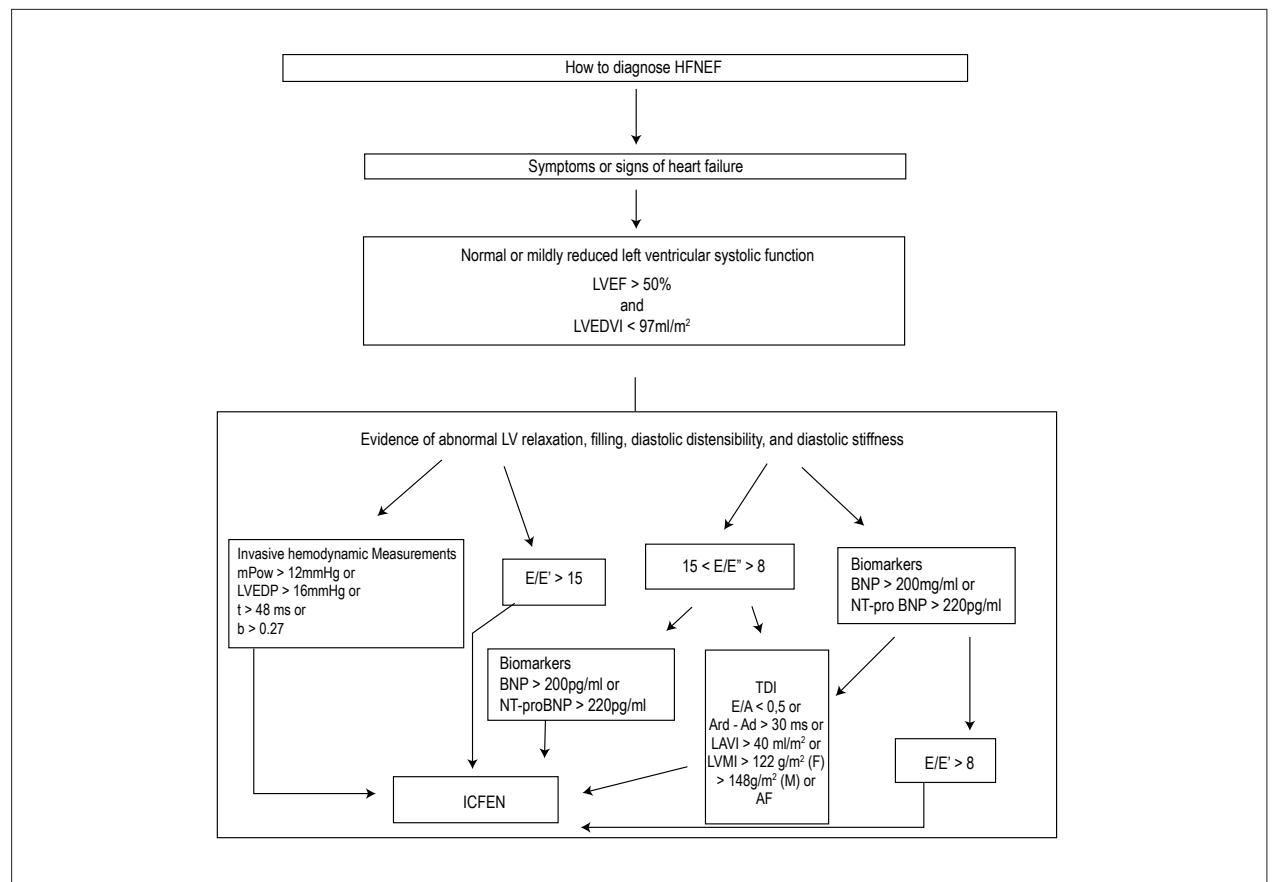

Figure 3 – *How to diagnose HFNEF – flowchart; mPCW – mean pulmonary capillary wedge pressure; t – time constant of LV relaxation; b – constant of LV chamber stiffness; E – early mitral valve flow velocity; E′ – Early TD lengthening velocity; NT-proBNP – N-terminal proBNP; E/A – ratio of early to late mitral valve flow velocity; TDI – tissue Doppler imaging; LAVI – left atrial volume index; Avd – duration of reverse pulmonary vein atrial systole flow; Ad – durarion of mitral valve atrial wave flow; European Heart Journal – How to diagnose diasolic 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 (5)*
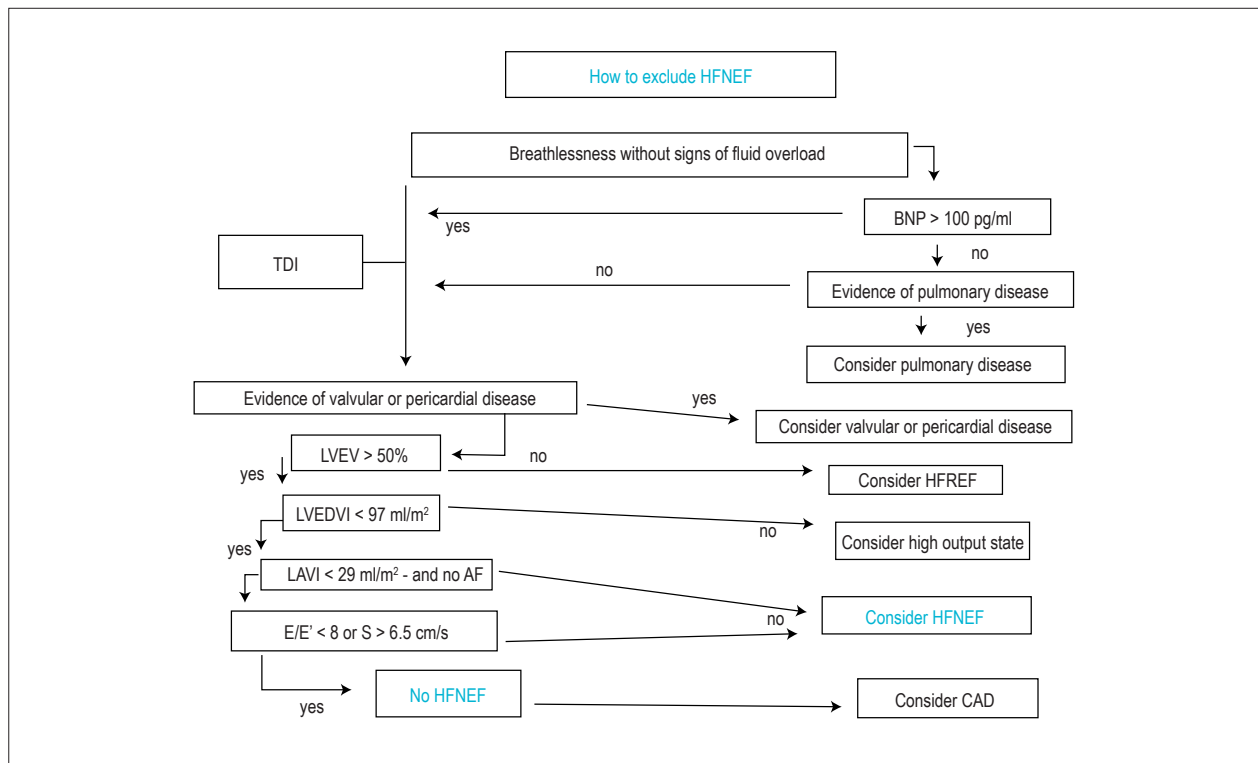
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Figure 4 – How to exclude HFNEF; E – early mitral valve flow velocity; E' – early TD lengthening velocity; BNP – N-terminal proBNP; LVEF – left ventricular ejection fraction; LAVI – left atrial volume index; EDVI – end diastolic volume index; TDI – tissue Doppler imaging; S – myocardial of mitral annulus shortening velocity; AF – atrial fibrillation; HFREF – heart failure with reduced ejection fraction; HFREF – heart failure with normal ejection fraction; CAD – coronary artery disease; European Heart Journal – How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Failure and Echocardiography Associations of the European Society of Cardiology [5]

Although uncommonly used in the clinical practice, TDI is currently the best tool for the diagnosis of HFNEF, and its utilization will gradually replace the conventional transmitral echocardiographic criteria in the assessment of diastolic dysfunction.

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Potential Conflict of Interest

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