Heart failure with normal ejection fraction (HFNEF): is it worth considering?

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Summary

A significant proportion of patients with heart failure happen to have a normal ventricular ejection fraction at echocardiography during examination. Previously called diastolic heart failure, it is nowadays referred to as heart failure with normal ejection fraction (HFNEF) or HF with preserved ejection fraction. The European Society of Cardiology, recognizing the importance of this type of heart failure, recently issued new definition criteria for it. This review will discuss the different steps that lead to such a diagnosis, as well as some new aspects of its pathophysiology. Finally, the management of this form of HF, that is not as straightforward as HF due to systolic dysfunction, will be discussed.

Key words: heart failure; HFPEF; HFNEF; Diastolic dysfunction; BNP

Introduction

Heart failure (HF) is a complex syndrome, resulting from structural or functional cardiac disorders that impair the ability of the cardiac pump to support a physiological circulation. HF is a frequent pathology in Switzerland, with a significant proportion of patients who need to be admitted to the hospital, and a high case fatality rate [1]. Advances in the management of patients with left ventricular (LV) systolic dysfunction have resulted in a significant extension of life expectancy, but this is not the case for patients with HF in the absence of echocardiographic LV systolic dysfunction [2–5]. This type of HF is now being called Heart Failure with Normal Ejection Fraction (HFNEF) although HF with Preserved EF (HF-PEF), which probably better delineates the fact that systolic function is not completely normal in such patients but only apparently preserved, and diastolic heart failure (DHF) have also been used [6]. The European Society of Cardiology (ESC) recently underlined the clinical importance and complexity of HFNEF, and issued new definition criteria, based on clinical signs and/or symptoms of HF, echocardiographic and biological parameters [7]. This review will focus on the most recent data gained on the mechanisms of HFNEF, as well as on the results of the latest clinical studies on HFNEF. It is intended to help the general practitioner understand and apply the new ESC definition of HFNEF into their daily practice.

Clinical recognition and epidemiology

Numerous publications report that many patients who present with symptoms or signs of HF do not have decreased LV ejection fraction (LVEF). Data from recent studies show a prevalence rate of HFNEF ranging from 30 to 50% in patients with HF, at least in patients with hospital admission [8–11]. HFNEF patients are likely to be older women, in whom systolic hypertension and myocardial hypertrophy with fibrosis are the main contributors to cardiac dysfunction.

The general prevalence of HFNEF seems to be on the rise, as a possible consequence of growing recognition, population ageing and increases in hypertension and obesity prevalence [8]. Even though HFNEF mortality may be lower than in HFREF, high NYHA functional capacity carry a poor prognosis, whatever the LV systolic function. Finally, HFNEF patients have a reduced life expectancy, due to an increased risk of sudden cardiac death and acute HF, implying that these individuals have a significant functional cardiac disease [8, 10, 12]. For these reasons, HFNEF has become a public health problem and deserves more attention [8–10].

Pathophysiology of HFNEF

HFNEF implies some degree of LV filling alteration despite an apparently normal LV systolic function: this so-called LV diastolic dysfunction (DD) results from various mechanisms, mainly abnormal relaxation and decreased compliance, with a rise in LV end-diastolic pressure (LVEDP) [13]. Systolic function seems preserved, at least as assessed by 2D echocardiography, but this may be more complex, as this technique does not take into account all aspects of LV contractility.

Diastolic function

Diastolic *function* of the LV depends on active relaxation and on the stiffness characteristics of the ventricular wall [13]. Diastolic *dysfunction* is not only the consequence of altered geometric and elastic properties of the myocardium, but is also influenced by pericardial distensibility, interventricular dependency, left atrial pressure, and electrical atrio-ventricular coupling. In addition, the vascular bed's compliance and resistance may play a significant role in the development of diastolic dysfunction.

Zile et al. invasively recorded ventricular pressures in patients with HFNEF, and confirmed the increase in LVEDP, together with smaller end-diastolic volumes, compared to controls [13]. They found evidence of a slower and incomplete relaxation associated with an increased passive ventricular stiffness, which could explain the high LVEDP. Westermann et al. confirmed these observations, with an invasive measure of ventricular pressure-volume loops in HFNEF patients: they showed an elevated LVEDP that might be due to higher LV stiffness and increased relaxation time [14]. These alterations were more marked during handgrip or tachycardia, but with a different pattern of alterations in these two situations, suggesting a complex mechanism of diastolic dysfunction during exercise, not only due to heart rate increase [15].

Tachycardia may reveal diastolic dysfunction and is often not well tolerated by patients with HFNEF: Wachter et al. demonstrated that relaxation time was prolonged in HFNEF, and that the normal frequency-dependent acceleration of relaxation was blunted, resulting in significant decrease of end-diastolic volume and stroke volume with higher heart rates [16].

Eventually, recent and precise descriptions of diastolic function, by the association of echocardiographic measures of ventricular dimensions coupled with invasive measures of ventricular pressures using an implantable device called e-PAD, added more evidence that diastolic distensibility is decreased in HFNEF [17, 18].

In the daily practice, the non-invasive evaluation of LV diastolic function is performed with transthoracic echocardiography (TTE). Early mitral diastolic flow (called E wave), due to the ventricular relaxation, and late mitral diastolic flow (called A wave), secondary to the atrial kick, can be measured with Doppler-imaging. The velocity ratio of these waves, called E/A ratio, has been used as an indirect evaluation of ventricular filling pressure, and as a surrogate marker of diastolic function. Three grades of diastolic dysfunction have been defined. Grade I (E/A <1) is referred to as relaxation abnormality and is often encountered in elderly patients. Grade II (E/A >1) is called pseudo-normalization, since it is also recorded in young healthy individuals. As LA pressure increases further, relaxation time decreases and the contribution of the LA kick to LV filling diminishes, with a "restrictive" pattern (E/A >1,5 and DT <140 msec), referred to as Grade III. This range of severity has been shown to represent a negative prognostic marker, especially in patients with systolic dysfunction [19, 20].

However, the E/A ratio may not precisely reflect diastolic function, partly because it is load dependant and it has variable performances [21, 22]. Other TTE parameters give some indication on diastolic function, such as the deceleration time of the E wave, the isovolumic relaxation time, the left atrial size, and the LV wall thickness, and, as elegantly stated by L. Hatle, diastolic dysfunction is better assessed when all TTE and Doppler parameters are put together [23].

Tissue Doppler imaging (TDI) is a novel technique, which allows analysis of global diastolic and systolic velocities of the myocardial wall. The E' wave is the peak velocity of early diastolic myocardial lengthening, recorded at the mitral annulus. When combined with the E wave, measured with conventional Doppler, the E/E' ratio is well correlated to LVEDP and is less load-dependent than E/A ratio [24–26]. It also correlates very well with HF symptoms, both in HFREF and HFNEF [27–29]. An E/E' ratio >15 has been chosen as a cut-off value for diastolic dysfunction, and a value <8 is sensitive enough to exclude it.

When E/E' ratio is between 8 and 15, other approaches, such as pulmonary vein Doppler analysis, M-mode color Doppler of LV filling, the "time constant" of LV relaxation (t), the 'stiffness' constant of LV (b), the left atricular volume index (LAVI), and the left ventricular mass index (LVMI) can be used in conjunction with LA size [30]. However, in clinical practice, these novel approaches are not yet widely available, and cardiac catheterization remains the gold standard for filling pressure assessment.

The E'/E ratio is of limited value in patients with abnormal relaxation but normal LVEDP at rest. Marked diastolic dysfunction can develop with exercise, and diastolic dysfunction can be missed, unless there is an LA enlargement. Likewise, some patients with a decrease in compliance without significant relaxation abnormality may have a normal E/E', and once again LA size and blood flow Doppler analysis might then be the only clues of a diastolic dysfunction [23, 31].

Systolic function

By definition, systolic function should be normal or preserved in HFNEF, at least when measured with echocardiography. However, TTE may be misleading, because it only evaluates radial shortening and doesn't take into account other aspects of systolic function, such as longitudinal shortening, circumferential twist, and regional abnormalities. This is important, since loss of longitudinal motion of the LV is the most obvious change associated with ageing, and because radial shortening is often increased in the early stage of diabetic and hypertensive heart disease [32–34]. As elderly, diabetic and hypertensive subjects represent a significant proportion of HFNEF patients, the relative preservation of LVEF may lead to a wrong impression.

LV systolic function can nowadays be evaluated more precisely with TDI. LV longitudinal shortening is assessed by the amplitude of mitral annular shortening, and when associated with the evaluation of systolic myocardial velocities, this approach yields a much better detection of global and regional systolic dysfunction than TTE. With this tool, it has been shown that systolic function may be altered not only in HFREF, but also in patients with HFNEF [35–37]. Other recently developed techniques, such as strain rate imaging (SRI) which uses the time integral of the velocity gradient between two adjacent myocardial segments, may also be better at detecting regional and global alterations of systolic function [38].

The application of these new techniques shows that LV systolic function is, in fact, probably slightly altered in patients with HFNEF: Tan et al. have studied HFNEF patients by various echocardiographic techniques, both at rest and at exercise, and have shown that HFNEF patients have systolic segmental alterations, such as lower apical rotation, decreased ventricular suction and reduced untwisting, and that these alterations are more pronounced at exercise [15]. One can conclude that standard TTE doesn't seem to have perfect diagnostic performance for systolic function, and that EF doesn't reflect systolic function in its entirety, and may seem normal because of a change in ventricular geometry. Based on a mathematical model, MacIver et al have shown that EF preservation in HFNEF is probably related to increased muscle mass and increased radial thickening of the ventricular wall, compensating for the reduced long-axis shortening [39].

All these data suggest that indeed HFNEF and HFREF may represent a continuum, and not separate entities.

Cellular alterations associated with HFNEF

Van Heerbeck et al. demonstrated that the myocardium of patients with HFNEF and HFREF present the same degree of histological fibrosis, but that cardiomyocytes express different isoforms of the constitutive cytoskeletal protein titin, which increases diastolic compliance upon phosphorylation [40]. The N2B isoform expressed in HFNEF is stiffer and its increased expression may contribute to the increased ventricular stiffness, and participate in the development of diastolic dysfunction.

Diagnosis of HFNEF

HF is a clinical syndrome and may present in either acute or chronic form. Acute onset of dyspnea and/or congestion will often lead to hospitalization, and the clinical suspicion of HF is high in most cases. More chronic symptoms, such as dyspnea on exertion, nocturnal paroxysmal dyspnea, orthopnea, or fatigue, may be the only features of HF, particularly in the outpatient setting and aren't specific of any type of HF.

Signs and symptoms of HF result from elevated LV filling pressure and/or low cardiac output, which may be the consequence of either incomplete emptying, as in systolic dysfunction, or impaired ventricular filling as in diastolic dysfunction. Therefore, the clinical presentation of HFPEF and HFNEF share similarities such as a third heart sound, elevated jugular venous pressure and signs of pulmonary congestion, which, in the past, had been considered to be the hallmark of LV systolic dysfunction but are also found in patients with diastolic dysfunction. As their performance characteristics may vary, classical symptoms and signs are not sufficient for the diagnosis of HF (fig. 1) [41]. The Framingham criteria are sensitive but moderately specific, and apply poorly to non congestive or moderate HF (table 1) [42–45].

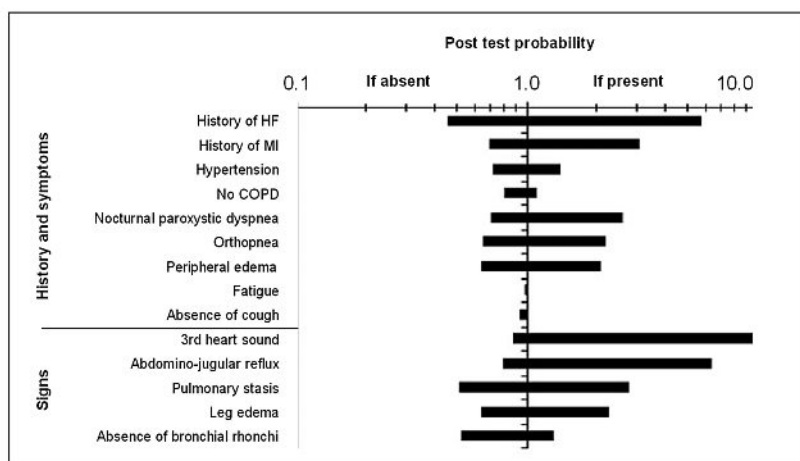In the daily practice, the physician firstly needs to confirm that HF is the cause of the pa-

Figure 1

Diagnostic value of symptoms and signs of HF.
Adapted with permission from Brunner-La Rocca [41] and Schweiz Med Forum 2007;7(Suppl. 39):3–14 S, http://www.medicalforum.ch HF: Heart failure
MI: myocardial infarction COPD: chronic obstructive pulmonary disease

Table 1

Framingham criteria for the diagnosis of heart failure (HF): HF is diagnosed when 2 major criteria OR 1 major criteria plus 2 minor criteria are present.

Major criteria
– Paroxysmal nocturnal dyspnea
– Neck vein distention
– Rales
– Radiographic cardiomegaly
– Acute pulmonary edema
– S3 gallop
– Increased central venous pressure (>16 cm H_2O at right atrium)
– Hepatojugular reflux
– Weight loss >4.5 kg in five days in response to treatment
Minor criteria
– Bilateral ankle edema
– Nocturnal cough
– Dyspnea on ordinary exertion
– Hepatomegaly
– Pleural effusion
– Decrease in vital capacity by one third from maximum recorded
– Tachycardia (heart rate >120 beats/min.)

tient's presenting symptoms and signs, and then to distinguish between HFREF and HFNEF. The most recent guidelines, including the ESC algorithm, recommend that the diagnosis of HF be based upon ECG, chest X-ray and measurement of natriuretic peptides, and confirmed by echocardiographic evaluation, which in addition will help differentiate HFREF from HFNEF (fig. 2 and 3) [6, 41].

Brain natriuretic peptide (BNP) and its precursor (NT-proBNP) are produced by cardiomyocytes in response to volume or pressure overload, and are very sensitive markers, so that HF is unlikely in presence of normal levels [46–48]. Specificity is not as good, because blood levels are influenced by many factors, such as age, BMI and kidney function, and may increase in various clinical situations. This is why the 'rule-in' cut-off values may differ in various guidelines, and the interpretation of these values always has to be cautious and linked to the clinical situation [46, 49]. It has to be emphasized that, in recent years, natriuretic peptides have been made readily available in each emergency room and private practice, and have

Figure 2

ESC diagnosis algorithm.
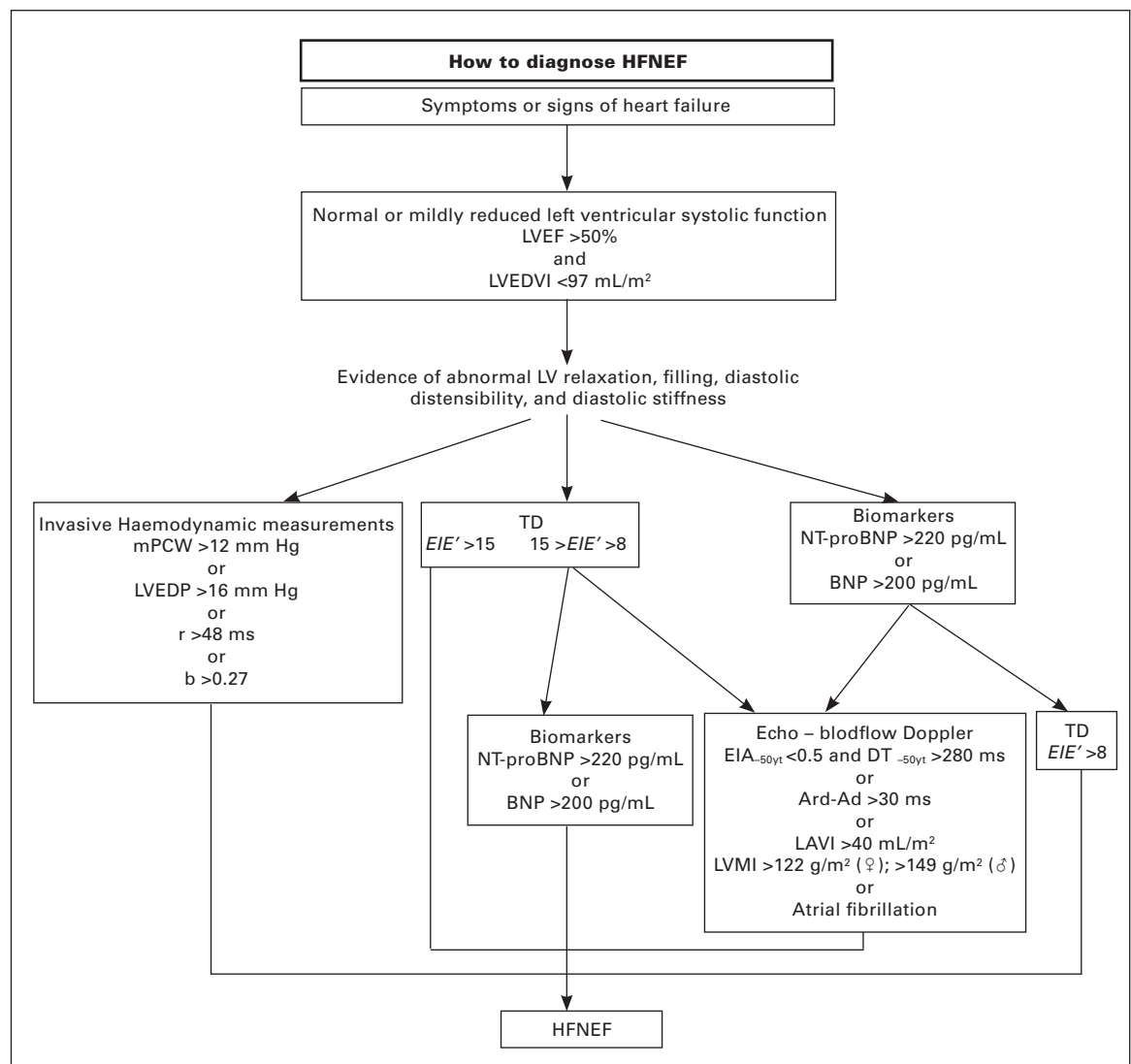
Reproduced with permission from Paulus et al. [7]. HFNEF: heart failure with normal ejection fraction LVEF: left ventricular ejection fraction LVEDVI: left ventricular end-diastolic volume indexed to body surface LV: left ventricular mPCW: mean pulmonary capillary wedge pressure LVEDP: left ventricular end-diastolic pressure TD: tissue Doppler LAVI: left atrial volume indexed to body surface area LVMI: left ventricular mass indexed to body surface area. See text for other abbreviations.
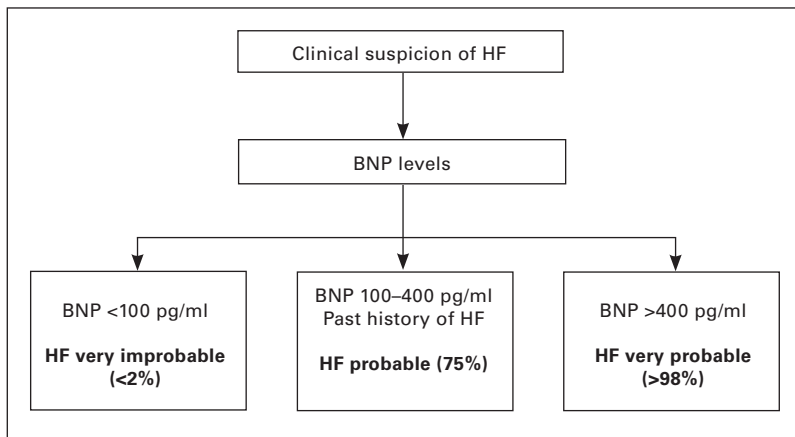
Clinical suspicion of HF

BNP levels

BNP <100 pg/ml

HF very improbable (<2%)

BNP 100–400 pg/ml
Past history of HF

HF probable (75%)

BNP >400 pg/ml

HF very probable (>98%)

Figure 3

Use of BNP for the diagnosis of HF.
Adapted and reproduced with permission from Maisel et al. [46]
HF: heart failure

been better validated than the various echo-Doppler variables for the diagnosis and prognosis of HF. Therefore, they are often put forward by most experts for the diagnosis of HFNEF (fig. 3) and

used as inclusion criteria in most ongoing studies of HFNEF [46].

After the diagnosis of HF has been made, diastolic dysfunction must be proved to confirm the presence of HFNEF. The hallmark of diastolic dysfunction is elevated filling pressures, such as LVEDP and pulmonary capillary wedge pressure (mPCWP), which can be measured invasively [7]. However, invasive haemodynamic studies are rarely undertaken and non invasive parameters are most often used to confirm diastolic dysfunction.

TTE is the most widely available confirmatory tool for HF, and the ESC and Swiss guidelines both recommend its use. As already discussed, it can distinguish between HFNEF and HFREF, but also gives clues for the etiology of HF. In addition, TTE has a prognostic value, since low EF, LV remodeling and LV restrictive filling patterns are associated with a high mortality. TTE has some limitations, and cardiac catheterization should be considered for more accurate measurement of LVEDP and PCWP.

Management of HFNEF

As HFNEF is associated with significant morbidity and mortality [1], patients should have regular medical visits to evaluate worsening of signs and symptoms, associated with regular echocardiographic evaluations, in order to initiate appropriate therapy in case of a worsening of systolic function. Cardiovascular risk factors should be detected and treated. Rapid or unexpected deterioration should be quickly assessed by cardiologists.

Medical therapy with beta-blockers, ACE-inhibitors and spironolactone has been shown to improve the prognosis of HFREF [2–5, 8]. In contrast, there is no convincing evidence that any medication could significantly improve survival of HFNEF patients.

Four randomized clinical trials (RCTs) have addressed the effect of various medications in HFNEF: DIG-CHF, PEP-CHF, CHARM-Preserved, and I-Preserve [12, 50–52]. They all failed to show a reduction of a composite endpoint of hospital admission and mortality. However, some aspects in the design of these studies could partially explain these negative results.

Nevertheless, observational data and studies using surrogate endpoints suggest that patients with HFNEF poorly tolerate acute elevations of blood pressure (BP), tachycardia, AF and ischemia. Hence, treatment aiming at lowering BP, avoiding tachycardia and relieving ischemia may improve diastolic relaxation [53]. The 2005 ACC/AHA guidelines state that BP should be kept in the low range of normal, with no clear indication as to which drug should be used (class I, level A) [54]. Ventricular rate should be controlled in patients with chronic AF (Class I, level C), and diuretics

should be used for peripheral and pulmonary congestion (Class I, level C). Yip and al conducted a small randomized trial in patients with HFNEF, comparing diuretics alone to diuretics with irbesartan or ramipril, and showed that diuretic therapy alone or in combination increased the quality of life and also marginally increased the six-minutes walking distance [55]. However, cardiac output of HFNEF patients may be load-dependent and diuretics need to be administered cautiously in these patients.

Results in HFREF suggest that other drugs might have a beneficial effect in HFNEF, such as beta-blockers and aldosterone blockers, but their effect on mortality or major cardiovascular outcomes has not yet been studied in RCTs. The ACC/AHA nevertheless encourage beta-blockers, renin-angiotensin system blockers, and calcium channels blockers to decrease HF symptoms (class IIb, level C) [54].

Coronary revascularization is also recommended in patients with demonstrable ischemia, but with a weaker level of evidence (class IIa, level C) [54].

Other developments could improve the management of HFNEF. Diastolic pulmonary pressure is a good surrogate for PCWP and LV filling pressure and can be invasively monitored in outpatients with HFNEF by an implantable device called e-PAD [13]. This continuous monitoring could better stratify the severity of diastolic dysfunction and detect earlier acute exacerbations, introducing a new mean of following patients with chronic HF, with an individualized impact on therapy.

Conclusions

The clinical importance of HFNEF is nowadays clearly recognized, and its incidence is increasing. HFNEF has a high morbidity and mortality, and is frequently associated with old age, hypertension, and female gender. The diagnosis of HFNEF is not straightforward, and clinical suspicion must be confirmed with TTE, which can be misleading in this situation. For this reason, the ESC proposed new diagnostic criteria, supported by a simple algorithm. No significant improvement in HFNEF prognosis has been detected in recent years, mainly because most HF trials have only included patients with systolic dysfunction. Four RCTs involving patients with HFNEF failed to show beneficial effects of digitalis, ACEI and ARBs. This does not necessarily mean that these therapies don't work in HFNEF, and the new ESC definition may allow identification of more homogeneous populations and may lead to better designed clinical trials. Until such trials are conducted and results are known, a pragmatic management is required, by treating associated and worsening conditions, such as hypertension, tachycardia and congestive symptoms, with regular controls of systolic ventricular function.

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