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Multimodality imaging in patients with heart failure and preserved ejection fraction: an expert consensus document of the European Association of Cardiovascular Imaging

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Nearly half of all patients with heart failure (HF) have a normal left ventricular (LV) ejection fraction (EF) and the condition is termed heart failure with preserved ejection fraction (HFpEF). It is assumed that in these patients HF is due primarily to LV diastolic dysfunction. The prognosis in HFpEF is almost as severe as in HF with reduced EF (HFrEF). In contrast to HFrEF where drugs and devices are proven to reduce mortality, in HFpEF there has been limited therapy available with documented effects on prognosis. This may reflect that HFpEF encompasses a wide range of different pathological processes, which multimodality imaging is well placed to differentiate. Progress in developing therapies for HFpEF has been hampered by a lack of uniform diagnostic criteria. The present expert consensus document

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from the European Association of Cardiovascular Imaging (EACVI) provides recommendations regarding how to determine elevated LV filling pressure in the setting of suspected HFpEF and how to use multimodality imaging to determine specific aetiologies in patients with HFpEF.

Keywords diastole • echocardiography • filling pressure • heart failure • multimodality imaging

Background and objective

Nearly half of all patients with heart failure (HF) have a normal left ventricular (LV) ejection fraction (EF) and the condition is termed heart failure with preserved ejection fraction (HFpEF). It is assumed that in these patients HF is due primarily to LV diastolic dysfunction. The prognosis in HFpEF is almost as severe as in HF with reduced EF (HFrEF). In contrast to HFrEF where drugs and devices are proven to reduce mortality, in HFpEF there is limited therapy available with documented effects on prognosis,[1] while recent data (EMPEROR-Preserved trial) indicate that patients with HF and EF > 40% could benefit from empagliflozin therapy. This may reflect that HFpEF encompasses a wide range of different pathological processes, which multimodality imaging is well placed to differentiate.

Progress in developing therapies for HFpEF has been hampered by a lack of uniform diagnostic criteria. A recent consensus report from the European Heart Failure Association (HFA) and the recent HF guidelines of the European Society of Cardiology (ESC) have provided diagnostic criteria for HFpEF.[1,2] The present document is a consensus report from the European Association of Cardiovascular Imaging (EACVI) and explains how multimodality imaging and assessment of LV filling pressure should be used in patients with HFpEF, and is complementary to the HFA report and to the ESC HF guidelines.

The clinical syndrome of HF

Congestive HF is a clinical syndrome consisting of symptoms (mainly dyspnoea and fatigue) and signs (lung crackles, high jugular venous pressure, and peripheral oedema) due to structural and/or functional cardiac abnormalities that lead to reduced cardiac output and/or elevated intracardiac diastolic pressures.[1]

Traditionally, HFrEF was defined as systolic HF and HFpEF as diastolic HF. This categorization is now rarely used since it is well established that patients with HFpEF often have systolic dysfunction as reflected in reduced LV long-axis shortening,[3] and patients with HFrEF typically have impaired diastolic function as indicated by elevated LV filling pressure at rest or during exercise. It is also important to make a distinction between HFpEF and diastolic dysfunction since although diastolic dysfunction is the most important underlying mechanism for HFpEF, not all patients with diastolic dysfunction have HF.

As described in the present document, cardiac imaging provides essential information for the diagnosis of HFpEF by identifying relevant structural heart disease, signs of impaired myocardial relaxation or increased diastolic stiffness, and elevated LV filling pressure. Importantly, symptoms and signs can be erroneously attributed to HFpEF when in fact they can also be due to non-cardiovascular comorbidities. Moreover, HFpEF represents a variety of different cardiovascular phenotypes. This could be one factor to explain why most clinical trials have been unsuccessful in HFpEF since different phenotypes may not respond uniformly to the same therapies. Importantly, some of the phenotypes, including hypertrophic cardiomyopathy (HCM), cardiac amyloidosis, and others, have specific therapies and therefore are important to identify. There are also non-myocardial conditions with HF symptoms, such as constrictive pericarditis, valvular heart disease, and non-cardiac pulmonary hypertension, but we do not consider these as HFpEF although clinically they may mimic HFpEF.

Comorbidities of HFpEF

Comorbid conditions in patients with HFpEF are common and may often act as important contributors to the diastolic dysfunction that characterizes this disease. The comorbidities include arterial hypertension, obesity, chronic renal failure, anaemia, diabetes mellitus, lung disease, sleep apnoea, and liver disease.[4–6] Arterial hypertension is the most common comorbidity, affecting more than 80% of HFpEF patients. Diabetes can lead to impairment of LV systolic and diastolic function, in part reflecting simultaneous arterial hypertension or coronary artery disease (CAD), but may also be due to specific diabetic changes in the myocardial extracellular space, which includes increased myocardial fibrosis. Comorbid conditions increase HFpEF mortality. As proposed by Paulus and Tschöpe,[7] comorbidities may contribute to the progression of myocardial dysfunction in HFpEF through microvascular endothelial inflammation.

In addition to non-cardiac comorbidities, HFpEF patients may suffer from CAD, atrial fibrillation (AF), and valvular heart disease of various severity, all of which are also associated with increased cardiovascular event rates. Furthermore, healthy ageing is associated with a reduction in LV end-diastolic volume, and healthy sedentary elderly appear to develop a stiffer LV after the mid-60s.[8,9] It is not known, however, if normal age-related stiffening contributes to the development of HFpEF. There are several disorders, including arterial hypertension, CAD, and diabetes, which may explain why HFpEF is primarily a disease of the elderly. Furthermore, as shown in a large population study in patients with HF, there are slightly more females than males with HFpEF.[10]

The diagnosis of HFpEF may be difficult in patients with comorbidities that mimic HFpEF symptomatology, in particular chronic respiratory conditions and obesity. Pulmonary disease can be found in ~30–40% of HFpEF patients and significantly affect prognosis. Thus, these patients need detailed work-up, including assessment of lung function. Obesity and diabetes mellitus are also common.[4] The published prevalence of diabetes ranges from 20% to 40% in HFpEF. Diabetes is associated with adverse cardiovascular outcomes, and the inherent

risk of adverse outcomes varies depending on the presence of microvascular complications.[5] Furthermore, renal failure leads to volume overload as well as elevation of systemic arterial pressure, but appears less associated with outcome.[11] CAD should be excluded in every HFpEF patient. Based on patient history alone, the diagnosis of CAD can easily be missed as it is particularly difficult to differentiate between dyspnoea and angina in obese, hypertensive, and often diabetic patients. AF is a major mechanism of diastolic dysfunction as it results in the reduction of LV filling due to the absence of atrial systole. AF is present in more than half of patients with HFpEF.[10] AF, however, also often results from the increased atrial stretch due to increased left atrial (LA) pressure in the setting of a stiff ventricle. AF complicates the diagnosis of HFpEF since the evaluation of diastolic function is different when there is no atrial contribution to LV filling.

Mechanisms of diastolic LV dysfunction

The term LV diastolic dysfunction describes a situation where sufficient LV filling to obtain adequate stroke volume at rest or during exercise requires abnormal elevation of diastolic filling pressures. The fundamental mechanisms of diastolic dysfunction are (i) impairment of myocardial relaxation due to inadequate sarcolemmal Ca^{2+} removal, (ii) increased passive elastic LV stiffness due to LV remodelling, and (iii) loss of diastolic suction due to attenuation of LV restoring forces[12–14] (*Figure 1*). In response to impairment of diastolic function, there is typically compensatory elevation of LV filling pressure as a mechanism to maintain stroke volume according to the Frank-Starling mechanism.

Increased LV diastolic stiffness in the hypertrophic ventricle in HFpEF can be attributed to increased wall thickness combined with stiffening of each unit of the myocardium due to excessive interstitial collagen deposition and changes in the giant cytoskeletal protein titin. Furthermore, ventricular stiffness is also modified by external forces exerted by the pericardium, the lungs, and the right ventricle.

LV restoring forces represent elastic potential energy which is stored in the myocardium when the ventricle contracts below its unstressed volume and by twisting deformation. When the ventricle relaxes, the energy is released and accounts for diastolic suction. This may be measured as negative LV early-diastolic pressure which represents the suction force that facilitates LV filling. As illustrated in *Figure 1*, this is analogous to the compression of an elastic spring which recoils back to its resting length when the compression is released. In ventricles with increased end-systolic volume or reduced twist, there is less compression of the myocardium and the result is attenuated restoring forces. Therefore restoring forces are generated in systole and exert their effect in diastole, and illustrate the tight coupling between LV systolic and diastolic function.

As shown in experimental studies, the magnitude of restoring forces is reflected in LV early-diastolic untwisting rate.[15] In patients with HFpEF, however, untwisting velocities may be normal at rest, although the onset of untwisting may be delayed.[16] This probably is explained by relatively small LV end-systolic volume in HFpEF which could mean preserved restoring forces at rest. Therefore, attenuation of restoring forces and loss of apical suction is probably not a major mechanism of elevated LV filling pressure in HFpEF patients at rest. During exercise, however, loss of diastolic suction may explain the need for elevated LA pressure to maintain adequate transmitral flow. *Figure 2*, lower panel, illustrates elevation of LV minimum pressure during exercise in a patient with HFpEF.

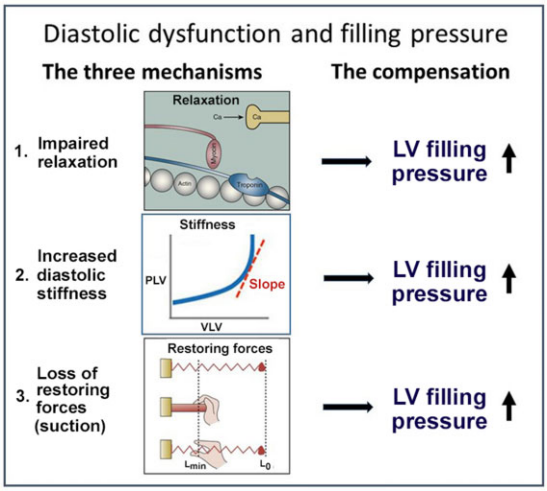

Figure 1 Mechanisms of LV diastolic dysfunction. The three fundamental mechanisms of LV diastolic dysfunction are impaired myocardial relaxation, increased passive elastic stiffness, and loss of restoring forces. Each one of these mechanisms may impair LV filling, and as a compensatory mechanism, there is elevated LV filling pressure. Based on Opdahl *et al.*[14] L_{min}, minimum length of the compressed spring; L_0, unstressed length.

Diagnostic work-up for HFpEF

Many patients are seen first in general practice and conventional tests, such as ECG, standard blood tests and natriuretic peptides are useful for an initial evaluation. In some cases, the chest X-ray may provide important information by showing signs of pulmonary congestion or finding a non-cardiac cause of dyspnoea.

When evaluating patients suspected of having HFpEF, it is important to search for a specific aetiology (*Figure 3*). The most common aetiology is CAD combined with arterial hypertension. These patients are managed effectively according to established treatment protocols. In some cases, there may be CAD unsuitable for revascularization.

If echocardiography suggests cardiomyopathy with characteristic findings, such as in HCM, this is often sufficient for a conclusive diagnosis. Other cardiomyopathies may need confirmation by additional imaging and in particular cardiac magnetic resonance (CMR). In a limited number of patients, a myocardial biopsy may be helpful. In some cases, right heart catheterization may be needed to rule out alternative diagnoses, such as non-cardiac types of pulmonary hypertension or constrictive pericarditis (CP). In most patients suspected of HFpEF, however, the diagnosis can be confirmed non-invasively by multimodality imaging. When non-cardiac disorders and specific phenotypes are excluded, and there are echocardiographic signs of increased LV filling pressure, it is reasonable to conclude that a

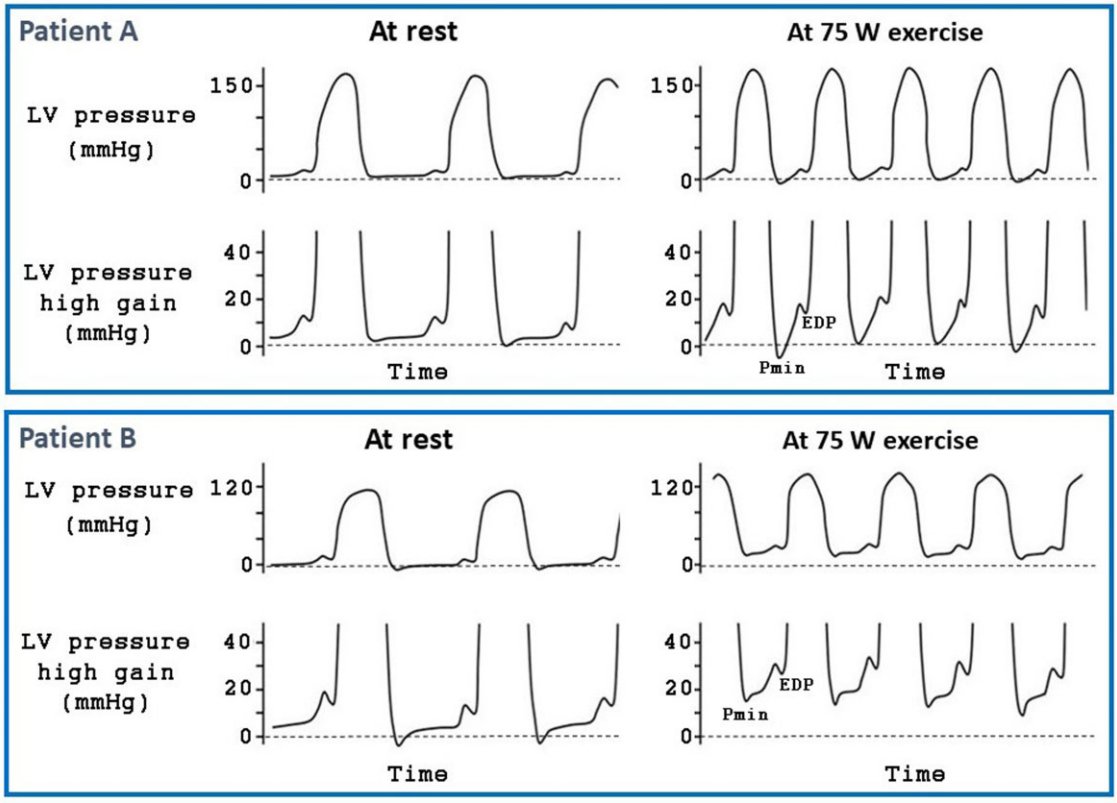

Figure 2 Recordings from two patients one year after percutaneous coronary intervention (PCI), but no coronary stenosis at the time of the study. Patient A responds to bicycle exercise with mild elevation of LV end-diastolic pressure (EDP) and a fall in minimum LV pressure (P_{min}), indicating maintained diastolic suction. In Patient B, however, LV EDP approaches 30 mmHg during exercise and there is a marked elevation of minimum LV pressure, indicating loss of diastolic suction. To maintain LV filling during exercise, Patient B would require marked elevation of left atrial pressure. Courtesy of Dr. Jong-Won Ha.

patient has HFpEF. In some cases, however, the study is inconclusive and an invasive investigation is needed. In other cases, supporting evidence for the diagnosis can be obtained by using a scoring system, such as the one from the HFA of the ESC.[2]

Invasive assessments

LV relaxation can be measured clinically as the time constant (*tau*) of LV pressure decline during isovolumic relaxation[17] (*Figure 4*). The pressure decline is usually nearly exponential, and therefore the slope of natural logarithm of LV pressure (ln PLV) vs. time is linear. Because it is more practical with a positive number and more intuitive that slow relaxation results in a larger number, *tau* is calculated as the negative inverse of this slope.[17] Values of tau >48 ms are considered a sign of slow relaxation.[19]

Diastolic compliance (inverse of stiffness) can be measured as the slope of the LV end-diastolic pressure–volume relationship. This measure is rarely used clinically due to the complexity of constructing pressure–volume relations over a sufficiently large range of volumes or pressures. *Figure 4* (right panel) shows LV diastolic pressure–volume relations in subjects with normal hearts and patients with HF. When compliance is calculated from LV pressure–volume data, it is named 'chamber compliance' since it reflects the lumped properties of the LV wall and external forces which include pericardium, lungs, and the right ventricle. Calculation of LV myocardial compliance is feasible in research studies by subtracting pericardial pressure from LV pressure, i.e. transmural LV pressure, and calculate slopes of the LV transmural pressure–volume curve.[20]

The terms LV preload and LV filling pressure are often used interchangeably when discussing cardiac function, and in most clinical conditions there are concordant changes in the two parameters. Preload refers to how much the myocardium is stretched before contraction and is linked to the Frank–Starling law and sarcomere length. The term LV filling pressure refers to the pressure that fills the LV and is used differently depending upon which pressure is available. Both LA mean pressure and LV end-diastolic pressure (LVEDP) are used to represent LV filling pressure, but the latter should be preferred when the focus of the study is LV mechanical function since it has a more direct relationship to LV end-diastolic volume. When the issue is pulmonary congestion, LA pressure is more relevant since it is more closely related to pulmonary venous pressure. Direct measurement of LA pressure is rarely feasible but can be estimated as the pulmonary capillary wedge pressure (PCWP) during right heart

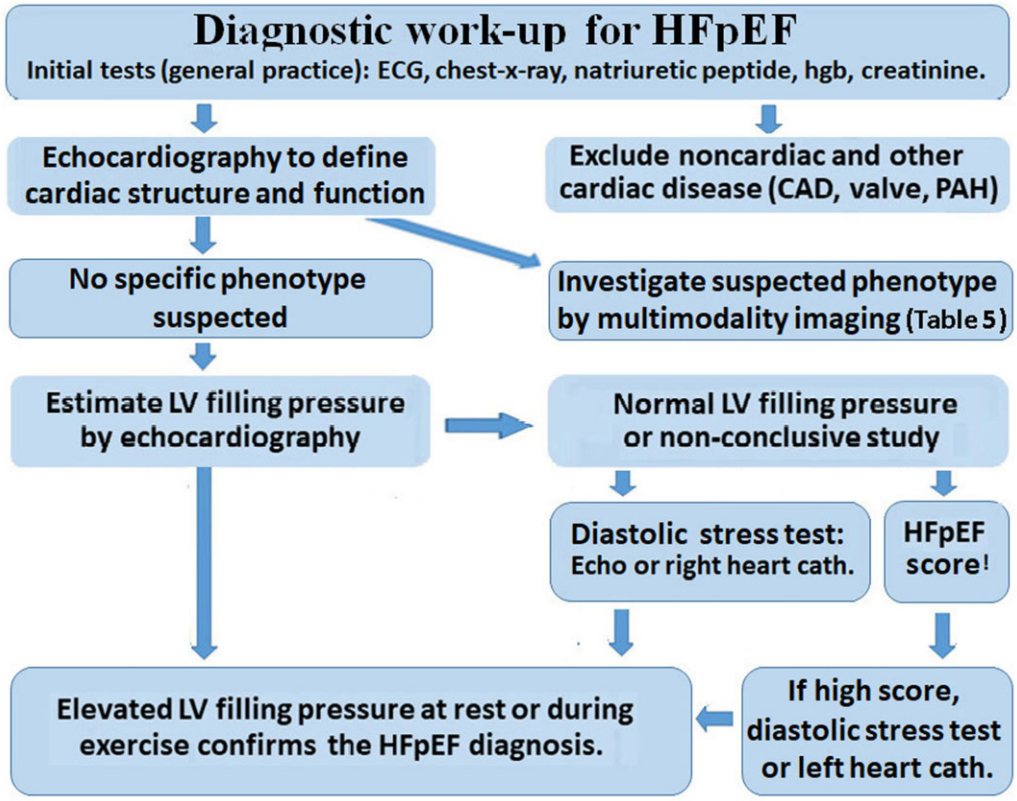

Figure 3 Diagnostic work-up for HFpEF.! According to Pieske *et al.*[2]

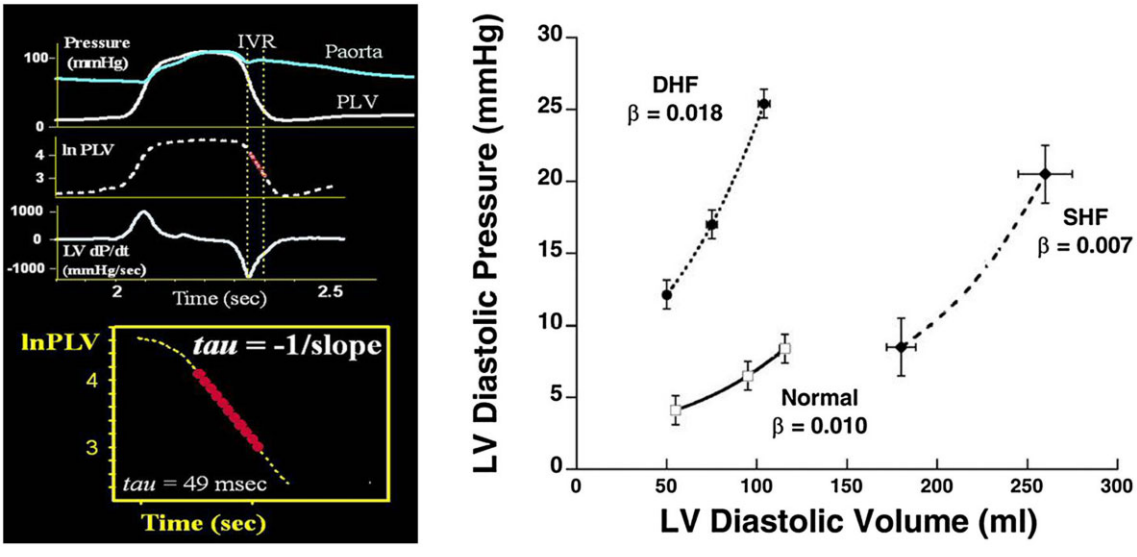

Figure 4 Left panel shows the calculation of the time constant of LV isovolumic relaxation (from Smiseth).[18] The right panel shows diastolic pressure-volume relations in subjects with normal LV function and in patients with HFpEF (labelled DHF for 'diastolic HF') and HFrEF, (labelled SHF for 'systolic HF'), respectively (from Aurigemma *et al.*[12]).

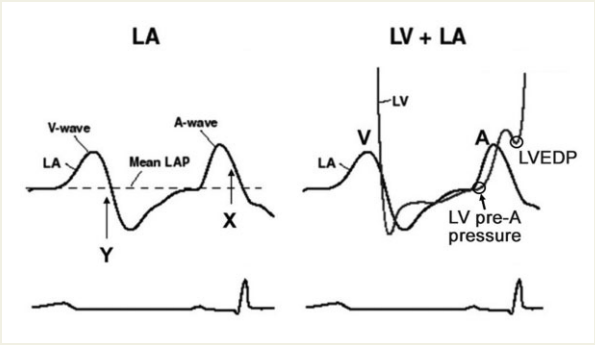

Figure 5 Left ventricular and left atrial pressures: LV end-diastolic pressure (LVEDP), LV pre-A pressure, and mean left atrial pressure (LAP) are indicated. Modified from Nagueh *et al.*[21]

catheterization and as the LV pre-A-wave pressure during left heart catheterization (*Figure 5*).[22]

A caveat is that there are clinical conditions where LV end-diastolic pressure and LA mean pressure do not represent preload. The most obvious one is in patients with substantial pericardial effusion. Furthermore, in patients on mechanical ventilation and positive end-expiratory pressure (PEEP) there may be a reduction of LV end-diastolic volume, but elevation of LV end-diastolic pressure due to an increase in extracardiac pressure (pericardial pressure). In these patients, LV preload can be measured as transmural end-diastolic pressure which is the effective filling pressure. Since pericardial pressure can be approximated as mean right atrial pressure, LV transmural filling pressure during PEEP can be calculated as PCWP minus mean right atrial pressure.[20,23]

As illustrated in *Figure 5*, mean LA pressure approximates LV pre-A pressure and is slightly lower than LV end-diastolic pressure. The difference between LV pre-A and end-diastolic pressure may be substantial when there is forceful LA contraction into a stiff ventricle. *Figure 2* shows LV pressure recordings during exercise in two different patients, including a patient with marked elevation of minimum LV pressure during exercise, indicating loss of diastolic suction.

When evaluating patients for potential HF, resting LV end-diastolic pressure ≥16 mmHg and PCWP ≥15 mmHg are considered elevated. Values of PCWP >12 mmHg have also been used to define elevated LV filling pressure.[19,24] Although higher values than these cut-offs are considered diagnostic, normal values of LVEDP or PCWP at rest do not exclude HFpEF. LV filling pressure may be normal at rest and may increase to abnormal values only during exercise, which can be measured as a rise in PCWP during supine bicycle exercise.[25] This constitutes the background of the diastolic exercise test. During exercise, PCWP ≥25 mmHg is considered abnormally elevated and confirms the HF diagnosis.

There is no feasible invasive measure of LV restoring forces, but in general, restoring forces track relaxation. The level of minimum LV diastolic pressure reflects restoring forces and negative pressures suggest active diastolic suction. Since ongoing filling may hide a negative early-diastolic pressure, quantification of suction by pressure estimate is challenging. As described under the section on non-invasive imaging, the speed of early-diastolic mitral-to-apical flow propagation reflects suction.[26,27]

Evaluation of LV function by strain imaging

LV strain by echocardiography was first introduced as a Doppler-based method,[28] but was later replaced by speckle tracking echocardiography (STE) which has become the clinical standard.[29] The most robust strain parameter is global longitudinal strain (GLS) which is shown to be more sensitive than EF as a measure of LV systolic dysfunction. GLS is calculated as the average of the peak systolic longitudinal strain from all LV segments in apical four-, three-, and two-chamber views.[30] Similar to EF, myocardial strain is dependent on loading conditions and is therefore not a pure measure of contractility.[31]

In a recent meta-analysis that included 24 studies with 2597 healthy subjects, normal values for GLS ranged from 15.9% to 22.1% (mean 19.7%; 95% confidence interval: 20.4–18.9%). Values are somewhat vendor dependent, but GLS <16% represents reduction in LV systolic function and GLS between 16% and 18% represents borderline values.[32] Reduced GLS is found in ~50–60% of HFpEF cases.[3,33,34]

The apparent discrepancy between GLS and EF is explained by EF being related predominantly to LV circumferential shortening, whereas GLS measures longitudinal shortening.[35,36] Myofibres that account for longitudinal shortening are located mainly in the vulnerable subendocardium and therefore reduction in GLS often precedes a reduction in EF. Furthermore, hypertrophic ventricles tend to have small cavities, and then even a small stroke volume results in a normal or supernormal EF. This geometry is typical for many phenotypes of HFpEF, and therefore GLS represents a better method than EF to identify co-existent LV systolic dysfunction in this setting.[30]

GLS should be measured routinely in addition to EF, in patients who are evaluated for potential HFpEF. In principle, mitral annular motion by M-mode (MAPSE) or systolic mitral annular velocities by tissue Doppler provide similar diagnostic information. The evidence supporting GLS, however, is stronger and the other two methods extrapolate local information as an indicator of global LV function. There are specific phenotypes where GLS maps provide clues about the substrate of HFpEF and these are addressed in other parts of this document (e.g. cardiac amyloidosis).

Imaging of LV structure and mass

Imaging of LV structure should be performed according to current American Society of Echocardiography (ASE) / EACVI recommendations.[30] LV geometry is traditionally classified based on LV mass and relative wall thickness (RWT), calculated as two times posterior wall thickness divided by LV internal diameter at end-diastole (normally RWT ≤ 0.42).[30] If both LV mass and RWT are normal, LV geometry is considered normal, and if both are elevated, there is concentric hypertrophy. When LV mass is normal and RWT is increased, there is by definition, concentric remodelling. Both concentric remodelling and hypertrophy are associated with increased morbidity and mortality.[37,38] Both these abnormal geometries are prevalent in HFpEF.[39] Another geometry that occurs more frequently in HFrEF, is eccentric hypertrophy, defined as increased LV mass with normal RWT. Although echocardiography is the most widely used method to

identify abnormal LV geometry, it is important to highlight that CMR provides the gold-standard for assessment of LV mass and wall thickness, and in addition, may be used to image myocardial fibrosis. Importantly, increased LV mass (by definition, not hypertrophy) may also be due to storage and infiltrative diseases, such as amyloidosis.

The most common cause of LV hypertrophy is arterial hypertension which may lead to hypertensive heart disease and HFpEF. HF symptoms are attributed to increased diastolic stiffness which implies the need for increased LV diastolic pressure to obtain adequate filling, in particular, during exercise. Impairment of LV systolic function, as indicated by the reduction in GLS, may also contribute to HF symptoms. LV filling pressure may be normal at rest, corresponding to grade I LV diastolic dysfunction.

Since arterial hypertension is common in the general population, one should always consider if LV hypertrophy may have other causes, such as HCM, while in the elderly cardiac amyloidosis is an important differential diagnosis. When the aetiology of LV hypertrophy is uncertain, and in particular when the echocardiographic images are suboptimal, it is important to consider CMR for a more accurate assessment of LV structure and a more definitive diagnosis. Furthermore, since arterial hypertension is often associated with CAD, it is important to exclude myocardial ischaemia by appropriate diagnostic tests. Another differential diagnosis of LV hypertrophy is the athlete's heart. This condition is differentiated from pathologic remodelling by balanced hypertrophy of myocytes and collagen and therefore these subjects have normal diastolic elasticity. Athletes' hearts also have normal myocardial relaxation, and therefore mitral annular e' is normal.

Despite the high prevalence of LV hypertrophy in HFpEF trials, LV structure was normal in 31% of HFpEF patients in a community-based study[40] and 46% of HFpEF patients in the I-PRESERVE and PARAGON-HF study.[39,41] Therefore, the finding of either concentric remodelling or LV hypertrophy provides support for the HFpEF diagnosis but is not obligatory criteria since they may be absent in many HFpEF patients (*Figure 6*). Furthermore, when there is LV hypertrophy or concentric remodelling, this is not sufficient to conclude that a patient has HFpEF. Demonstration of elevated LV filling pressure at rest or with exercise is needed for a definitive diagnosis of HFpEF.

Myocardial tissue characterization by CMR

Besides allowing comprehensive evaluation of patients with HFpEF, including precise assessment of cardiac chamber size and function and detection of ischaemia, CMR is the only imaging technique to provide detailed tissue characterization of the myocardium and assessment of myocardial fibrosis. Indeed, late gadolinium enhancement (LGE) allows identification of silent myocardial infarction and provides important diagnostic information in specific cardiomyopathies, such as amyloidosis, HCM, sarcoidosis, and cardiac haemochromatosis, and in the diagnostic approach of constrictive pericarditis.[42]

An important feature of CMR is its ability to quantify not only post-infarction focal fibrosis by LGE but also diffuse myocardial fibrosis by T1 mapping. Since diffuse fibrosis increases the extracellular volume (ECV) relative to cardiomyocyte volume, ECV fraction is a marker of fibrosis. Signs of myocardial fibrosis by T1 mapping and increased ECV fraction were found in patients with HFpEF,[43,44] and demonstrated good correlations with histologically detected fibrosis,[43] LV stiffness,[45] and impaired LV diastolic function.[46] ECV expansion also correlates with markers of disease severity, such as N-terminal prohormone brain natriuretic peptide (NT-proBNP), 6-min walk distance, New York Heart Association (NYHA) class, and right atrial pressure. Moreover, ECV expansion can be observed in conditions, such as arterial hypertension and diabetes before the development of overt HF. Thus, CMR is a useful advance for the diagnosis of HFpEF and in understanding the underlying aetiology. It is also an important tool for risk prediction and stratification not only in patients with established HFpEF but also in patients at risk of developing HFpEF. However, with the exception of application in cardiac amyloidosis, the clinical role of T1 mapping in HFpEF remains unclear. Further research is required to better understand how this interesting imaging technique can be utilized for patient management.

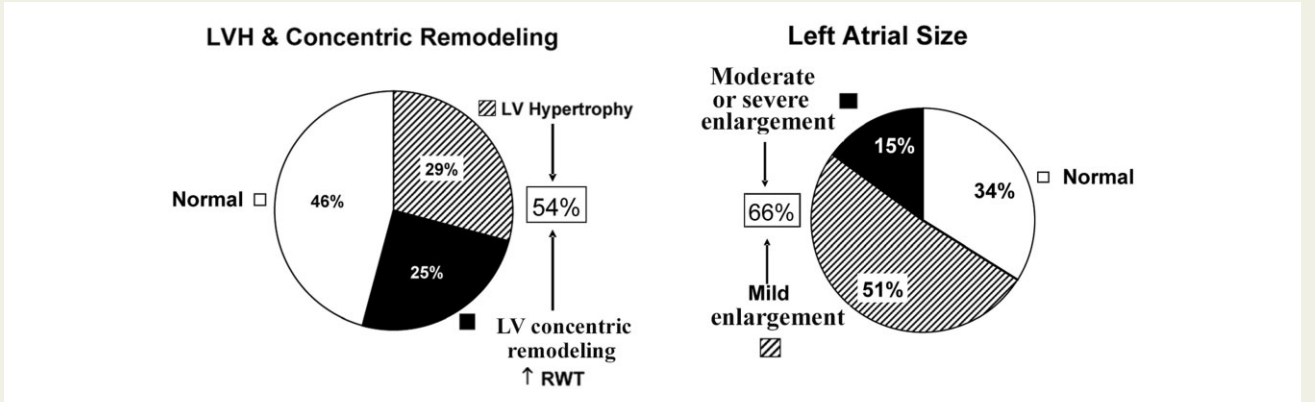

Figure 6 Left panel: prevalence of LV hypertrophy and concentric remodeling in patients with HFpEF. Right panel: prevalence of LA enlargement in HFpEF patients. RWT, LV relative wall thickness. Modified from Zile *et al.*[39]

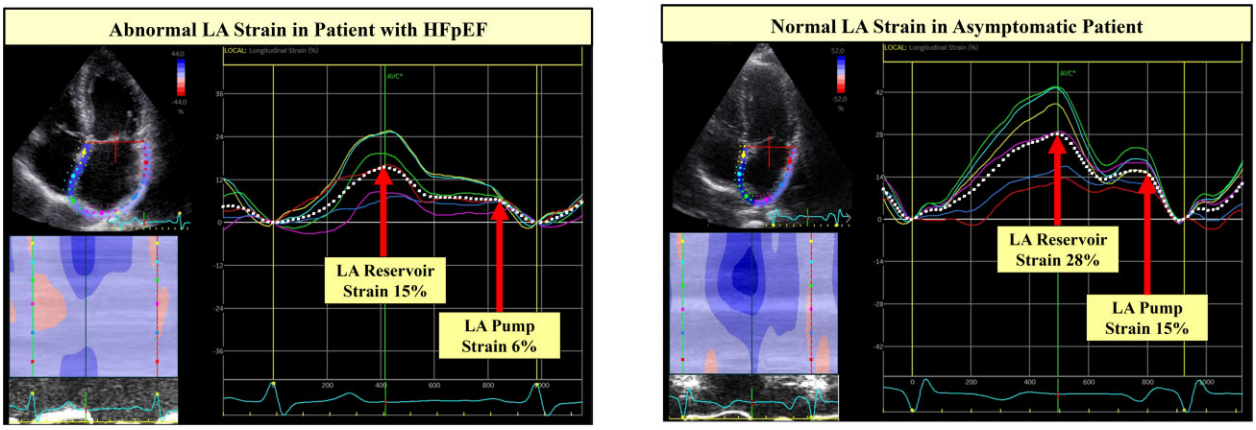

Figure 7 Measurement of left atrial strain in apical four-chamber view. The left panel shows a patient with HFpEF and abnormal LA reservoir and pump strains and in the right panel a patient with normal LA strains.

Evaluation of left atrial structure and function

Assessment of LA size by echocardiography should be performed using dedicated LA views, thereby avoiding foreshortening. LA volume is measured using the biplane disk summation technique, and volumes are indexed to body surface area (LAVi). Conventionally, maximum LA volume is reported. Minimal LA volume appears to provide diagnostic information relatively similar to maximum LA volume but may have greater measurement variability. The upper normal limit for LAVi by 2D echocardiography is defined as 34 mL/m^2.[30] However, ~10% of apparently heart-healthy individuals have LAVi above 34 and ~5% have values exceeding 37 mL/m^2.[47] LA volume can also be quantified by 3D transthoracic echocardiography and by CMR (of note, values derived from 3D echocardiography and CMR are usually greater than those derived from 2D echocardiography).[30]

Enlarged left atrium is frequent in patients with HFpEF and is associated with increased cardiovascular risk and is a marker of elevated LV filling pressure.[21,48] Therefore, LAVi should be measured in all patients with suspected or definite HFpEF.

The maximal LA volume is an adequate parameter to estimate the chronic effect of increased LV filling pressure on the LA.[21,49] However, LAVi has limitations to detect early raises of LV filling pressure (i.e. low sensitivity).[21,49] Recent findings have shown that combining LAVi with a sensitive LA functional parameter, such as LA reservoir strain leads to a significant increase in the rate of detection of LV diastolic alterations and elevated LV filling pressure than using only LAVi in patients with preserved EF.[50] Elevated LV filling pressure is reflected in reductions in LA reservoir and pump strain (*Figures 7 and 8*). Recent studies have shown that LA reservoir strain has a stronger correlation with invasive LV filling pressure than LAVi.[52,53] In line with this, other studies have shown that LA reservoir strain can detect LV diastolic alterations and elevated LV filling pressure even when LAVi is normal.[50,54] Furthermore, measurement of LA reservoir strain by STE has excellent feasibility of ~95%.[51]

Median values for LA reservoir strain in healthy individuals are reported as 47%, 41%, and 36% in age groups 20–40, 40–60, and ≥60 years, respectively.[55] The lower limit of normality of LA reservoir strain is vendor and age-dependent, but values <19–23% are considered abnormally low.

A recent study that included more than 300 patients with a median LVEF of 55%, showed that both LA reservoir and pump strain were associated with LV filling pressure (*Figure 8*).[51] The optimal cut-off to differentiate between normal and elevated LV filling pressure was 18% for LA reservoir strain and 8% for pump strain when defining PCWP >12 mmHg as elevated, and 16% and 6% when using PCWP ≥15 mmHg as the criterion for elevated LV filling pressure. As illustrated in *Figure 8*, the strongest determinant of LA reservoir strain was GLS, followed by LV filling pressure and with LAVi as a third, but weaker independent determinant. For LA pump strain, LV filling pressure and GLS were equally strong determinants.

For both LA strains, the relationship to LV filling pressure was strongest in patients with reduced LV systolic function (*Figure 9*).[51] In patients with GLS >16% and EF ≥50, there were only weak associations between LA strains and LV filling pressure. In patients with GLS >18%, there were no significant correlations between LA reservoir and pump strains with LV filling pressure. Importantly, high normal values of LA pump strain (>14%) identified normal LV filling pressure with accuracy of 92% in patients with GLS ≥18%.[51] High normal values of LA reservoir strain (>24%) were also associated with normal LV filling pressure, but there was more overlap with elevated LV filling pressure. Importantly, the relatively weak relationship between LA strain and LV filling pressure observed in the study by Inoue *et al.*[51] in patients with apparently normal LV systolic function, does not exclude a role for LA strain in specific cardiac disorders. Furthermore, in HFpEF it remains to be studied if LA strain provides incremental diagnostic value when combined with other parameters of LV function than studied in the article by Inoue *et al.*[51]

When measuring LA strain, methodological factors should be taken into consideration. The term 'LA reservoir strain' refers to the average

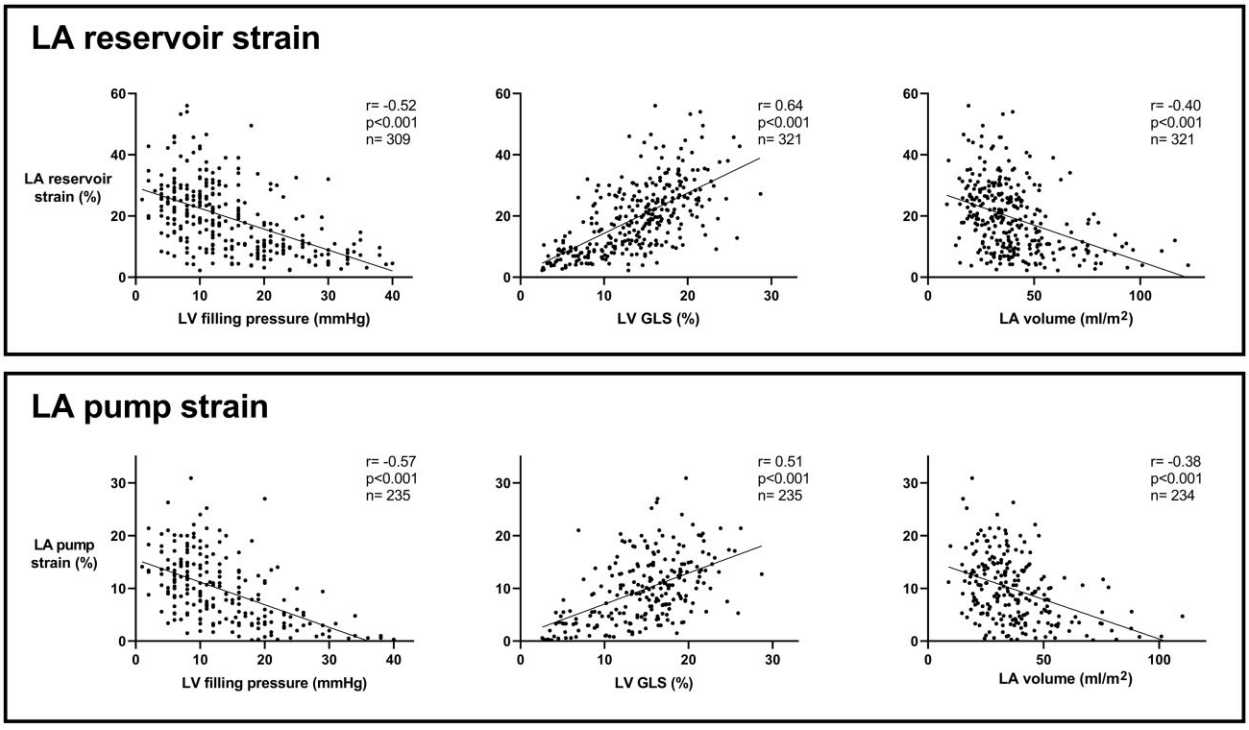

Figure 8 Determinants of LA reservoir and pump strain. From Inoue *et al.*[51]

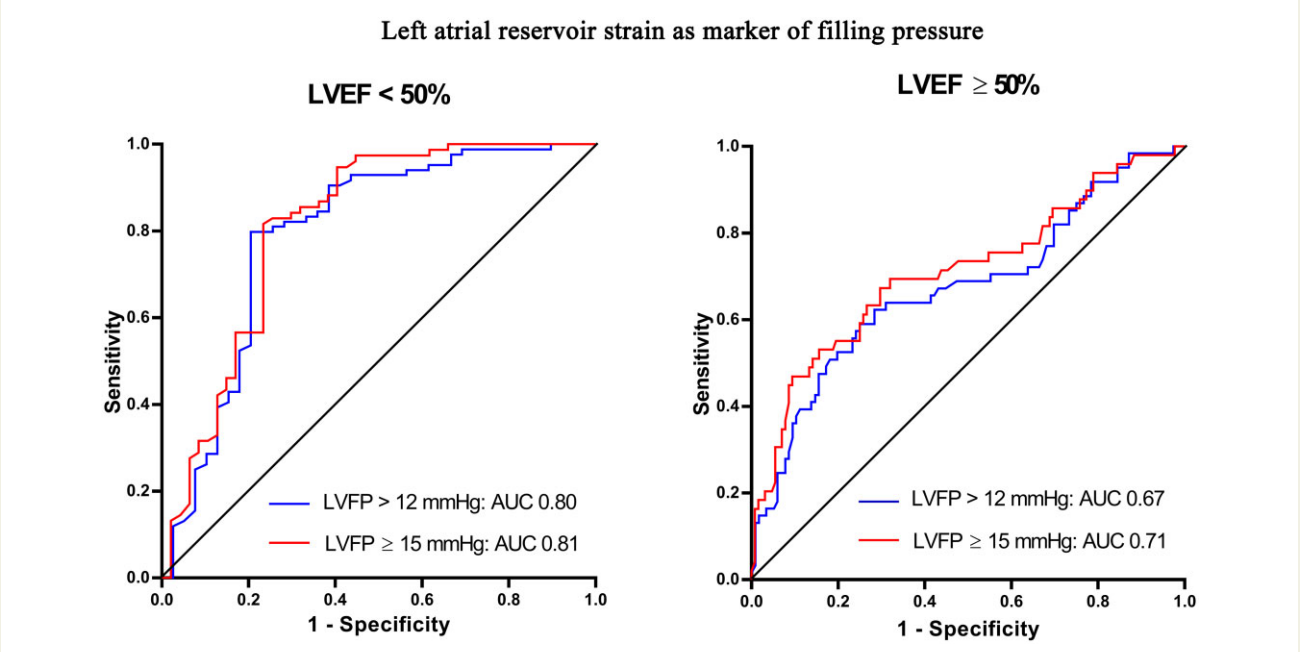

Figure 9 Classification of LV filling pressure by LA strains. ROC curves showing the ability of LA reservoir strain ($n = 309$) to classify LV filling pressure as normal or elevated. Systolic function is classified by EF. Two different definitions of elevated LV filling pressure were used with cut-offs of >12 and ≥15 mmHg. The classification was best in patients with reduced systolic function as reflected in larger AUC in ROC curves. Modified from Inoue *et al.*[51]

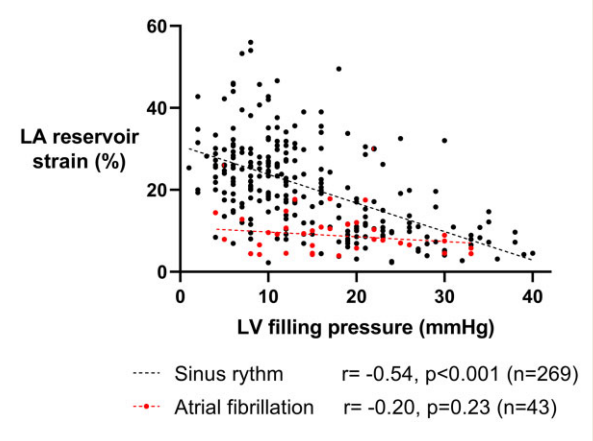

Figure 10 Atrial fibrillation and relationship between LA reservoir strain and LV filling pressure: There was no significant correlation between LA strain and LV filling pressure in patients with atrial fibrillation. LA strain values were low regardless of the level of LV filling pressure. From Inoue *et al.*[51]

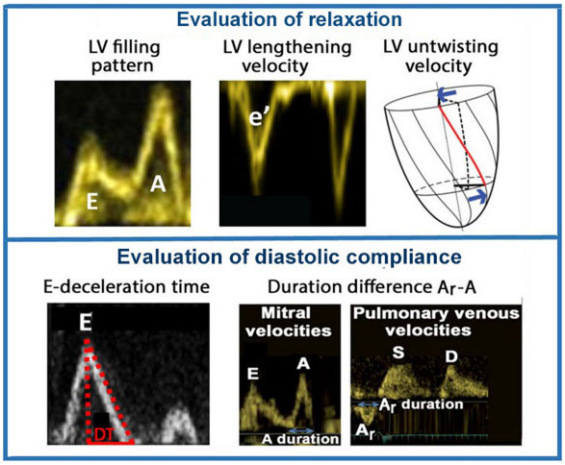

Figure 11 Echocardiographic indices of LV diastolic function. From Smiseth.[18]

of the peak positive longitudinal strain from all LA segments in the apical four-chamber view (or four plus two-chamber views) during the reservoir phase. The cut-off value for an abnormal LA strain was selected based on previous studies in healthy subjects by using the most common strain software packages (such as EchoPac and TomTec).[54–57] Hence, the optimal cut-off for abnormal LA reservoir strain using other software remains uncertain. In addition, and similar to LAVi, patients with poor 2D image quality in ≥2 LA segments in four or two-chamber views as well as those with AF should be excluded from this approach. As illustrated in *Figure 10*, LA reservoir strain should not be used to assess LV filling pressure in patients with AF. Moreover, it should be noted that patients with a history of AF ≥48 h of duration in the last 90 days could present with LA stunning and thus lower values of LA strain. Therefore, we consider that LA strain should not be used to diagnose HFpEF in the setting of possible LA stunning.

How to image key processes in LV diastolic dysfunction

No single non-invasive parameter provides a direct measure of LV diastolic function.[18] By combining several parameters, however, it is feasible in most patients to determine if LV diastolic function is normal or abnormal. *Figure 11* illustrates echocardiographic parameters which are used to assess LV relaxation and diastolic compliance. Since the LV apex is relatively stationary during the cardiac cycle, peak early-diastolic annular e′ velocity measured in apical views reflect LV lengthening velocity which is determined to a large extent by the rate of relaxation.[14] Therefore, e′ is used as an index of LV relaxation. Furthermore, slowing of relaxation leads to a reduction in the early-diastolic transmitral pressure gradient, and therefore reduction in mitral *E* and a low *E*/*A* velocity ratio with prolonged E-deceleration time. This filling pattern which is named 'impaired relaxation' and is consistent with LV diastolic dysfunction.

LV untwisting velocity is another parameter that may be used to evaluate the early-diastolic function as it reflects both LV relaxation and restoring forces.[15] Restoring forces are reflected in LV diastolic untwisting velocity and can be measured by STE.[58] There are, however, unresolved issues with regard to standardization of the methodology to measure twist. Therefore, the method is not ready for use in clinical routine. An alternative approach for assessing restoring forces is imaging of LV apical suction. This is feasible by measuring mitral-to-apical flow propagation by colour M-mode Doppler,[26,27] but the method has so far not proven to provide incremental diagnostic information. Potentially, developments within 2D or 3D flow imaging, including velocity vector imaging, will provide more useful tools for imaging flow patterns of suction.

Reduced LV diastolic compliance is reflected in a short mitral E deceleration time (<150 ms), but should always be used in combination with other indices when evaluating compliance (*Figure 11*). Reduction in LV chamber compliance is also reflected in attenuated and abbreviated transmitral A-velocity and is typically combined with accentuation and prolongation of the pulmonary vein reversed A velocity (Ar). When the duration of Ar markedly exceeds the duration of antegrade mitral A (>30 ms difference), this is consistent with elevated LV end-diastolic pressure and suggests reduced LV compliance.[59,60] Limitations of the Ar-A duration difference as a marker of compliance include atrial mechanical failure, substantial antegrade pulmonary venous flow at the time of atrial contraction (effect of blood inertia) as in tachycardia or prolonged PR interval, and technical challenges with obtaining the reversed pulmonary venous flow signal. There is promising ongoing research to image myocardial stiffness by myocardial shear wave imaging using high frame rate ultrasound imaging.[61]

Figure 12 shows patterns of mitral filling in a normal individual and three different patterns which are typical for patients with LV diastolic dysfunction. The pattern labelled relaxation abnormality is typical for ventricles with impaired LV relaxation but is also a normal pattern in old people. The pattern to the far right is named restrictive filling

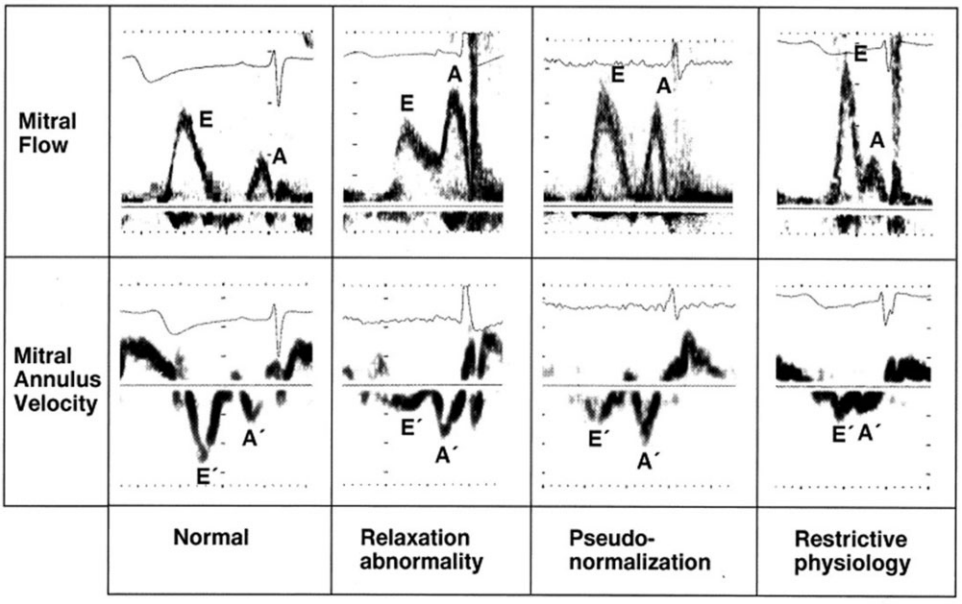

Figure 12 Mitral inflow (top) and mitral annulus velocity (bottom) for normal diastolic function, relaxation abnormality, pseudonormalized filling, and restrictive physiology. Reduced E' differentiates pattern with pseudonormalized filling from the normal pattern. From Sohn *et al.*[62]

or restrictive physiology, and is seen in ventricles with increased diastolic stiffness and elevated LV filling pressure, usually with reduced LV systolic function. The pattern named pseudonormalized filling has mitral flow velocities rather similar to those in normal hearts and is identified by the reduced *e′*. Individual patients with LV diastolic dysfunction may shift between the three patterns. This reflects an effect of filling pressure which may change a pattern of relaxation abnormality to a pattern of pseudonormalized filling when pressure is rising, and when filling pressure is further increased, to the pattern of restrictive filling. Similarly, reduction of filling pressure or performance of the Valsalva manoeuver may cause shifts in the opposite direction. Importantly, the three patterns of abnormal LV filling should not be used alone for grading of LV diastolic dysfunction since LV filling pressure is incorporated in the definitions of grades of LV diastolic function. This is discussed in the next section.

Clinical evaluation of LV diastolic function and filling pressure

Rationale behind echocardiographic markers of LV filling pressure

Figure 13 illustrates indices for evaluation of LV filling pressure. Each of these indices has both a theoretical rationale and documentation from correlation analysis of a relationship to LV filling pressure. When each index is considered separately, however, the relationship to filling pressure is not very strong (*Figures 8 and 14*). Therefore, several indices need to be used in combination. Utility, methodology for performing measurements, and limitations of the different parameters of LV diastolic function are detailed in the 2016 ASE/EACVI guideline.[21]

The rationale for using mitral *E*-velocity is that its magnitude is determined largely by the transmitral pressure difference. Therefore, a low *E* (≤0.5 m/s) with a low *E/A*-velocity ratio (≤0.8) is consistent with normal or low LA pressure, whereas a tall *E* and high *E/A* ratio (≥2.0) is consistent with high LA pressure. The rationale for incorporating *e′* in the mitral *E/e′* ratio is that low *e′* is consistent with slow relaxation, which implies elevated LV minimum diastolic pressure. Therefore, when mitral *E* is high and *e′* is low, there tends to be a high mitral pressure gradient on top of elevated LV minimum pressure, which implies high LA pressure. As shown in *Figure 14* (left panel), the association between *E/e′* and LV filling pressure is not very strong and this index should therefore not be used as a stand-alone marker of LV filling pressure. Both mitral *E and A* waves, as well as *e′*, are age-dependent and this should also be taken into account when using these variables to evaluate LV diastolic function[47] (*Table 1*). The *E/e′* ratio is less age-dependent, and importantly, average *E/e′* >14 is very uncommon in healthy individuals regardless of age[47] and has a high specificity to identify increased LV filling pressure. It is important to be aware that the cut-off values for *E/e′* are based on *e′* recorded by pulsed-wave TDI which gives peak velocities and not by colour mode TDI which provides mean velocities (i.e. lower values).

Elevated LAVi is used as a marker of long-term elevation of LA pressure. As illustrated in *Figure 14*, the association between LAVi and LV filling pressure is relatively weak. Therefore, LAVi should always be used in combination with other indices when evaluating LV filling pressure. LA reservoir and pump strain may be used as additional markers of LV filling pressure.[51]

Another important measure is systolic pulmonary artery pressure estimated from peak tricuspid regurgitation (TR) velocity. This method is limited by the absence or inadequate visualization of TR in

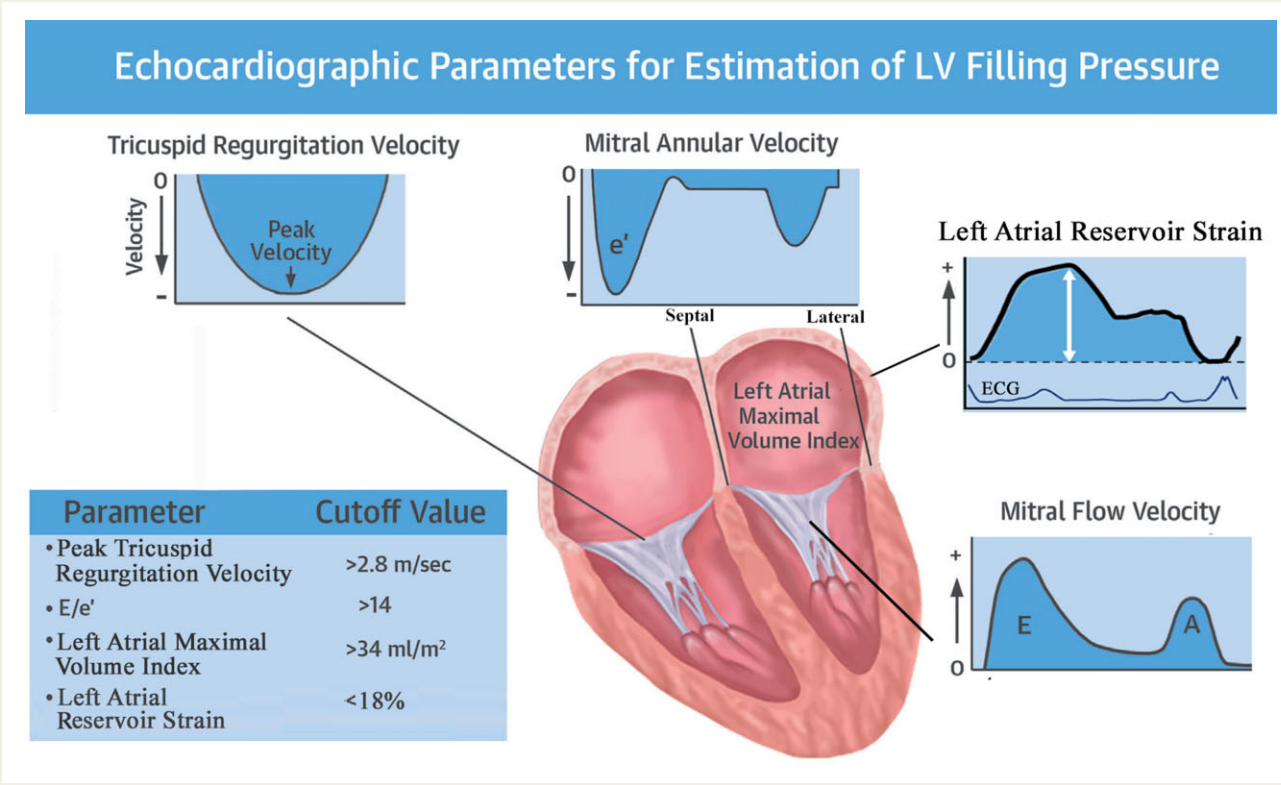

Figure 13 Echocardiographic parameters for evaluation of LV filling pressure.

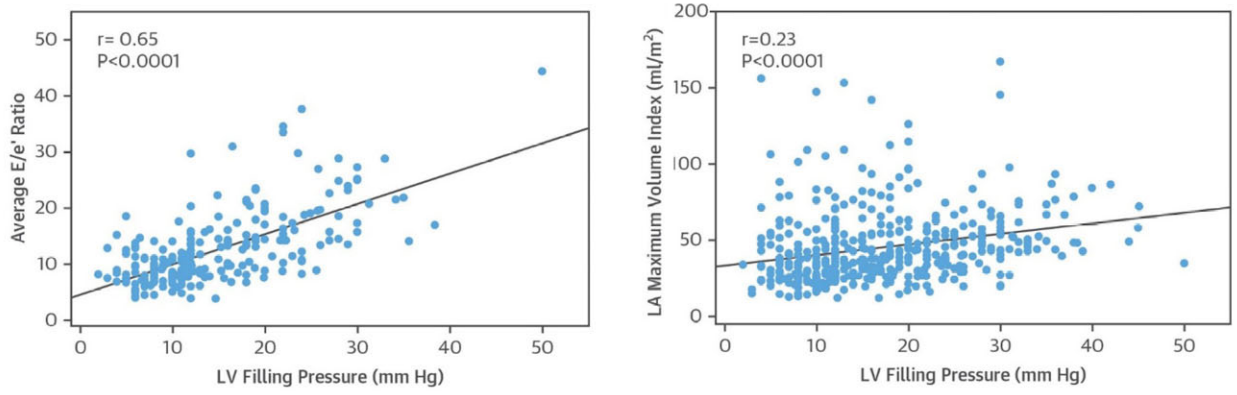

Figure 14 Regression plots of LV filling pressure vs. *E/e'* (left) and vs. LAVi (right panel). Both patients with normal and depressed EF are included. Patients with left bundle branch block paced rhythm, and significant mitral regurgitation were excluded. From Andersen *et al.*[24]

many patients. In fact, a properly measurable TR jet velocity was only available in between 40% and 60% of patients in two recent studies,[63,64] and this is especially a problem in patients with normal EF. Systolic pulmonary artery pressure is estimated as the sum of the estimated right atrial pressure and the systolic tricuspid pressure gradient. In the absence of pulmonary arterial hypertension or other suspected aetiology of non-cardiac pulmonary hypertension, an elevated pulmonary artery pressure can be a useful sign of elevated LA pressure. Severe mitral regurgitation can also give elevated pulmonary artery systolic pressure, but this is easily identified. Pulmonary artery acceleration time <100 ms is a marker of elevated pulmonary artery pressure and is useful when there is no recordable TR.[65] There is a need for further testing of this parameter against invasively measured pulmonary artery pressure in a large population with different cardiac disorders.

Table 1 Echocardiographic reference ranges for normal cardiac Doppler data: results from the NORRE Study (Caballero et al.[47])

Parameters	20–40 years		40–60 years		≥60 years		P
	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	
Pulse Doppler at the mitral valve							
E-wave velocity (m/s)	0.82 ± 0.16	0.53–1.22	0.75 ± 0.17	0.46–1.13	0.70 ± 0.16	0.39–1.03	<0.001
A-wave velocity (m/s)	0.50 ± 0.13	0.30–0.87	0.62 ± 0.15	0.37–0.97	0.77 ± 0.16	0.40–1.04	<0.001
E-wave deceleration time (ms)	178 ± 43	105–269	187 ± 45	114–288	208 ± 62	114–385	<0.001
E/A ratio	1.71 ± 0.52	0.89–3.18	1.24 ± 0.39	0.71–2.27	0.98 ± 0.29	0.53–1.80	<0.001
Tissue Doppler data							
Septal e′ wave (cm/s)	12.1 ± 2.5	8.0–17.0	9.8 ± 2.6	5.0–16.0	7.6 ± 2.3	3.0–13.0	<0.001
Septal *a*′ wave (cm/s)	8.5 ± 1.7	5.3–12.0	9.8 ± 2.0	6.9–14.0	10.5 ± 1.7	7.0–14.0	<0.001
Lateral e′ wave (cm/s)	16.4 ± 3.4	10.0–23.0	12.5 ± 3.0	6.0–18.0	9.6 ± 2.8	4.0–17.0	<0.001
Lateral *a*′ wave (cm/s)	8.2 ± 2.2	5.0–13.0	9.4 ± 2.6	5.0–15.0	10.6 ± 2.9	6.0–17.0	<0.001
Average septal and lateral e′ wave (cm/s)	14.3 ± 2.7	9.1–19.5	11.1 ± 2.5	6.0–16.0	8.6 ± 2.3	3.5–15.0	<0.001
E/e′ ratio							
Septal *E*/e′	6.9 ± 1.6	4.4–10.6	8.1 ± 2.3	4.3–13.2	9.7 ± 2.8	5.0–16.9	<0.001
Lateral *E*/e′	5.1 ± 1.3	3.1–8.5	6.3 ± 2.2	3.7–12.0	7.8 ± 2.2	4.2–12.8	<0.001
Average septal and lateral *E*/e′	5.8 ± 1.3	3.6–9.1	7.0 ± 2.1	4.2–11.5	8.5 ± 2.2	4.6–13.5	<0.001
Average *E*/e′	5.6 ± 1.1	3.7–7.9	6.8 ± 1.8	4.0–11.6	8.3 ± 2.2	4.4–14.8	<0.001

P differences between groups according to age category (one-way ANOVA).

Healthy young people may have an *E/A* ratio >2, possibly reflecting vigorous restoring forces which generate negative early-diastolic LV pressure and therefore a high transmitral gradient. These healthy subjects, however, differ from patients with LV diastolic dysfunction by having normal e′ and otherwise normal echocardiogram.

Diagnostic criteria for LV diastolic dysfunction

Since patients with HFpEF often have a mild reduction of LV systolic function, measurement of GLS should be done in every patient who is evaluated for potential HFpEF. Absolute values of GLS <16–18% are consistent with LV systolic dysfunction. When GLS is reduced, this is a sign of LV systolic dysfunction, and further investigations should be considered to determine specific aetiology. This includes evaluation of LV filling pressure.

In population studies, the prevalence of LV diastolic dysfunction varies depending upon which criteria are used to diagnose it and on the cardiovascular risk profile of the population which is studied.[66–68]

When evaluating patients suspected of HFpEF, it is essential to consider the medical history and cardiovascular risk profile. A history of myocardial infarction or arterial hypertension increases the likelihood that a patient has LV diastolic dysfunction and provides support for the HFpEF diagnosis. Furthermore, LA enlargement, LV hypertrophy, reduced GLS, regional myocardial dysfunction, and elevated natriuretic peptides also support the HFpEF diagnosis. Conditions, such as obesity, diabetes mellitus, and AF are also associated with LV diastolic dysfunction. None of these risk factors and comorbidities, however, provide conclusive evidence of HFpEF, and further evaluation is needed. This should include consideration of specific phenotypes or aetiologies (*Figure 3*).

When no specific aetiology or HF-associated phenotype is identified, echocardiography should be applied to determine if there is LV diastolic dysfunction. Similar to the 2016 ASE/EACVI guideline,[21] we advise using a combination of four echocardiographic markers with defined cut-off values to identify LV diastolic dysfunction; mitral annular e′ velocity (septal e′ < 7 cm/s or lateral e′ < 10 cm/s), average *E*/e′ ratio >14, LAVi >34 mL/m^2, and peak TR velocity >2.8 m/s. By convention, a diagnosis of LV diastolic dysfunction requires more than half of these variables to meet the cut-off values, i.e. at least 3 of 4 or 2 of 3 if one variable is missing. Conversely, LV diastolic function is considered normal when more than half of the available variables do not meet the cut-off values for identifying abnormal LV diastolic function. The study is considered inconclusive when half of the parameters are normal and half are abnormal. This definition of LV diastolic dysfunction is somewhat arbitrary and is intended for screening and not to make a definitive diagnosis. When the conclusion is that a patient has LV diastolic dysfunction, the next step is to evaluate LV filling pressure. Furthermore, when patients suspected of HFpEF have arterial hypertension, a history of coronary artery disease, relevant comorbidities, LV hypertrophy, or regional myocardial dysfunction, evaluation of LV filling pressure should be done regardless of the result from the initial evaluation of LV diastolic function.

Algorithm for evaluation of LV filling pressure

The algorithm for the evaluation of LV filling pressure is illustrated in *Figure 15*. This starts with measuring transmitral filling velocities. If mitral *E* is <0.5 m/s and *E/A* is ≤0.8, LV filling pressure is likely normal or low, whereas a tall *E and E/A* ≥ 2 indicates elevated LV filling pressure. When the mitral *E/A* is between 0.8 and 2.0, additional criteria are needed to assess LV filling pressure, and this includes average *E*/e′ >14, peak TR velocity >2.8 m/s, and LAVi >34 mL/m^2. If ≥2 of the criteria are above the cut-off, LV filling pressure is most likely

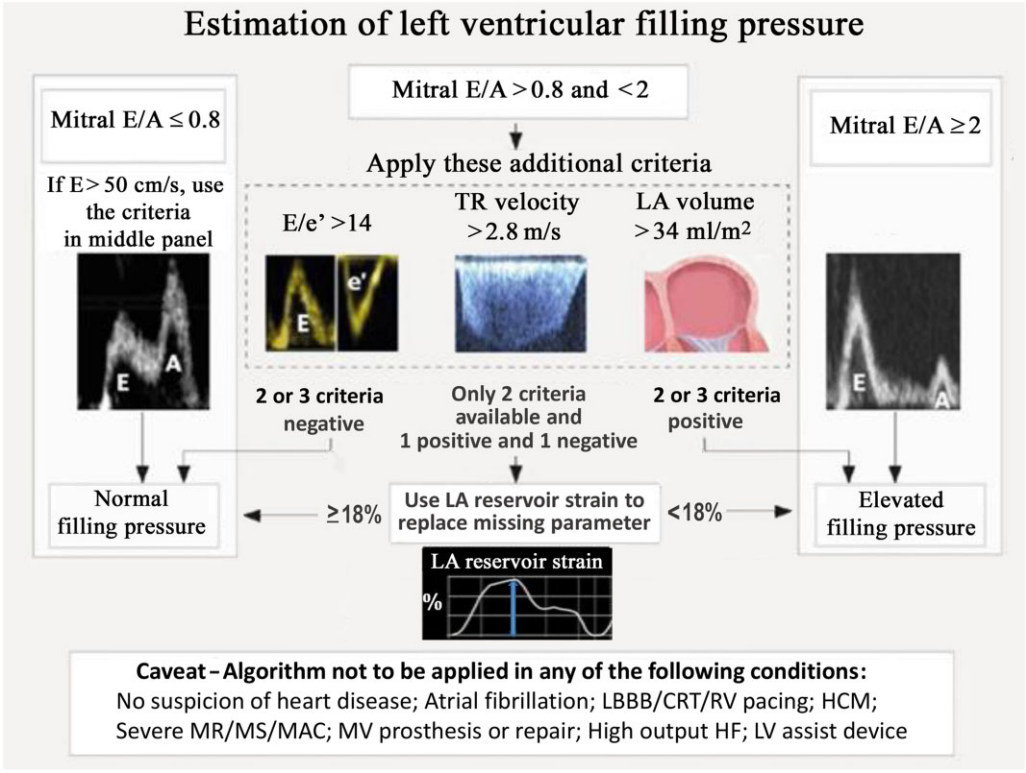

Figure 15 Algorithm for estimation of LV filling pressure.

elevated. If ≥2 are below the cut-off, LV filling pressure is most likely normal. In this document E/e' is calculated using the average of septal and lateral e'. When only septal or lateral e' are used, the recommended cutoffs for identifying elevated LV filling pressure, are 15 and 13, respectively.

As illustrated in *Figure 15*, LA reservoir strain is the third parameter when one of the three other criteria is missing and the remaining two are conflicting. The validity of this approach was shown in a recent multicentre study where invasive LV filling pressure was used as a reference.[51] The study showed that LA reservoir strain <18% was consistent with elevated LV filling pressure. LA strain has excellent feasibility and is therefore well suited as the third criterion when either *E*/*e*′, TR velocity, or LAVi is not available. One should be aware, however, that accuracy of LA strain is best in patients with reduced LVEF.

In addition to LA reservoir strain, one may use LA pump strain, which is useful in particular when pump strain is larger than 14% which is an excellent marker of normal LV filling pressure. As an alternative to LA strain, Ar-A time difference >30 ms may be used as an additional marker of elevated LV filling pressure, but feasibility is limited due to frequently suboptimal pulmonary venous velocity recordings.[21] Furthermore, the Ar-A reflects late diastolic LV pressure and may be elevated when LVEDP is increased while mean diastolic pressure is still normal. Pulmonary venous systolic/diastolic velocity ratio <1 is also a sign of elevated LV filling pressure in patients with reduced EF. As shown recently, this parameter provides essentially similar information as LA reservoir strain, but feasibility is not as good as for LA strain.[51]

This approach (Figure 15) for evaluation of LV filling pressure can be used in HFrEF as well as HFpEF.

An important limitation of the algorithm in *Figure 15* is that it cannot be applied in patients with AF. Furthermore, in patients with left bundle branch block (LBBB), right venrticular (RV) pacing, or cardiac resynchronization therapy (CRT) the accuracy may not be as good as in patients with narrow QRS. Furthermore, it is not to be applied in patients with HCM, more than moderate mitral regurgitation (MR), mitral stenosis (MS), mitral annular calcification (MAC), mitral valve repair/prosthetic mitral valve, LV assist device, and high output HF. Alternative approaches in these patients are presented in detail in the 2016 ASE/EACVI recommendation document.[21]

One should also be aware that LA dilation may be seen in the absence of LV diastolic dysfunction in patients with bradycardia, high-output states as in anaemia, in patients with heart transplants, and well-trained athletes. Another limitation of the algorithm in *Figure 15* is that *e*′ is often reduced at least for a year after heart transplantation.

In AF, LV filling pressure can be evaluated by averaging parameters over multiple heart beats. Septal *E*/*e*′ > 11, E-deceleration time ≤160 ms, IVRT ≤65 ms, and elevated TR velocity >2.8 m/s (in the absence of pulmonary disease) are consistent with elevated LV filling

Table 2 Diagnostic accuracy of the echocardiographic estimation of LV filling pressure using the 2016 ASE/EACVI guideline in patients with heart failure symptoms. From Andersen et al.[24]

Accuracy of diagnosis of elevated LV filling pressure: total population			
	Clinical (95% CI)	Echocardiographic (95%CI)	*P*-value[a] Clinical vs. Echo
Sensitivity	74 (68–79)	87 (81–91)	0.001
Specificity	69 (62–75)	88 (82–93)	<0.001
PPV	77 (71–82)	91 (86–94)	<0.001
NPV	65 (58–72)	83 (76–88)	<0.001
Overall accuracy	72 (67–76)	87 (84–91)	<0.001

Values are expressed as %.
[a]Based on McNemar test.

pressure. There is, however, limited data on the accuracy of this approach. For patients with LV dyssynchrony, as in LBBB and RV pacing, the association between *E*/*e*′ and PCWP is weaker than in patients with normal electrical conduction.[69]

As shown in *Table 2* which is from a multicentre study of 450 patients, evaluation of LV filling pressure by the algorithm from the 2016 ASE/EACVI guideline, can identify patients with elevated LV filling pressure with an accuracy of 85–90%.[24] This implies, however, that in at least one in ten patients, the estimate will be wrong. Therefore, it is important to incorporate clinical signs and other laboratory tests, such as chest X-ray (which may show pulmonary congestion) and natriuretic peptides in support of the HF diagnosis. Clinical use of the algorithm was also supported by a European multicentre study.[64]

Because LV filling pressure may be elevated only during exercise, in patients with an inconclusive study at rest, it is important to consider performing a diastolic stress test by echocardiography or referring the patient for right heart catheterization with exercise. Importantly, HFpEF patients treated with diuretics or other HF medication may have normal LV filling pressure at rest. Therefore, normal resting LV filling pressure does not exclude HFpEF.

In some cases, right or left heart catheterization is needed. This is important in particular when the echocardiographic assessment of LV filling pressure is inconclusive, to rule out non-cardiac aetiologies, such as pulmonary arterial hypertension (PAH), and to identify CAD.

The algorithm in *Figure 15* is not to be used in individuals with no suspicion of HF or other heart diseases since that would result in too many false-positive diagnoses of elevated LV filling pressure.

Grading of LV diastolic dysfunction

In keeping with the 2016 ASE/EACVI document,[21] we advise grading of LV diastolic dysfunction based on a combination of mitral blood flow velocities and LV filling pressure (*Table 3*). The patterns of mitral flow velocities are shown in *Figure 12*.

There are studies confirming that markers of LV diastolic function, including the classification into grades 1–3 in the 2016 ASE/EACVI recommendations[21] predict cardiovascular risk.[70,71] There are important observations suggesting that assessment of LV diastolic function may be useful to risk-stratify patients with aortic stenosis who are considered for aortic valve replacement.[72]

Table 3 Criteria for grading of LV diastolic dysfunction according to level of LV filling pressure and mitral flow velocities

Grading of LV diastolic dysfunction by echocardiography			
	Grade I	Grade II	Grade III
LV filling pressure	Low or normal	Elevated	Elevated
Mitral E/A ratio	≤0.8	>0.8 to <2	≥2

Diastolic stress test by echocardiography

Recent studies have shown that in some patients with HFpEF increased LV filling pressure occurs only during exercise and that echocardiographic parameters at rest have relatively low sensitivity to diagnose HFpEF in these patients.[73–78] Measurements of the *E*/*e*′ ratio and peak TR velocity during exercise are feasible and have been invasively validated for the estimation of elevated LV filling pressure during exercise.[25,74,75,77,79] In this respect, recent studies have shown that adding diastolic stress testing (i.e. analysis of the *E*/*e*′ ratio and TR velocity during exercise) to the standard resting echocardiography increases diagnostic sensitivity in patients suspected of HFpEF who have normal estimated LV filling pressure at rest.[73–75,77,80] Therefore, a diastolic stress test can be added to the echocardiographic diagnostic approach in the setting of suspected HFpEF and normal resting LV filling pressure (*Figure 16*, *Table 4*). Importantly, GLS should be measured and when <16–18% in absolute value, suspicion of HFpEF is strengthened, and diastolic stress testing should be considered.

Some methodological factors should be considered for performing a diastolic stress test. The most validated protocol is the bicycle (in semi-supine position) exercise testing.[81] This testing starts with a 25 W load, increasing every 3 min with 25 W at 50–60 rpm until reaching a maximal predicted workload, a maximal predicted heart rate (220 - age), or the echocardiographic predicted goal [i.e. *E*/*e*′ > 14 (or *E*/*e*′ septal > 15) and TR velocity > 2.8 m/s].[81] It is important to note that in some patients the *E and A* waves from the mitral inflow and the *e*′ and *a*′ waves from the mitral annulus may fuse during

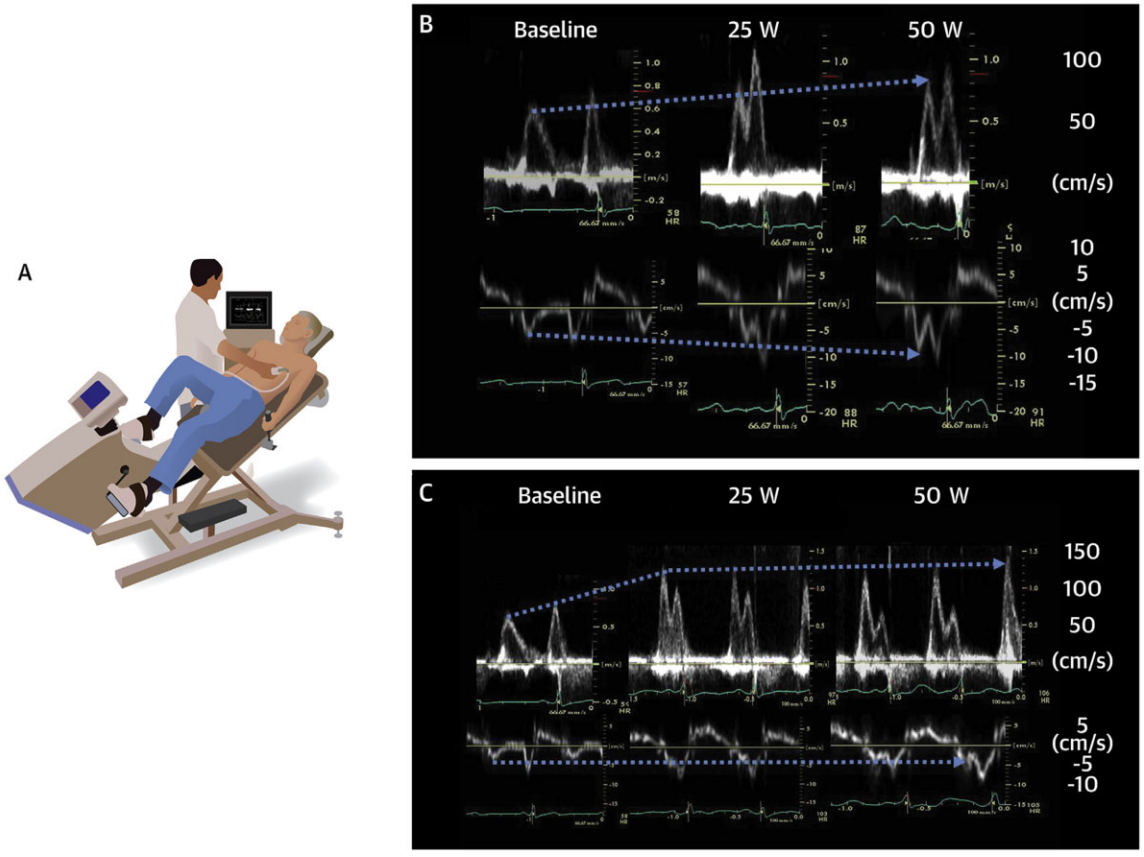

Figure 16 (*A*) Illustrative photo of a non-invasive diastolic stress test using echocardiography. (*B and C*) and shows diastolic stress echocardiographic data acquired before and during symptom-limited supine bicycle exercise in two individuals with impaired relaxation and almost identical mitral inflow and annular velocities at rest. In the patient illustrated in panel *B*, there is a concordant rise in mitral E velocity and mitral annular e′ velocity with exercise, without an overall change in the *E*/e′ ratio. In the patient in panel *C*, there is an increase in mitral E velocity but minimal change in e′ with exercise, resulting in increased *E*/e′, suggestive of elevated LV filling pressure with exercise. Modified from Ha *et al.*[25]

Table 4 Diastolic stress test: Indications and criteria for response

Diastolic stress test
Do not need the diastolic stress test:
• Preserved e′ at rest: mitral annulus septal e′ >7 cm/s and lateral e′ >10 cm/s. Unlikely to develop elevated LV filling pressures with exercise.
• Elevated LV filling pressure at rest, by echocardiography.
Candidates for the test:
• Grade 1 LV diastolic dysfunction with normal LV filling pressure at rest and signs of delayed myocardial relaxation.
Diastolic stress test is positive when all of the following three conditions are met:
• Average *E*/e′ > 14 or septal *E*/e′ ratio >15 with exercise.
• Peak TR velocity >2.8 m/s with exercise.
• Septal e′ < 7 cm/s or if only lateral velocity is acquired, lateral e′ < 10 cm/s at baseline.
Normal response to diastolic stress test if both of the following two conditions are met:
• Average or septal *E*/e′ < 10 with exercise.
• Peak TR velocity <2.8 m/s with exercise.

exercise, thereby decreasing the feasibility of the test.[21,81] Nonetheless, in this setting attempts should be made to acquire the mitral *E*/*e*′ ratio after the peak exercise (during the first 1–2 min of the recovery phase when the heart rate is slower and fusing is lesser).[21,81] In line with this, a treadmill exercise by measuring the mitral *E*/*e*′ ratio and TR velocity within 1–2 min after the test can be an alternative to the bicycle protocol.[81] Moreover, it is important to highlight that some patients can reach the echocardiographic goal at just 25 or 50 W level, and thus, measurements of the mitral *E*/*e*′ ratio and TR velocity should be analysed at each stage.[75,77] On the other hand, large inspiratory variations in the mitral *E*/*e*′ ratio can occur at peak exercise as patients develop dyspnoea. Therefore, it is important to note that the final value of the mitral *E*/*e*′ ratio should represent measurements of the mitral *E and e*′ at end-expiration and from the average of ≥3 cardiac cycles.[21] Furthermore, indeterminate results can occur during the diastolic stress test, such as a mitral *E*/*e*′ (using the average of septal and lateral e') average septal-lateral ratio >14 (or mitral *E*/*e*′ septal ratio >15) but a TR velocity ≤2.8 m/s (or no detectable TR). In this indeterminate setting, the results should be interpreted according to the clinical scenario or probability of HFpEF. In effect, an isolated elevation of the mitral *E*/*e*′ ratio with normal values or not detectable TR velocity is more likely to indicate elevated LV filling pressure than an isolated elevation of TR velocity with normal values of the mitral *E*/*e*′ ratio.[21,77,81] Furthermore, it should be noted that the level of evidence for diastolic stress testing to estimate LV filling pressure in patients with AF is low. Hence, we consider that the current cut-off values for mitral *E*/*e*′ ratio and TR velocity during exercise should not be taken as conclusive evidence to diagnose or exclude HFpEF in patients with AF. The demonstration of B-lines during exercise has been suggested as a means to identify pulmonary congestion, but there are challenges with the standardization of this method.[81]

When to proceed with invasive diagnostics

Since LV diastolic pressures cannot be measured directly by imaging, catheter-based pressure measurement is the ultimate diagnostic confirmation of HFpEF. Depending on the underlying question, this may require right, left, or combined right-left heart catheterization. The following clinical diagnostic dilemmas should lead to strong consideration of invasive diagnostics:

(1) Discordant and/or insufficient data from imaging, natriuretic peptides, and clinical status.
(2) When considering aetiologies that can mimic HFpEF, such as non-cardiac pulmonary hypertension, obesity, lung disease, or mitral regurgitation. These diseases may also co-exist with LV diastolic dysfunction.
(3) Rule out obstructive CAD.
(4) Unmask LV diastolic dysfunction by pressure recording during exercise or volume loading. Right heart catheterization allows monitoring of changes in pressure, cardiac output, and pulmonary vascular resistance during exercise, which may be difficult or impossible to detect with confidence by imaging methods.[77,82,83]

Aetiological phenotyping by multimodality imaging

Whilst there are several approaches to phenotype HFpEF patients, we consider an aetiological approach to identify diseases with specific therapies as the most useful in clinical practice. Phenotypes with established and specific therapies include CAD, HCM, cardiac amyloidosis, Fabry disease, and sarcoidosis. It is important to exclude constrictive pericarditis and non-cardiac pulmonary hypertension. In the following sections, we will address in more detail how to evaluate patients suspected of having some of these phenotypes. *Table 5* summarizes the imaging modalities to be used in different conditions. For a more comprehensive review of the aetiologies and specific diseases which may result in HFpEF, readers are referred to the consensus report from the European HFA and to the ESC HF guidelines.[1,2]

Taking into account all specific causes of HFpEF, we consider in this consensus document that a multimodality imaging approach plays a key role in the aetiological phenotyping of patients with HFpEF. In addition, biochemical and genetic testing may be used.[1,2]

Non-cardiac pulmonary hypertension

When pulmonary hypertension (PH) is observed in patients evaluated for potential HFpEF, it is important to determine if this is due to left-sided heart disease (i.e. post-capillary pulmonary hypertension) or different types of non-cardiac pulmonary hypertension (i.e. pre-capillary pulmonary hypertension). The latter category includes PAH, lung disease, thromboembolic disease, and various rare aetiologies. Whereas pre-capillary PH has normal LA pressure, post-capillary PH is characterized by elevated LA pressure, measured as PCWP >15 mmHg. Patients with PH which is conventionally defined as mean pressure ≥25 mmHg (proposal to redefine as >20 mmHg), can in most cases be identified by measuring TR velocity in combination with an estimate of right atrial pressure. When TR velocity is not available, advanced pre-capillary PH is often identified by a dilated and hypertrophied right ventricle with reduced RV systolic function, and there is typically septal flattening. Furthermore, the pulmonary trunk is usually significantly dilated.

With regard to PAH and other forms of non-cardiac pulmonary hypertension, imaging methods can only be used to raise suspicion of such disorders, and it is mandatory to use right heart catheterization to confirm the diagnosis. Furthermore, a clear distinction between pre- and post-capillary PH can only be made by right heart catheterization. Due to limited access to invasive diagnostics, echocardiography may be used to decide who needs a referral for an invasive study. Differentiation between pre- and post-capillary PH by echocardiography cannot be done with the same algorithm that is used to assess LV filling pressure in patients with left-sided heart disease where peak TR velocity is used as one of the markers of elevated LV filling pressure. This is because TR velocity is elevated regardless of the LA pressure level. Furthermore, septal motion is often disturbed in severe PAH, and therefore, the *E*/*e*′ average ratio does not work well as an indicator of LA pressure. Although echocardiography is useful for making a tentative diagnosis of pre-capillary PH and

Table 5 Multimodality imaging and aetiological approach in patients with HFpEF.

HFpEF aetiologies	Echocardiography	Coronary angiography (CT or invasive)	CT	CMR	PET	SPECT	Bone and cardiac scintigraphy	Right heart catheterization at rest/exercise
Coronary artery disease	+++	+++		+++	+++	+++		
Arterial hypertension	+++	+		+				
Hypertrophic cardiomyopathy	+++			++				
Cardiac amyloidosis	+++			++	+		+++	
Cardiac sarcoidosis	++			+++	+++			
Fabry and other storage diseases	+++			+++				
Constrictive pericarditis	+++		+++	+++				+++
Non-cardiac pulmonary hypertension	+++		++					+++

CMR, cardiovascular magnetic resonance imaging; SPECT, single photon emission computed tomography; CT, computed tomography; bone and cardiac scintigraphy, planar scintigraphy and SPECT; PET, positron emission tomography, useful to assess cardiac sarcoidosis; CT in the setting of suspected constrictive pericarditis can be used for detection of pericardial calcification and thickness and in the setting pulmonary hypertensions to rule out or rule in pulmonary embolism; CMR in arterial hypertension may be used to assess LV hypertrophy and fibrosis; stress echocardiography, CT angio, stress CMR, PET, or SPECT may be used to diagnose coronary artery disease, and which method to use depends on availability of and local expertise with methodology, and pre-test probability of disease.

deciding who should be referred for invasive diagnostics, it is not sufficiently accurate to serve as a basis for deciding therapy.

Computed tomography (CT) can provide diagnostic features, such as changes in pulmonary arteries (dimensions, peripheral calcification, eccentric filling defects, intra-arterial soft tissue) and changes in the lung parenchyma, heart, and mediastinum that may facilitate placing the patient in the correct diagnostic category.

Hypertrophic cardiomyopathy

Sarcomeric HCM is an important cause of the incidental finding of LV hypertrophy and is an important cause of HFpEF. Usually, HCM has been excluded from HFpEF trials since it is considered a specific phenotype. The echocardiographic features were reviewed in a previous EACVI consensus document.[84] It is a primary myocardial disease, defined by inappropriate LV hypertrophy, disproportionate to the degree of LV loading conditions, occurring in the absence of another cardiac or systemic disease, metabolic or multiorgan syndrome associated with increased LV mass. LV hypertrophy is most often seen in the basal and mid interventricular septum but may involve any LV segment and sometimes several segments. It usually results from mutations in genes encoding sarcomeric proteins and is transmitted in an autosomal dominant pattern, with variable expression.

The pathological findings include not only myocyte hypertrophy, but also myocyte disarray, small vessel disease, and myocardial fibrosis. HF in HCM may result from both LV systolic and diastolic dysfunction, and in addition, there is often intraventricular obstruction. Myocardial ischaemia is common in HCM and is mainly due to increased oxygen demand due to LV hypertrophy, outflow obstruction, and coronary microvascular dysfunction. In some patients, there may be asymptomatic microvascular ischaemia which can lead to replacement fibrosis and subsequent adverse LV remodelling. Mitral regurgitation is another important factor that often contributes to HF.

When using a 2D echocardiography, the diagnostic criterion of HCM is unexplained wall thickness ≥15 mm in any myocardial segment.

Most cardiovascular centres will perform CMR with LGE in all HCM patients, at least in the initial evaluation. The most important finding provided by CMR is LGE assessment to identify myocardial scar which is probably useful in sudden cardiac death risk stratification, although its clinical role is yet not clearly established. Furthermore, CMR provides a complete evaluation of both ventricles, detects LV hypertrophy more frequently than echocardiography, and can identify RV structures that are incorrectly included in the echocardiographic measurements of septal thickness. No other technique provides these data as accurate as CMR.[84–86]

More than 50% of HCM patients have abnormal mitral leaflets, and there are often abnormalities of the chordae and papillary muscles which include leaflet and chordal elongation and prolapse. The systolic anterior motion of the mitral valve, an important determinant in LV outflow obstruction in HCM, is common, but non-specific. Obstruction may occur at the LV outflow tract or at the midventricular level and is defined by the presence of a peak gradient ≥30 mmHg at rest or after provocative manoeuvers. In about one-third of HCM patients, intraventricular obstruction is detected at rest. However, another third of HCM patients only show labile obstruction, detected by bedside provocative manoeuvers (Valsalva, standing), or by exercise echocardiography (treadmill or bicycle).

No single echo-Doppler parameter has been validated to be accurate in the assessment of LV filling pressure in HCM. An integrative approach may be used, as previously described.[87]

Cardiac amyloidosis

Cardiac amyloidosis is a form of restrictive and hypertrophic cardiomyopathy due to cardiac amyloid fibril deposits, either monoclonal light chain (AL) or transthyretin (ATTR) type.[88–92] ATTR amyloidosis may be either hereditary (ATTRm) or wild-type (ATTRwt), occurring at an older age as the ATTRwt form.[88,90–92] Both AL and ATTR amyloidosis have a poor prognosis with cardiac involvement as the most important determinant of prognosis.[88–92] It appears that a substantial proportion of patients with HFpEF have cardiac ATTR

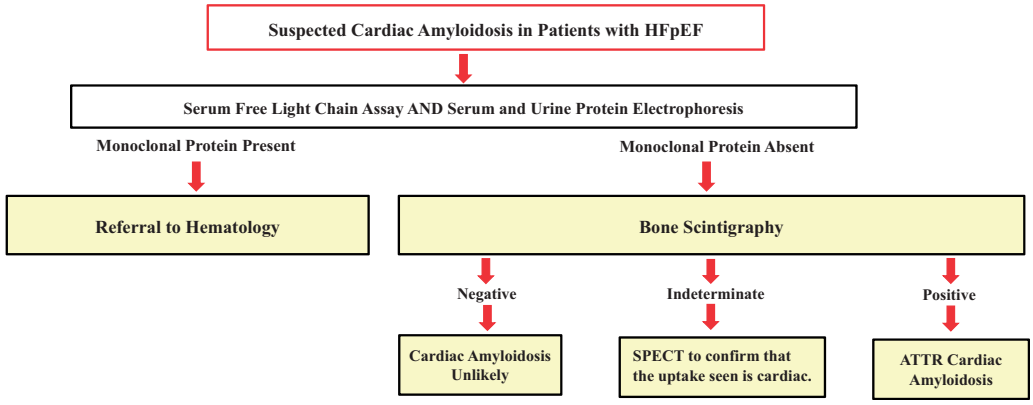

Figure 17 Evaluation of patients suspected of having cardiac amyloidosis in patients with HFpEF (based in part on current expert consensuses on cardiac amyloidosis: Dorbala *et al.*,[93] Maurer *et al.*,[91] and Kittleson *et al.*[90]).

Table 6 Clinical context or 'Red Flags' for suspicion of cardiac amyloidosis in patients with HFpEF (based in part on current expert consensuses on cardiac amyloidosis: Dorbala *et al.*,[93] Maurer *et al.*,[91] Witteles *et al.*,[92] and Kittleson *et al.*[90])

'Red flags' for ATTR cardiac amyloidosis
Increased LV wall thickness with no other explanation
Myocardial 'granular sparkling' by echocardiography
Thickening of RV free wall, atrial septum or AV-valves
Biatrial enlargement, pericardial effusion
Reduced LV longitudinal strain with apical sparing
Low ECG voltage or normal voltage and increased LV wall thickness
Unexplained atrioventricular block
Increased LV myocardial extracellular volume by CMR
Diffuse subendocardial or transmural LGE on CMR
Symptoms of polyneuropathia
Bilateral carpal tunnel syndrome

amyloid deposits with consequent cardiac amyloidosis and the same applies to patients with aortic stenosis.[90–96]

In the last years with the development of new accurate cardiovascular imaging techniques and potentially effective treatments for both AL and ATTR amyloidosis,[97–99] cardiac amyloidosis has emerged as a very important condition to identify in the setting of HFpEF (*Figure 17*). Importantly, if positive for any of the red flags listed in *Table 6*, including several echocardiographic and CMR changes as shown in the cases in *Figures 18 and 19*, the next step is performing bone scintigraphy (planar and SPECT; using SPECT to confirm a cardiac uptake by positive or indeterminate planar scintigraphy). The scintigraphic approach has excellent sensitivity and good specificity to diagnose ATTR cardiac amyloidosis.[100] In some cases of indeterminate diagnosis by bone scintigraphy (planar and SPECT) or concomitant positive bone scintigraphy and positive monoclonal protein test, there may be needed to perform an endomyocardial biopsy to verify the diagnosis and/or to determine the form of cardiac amyloidosis.[90–93] One should always exclude AL amyloidosis by testing for monoclonal protein production.[88,90–92]

CMR has proven to have potential usefulness as a supplementary method to raise suspicion about cardiac amyloidosis in the setting of HFpEF.[101–103] In this regard, findings, such as diffuse or global subendocardial or transmural LGE of the LV [with difficulty in achieving myocardial nulling or significantly increased ECV (>0.40)] are indicative of probable cardiac amyloidosis in patients with HFpEF without an obvious cause of increased LV wall thickness.[101–103] Recent studies have also highlighted the potential role of positron emission tomography to detect AL cardiac amyloidosis[104,105] which warrants validation in further larger studies in patients with HFpEF.

Taking into account the relatively high prevalence of cardiac ATTR amyloidosis in patients with HFpEF[94–96] as well as the high rate of cardiac involvement in patients with AL amyloidosis,[89] we consider that in some specific settings (*Table 6*) patients with HFpEF should be screened for cardiac amyloidosis (*Figure 17*).

Pericardial diseases

Constrictive pericarditis (CP) is an important differential diagnosis for HFpEF[106] as patients typically also present with symptoms and signs of right HF and a low output state with a preserved EF. Constrictive pericarditis is caused by several disorders which increase pericardial stiffness due to pericardial thickening, inflammation, and scarring, and there is often pericardial calcification. Echocardiography is the initial test of choice, although CMR or CT may be adjunctive if echocardiography is non-diagnostic or if additional anatomic information is needed, such as the degree of pericardial thickness, inflammation, or calcification.[107]

Differentiation between constrictive pericarditis and restrictive cardiomyopathy is challenging even when invasive data are available. As shown in the diagnostic algorithm in *Figure 20*, in constrictive pericarditis there is typically both a dilated vena cava and a mitral $E/A > 0.8$. In addition, there are several echocardiographic features characteristic of constrictive pericarditis. This includes, (i) enhanced

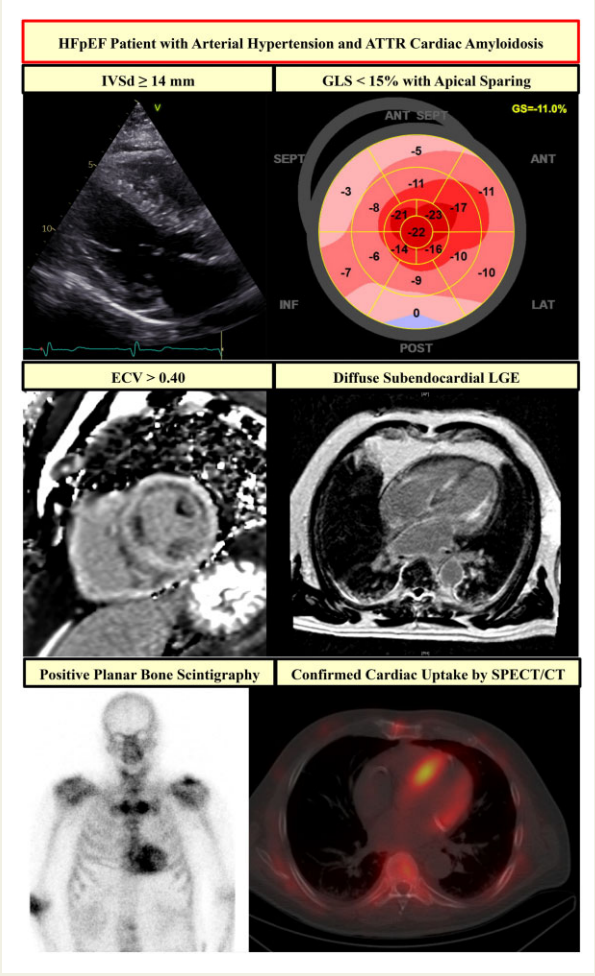

Figure 18 Case example showing a patient with HFpEF and ATTR cardiac amyloidosis and concomitant arterial hypertension. Please note the significant increase in LV wall thickness [interventricular septum at end-diastole (IVSd)] by echocardiography with the typical GLS pattern of 'apical sparing' and low GLS value <15% as well as the diffuse and subendocardial late gadolinium enhancement (LGE) in the IVS with a septal extracellular volume (ECV) by T1 mapping above the normal range. Finally, note how the diagnosis of ATTR cardiac amyloidosis is made by planar bone scintigraphy and confirmation of cardiac involvement by SPECT/CT.

respiratory variations in RV and LV filling velocities, (ii) abnormal motion of the interventricular septum during respiration, (iii) maintained mitral annular e′ with septal e′ often exceeding lateral e′, and (iv) enhanced expiratory reversal of hepatic venous flow during atrial contraction. Furthermore, CT and CMR demonstrate thickened pericardium.

The hallmark of constrictive physiology is increased ventricular interdependence and dissociation of intrathoracic–intracardiac pressures caused by a constricting pericardium. In contrast to a normal heart where inspiration leads to a small increase in peak tricuspid E and a small decrease in mitral E-velocities,[109] constrictive pericarditis is associated with a marked increase in the tricuspid E-velocity (>40%), and a marked decrease (>25%) in mitral E-velocity. *Figure 21D* shows a typical expiratory reversal of end-diastolic flow within the hepatic veins in a patient with constrictive pericarditis.

The enhanced respiratory variation in RV and LV filling and the abnormal septal motion in CP reflect both a restricted cardiac volume within the stiff pericardium and reduced transmission of respiratory changes in pleural pressure across the pericardium. To accommodate an increased RV volume during inspiration, the septum shifts to the left, causing a reduction in LV volume. The leftward septal shift is enhanced by the reduction in LV inflow due to a reduced pressure gradient between the pulmonary veins and the left side of the heart. This is a result of the reduced transmission of inspiratory fall in intrathoracic pressure to the LV, whereas transmission to pulmonary vasculature is preserved. Expiration has the opposite effect as the septum shifts back toward the RV. This leads to reduced capacity for filling of the RV, and therefore expiration is associated with increased reversal of flow into the hepatic veins during right atrial contraction. The magnitude, of the respiratory variations in filling velocities, is often less marked, and respiratory variation of the mitral inflow may not be seen in 30% of constrictive patients. Therefore, additional diagnostic criteria are needed to verify constrictive pericarditis.

Typical findings in restrictive cardiomyopathy are short mitral E deceleration time, elevated *E*/*e*′, dilated atria, a plethoric inferior vena cava, and an abnormal pulmonary venous flow pattern (*S*/*D* < 1).[110,111] However, in contrast to diseases of the myocardium, where elevated LV filling pressure is associated with high *E*/*e*′, in patients with constrictive pericarditis elevated LV filling pressure tends to be associated with low values of *E*/*e*′ ('annulus paradoxus'). This is attributed to a 'paradoxical' increase in septal *e*′ (>8 cm/s) while the constrictive pathology progresses, resulting in a preserved or decreased septal *E*/*e*′ ratio.[107]

Tethering of the LV lateral and RV free walls also contribute to the constrictive physiology and is demonstrated by an increased ratio of the septal to lateral mitral annular systolic velocities on tissue Doppler imaging ('annulus reversus') (*Figures 21A and C*). Similarly, the lateral LV and RV free wall peak systolic strain are diminished when compared to the septal peak systolic strain ('strain reversus') (*Figure 21B*).[107] Important caveat to note is the influence of primary and mixed constriction on the haemodynamics as well as septal annular velocities.[112,113] With mixed constriction/restriction as in radiation heart disease, the septal annular e′ velocity may actually be decreased (<6 cm/s). The septal *e*′ velocity may be the best prognostic parameter for long-term outcome after pericardiectomy.[114] It should also be emphasized that one-third of the patients with constriction may present with TR which could impact patients' prognosis and often tricuspid repair may be warranted during pericardiectomy.

Other imaging techniques, such as cardiac gated CT and CMR, have emerged as important tools when faced with diagnostic uncertainty in separating constrictive pericarditis from restrictive cardiomyopathy.[115] Aside from establishing constrictive haemodynamics, CMR can characterize the pericardium, prognosticate, and guide therapy.[116] A thickened pericardium, a high pericardial signal on T2-weighted images, and delayed gadolinium enhancement acquisitions, representing abnormal vascular permeability and oedema, indicates active pericardial inflammation and should prompt a trial of anti-inflammatory medication to reverse the constrictive physiology ('transient constrictive pericarditis'). Cardiac CT offers accurate

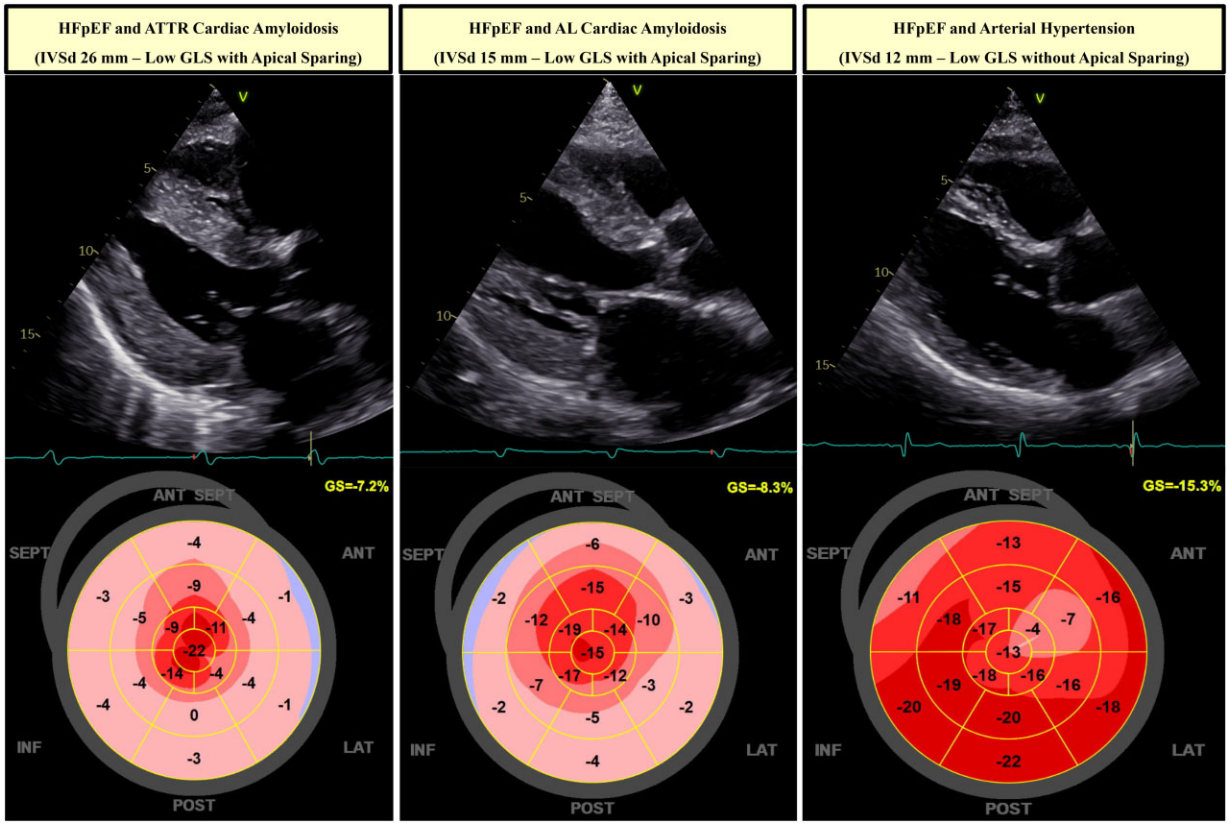

Figure 19 Case examples of ATTR and AL cardiac amyloidosis and cardiac involvement in arterial hypertension (without amyloidosis) in patients with HFpEF. Please note the significant increase in LV wall thickness (interventricular septum at end-diastole [IVSd]) in cardiac amyloidosis in comparison with arterial hypertension as well as the typical GLS pattern of 'apical sparing' in cardiac amyloidosis.

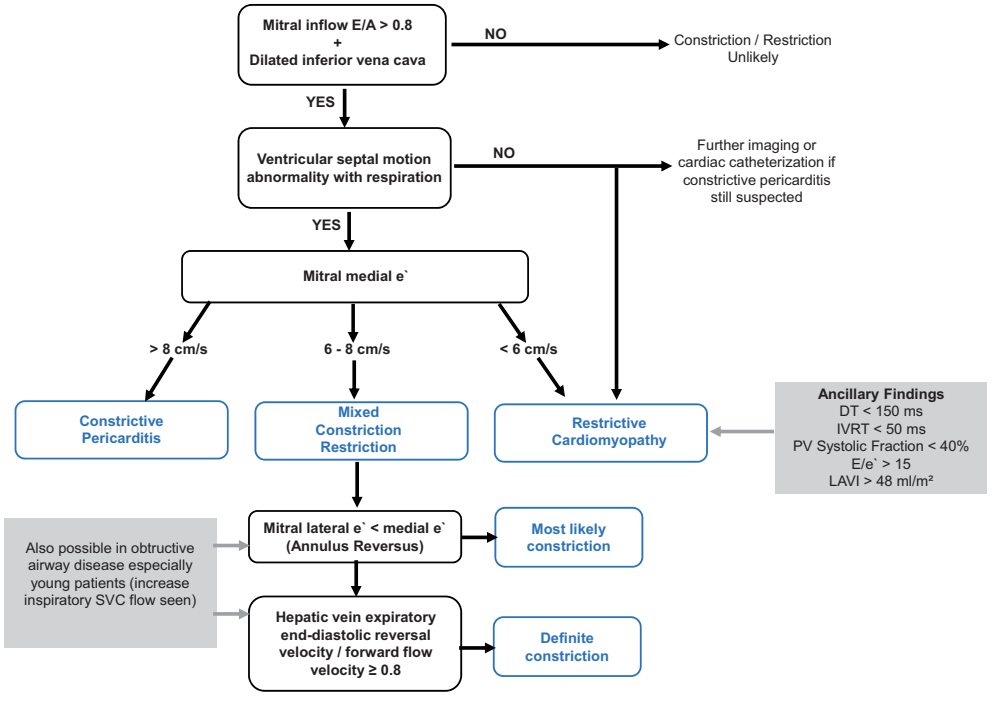

Figure 20 Algorithm for the diagnosis of constrictive pericarditis as well as comparison with restrictive cardiomyopathy. The figure is based on data from Syed *et al.*[108]

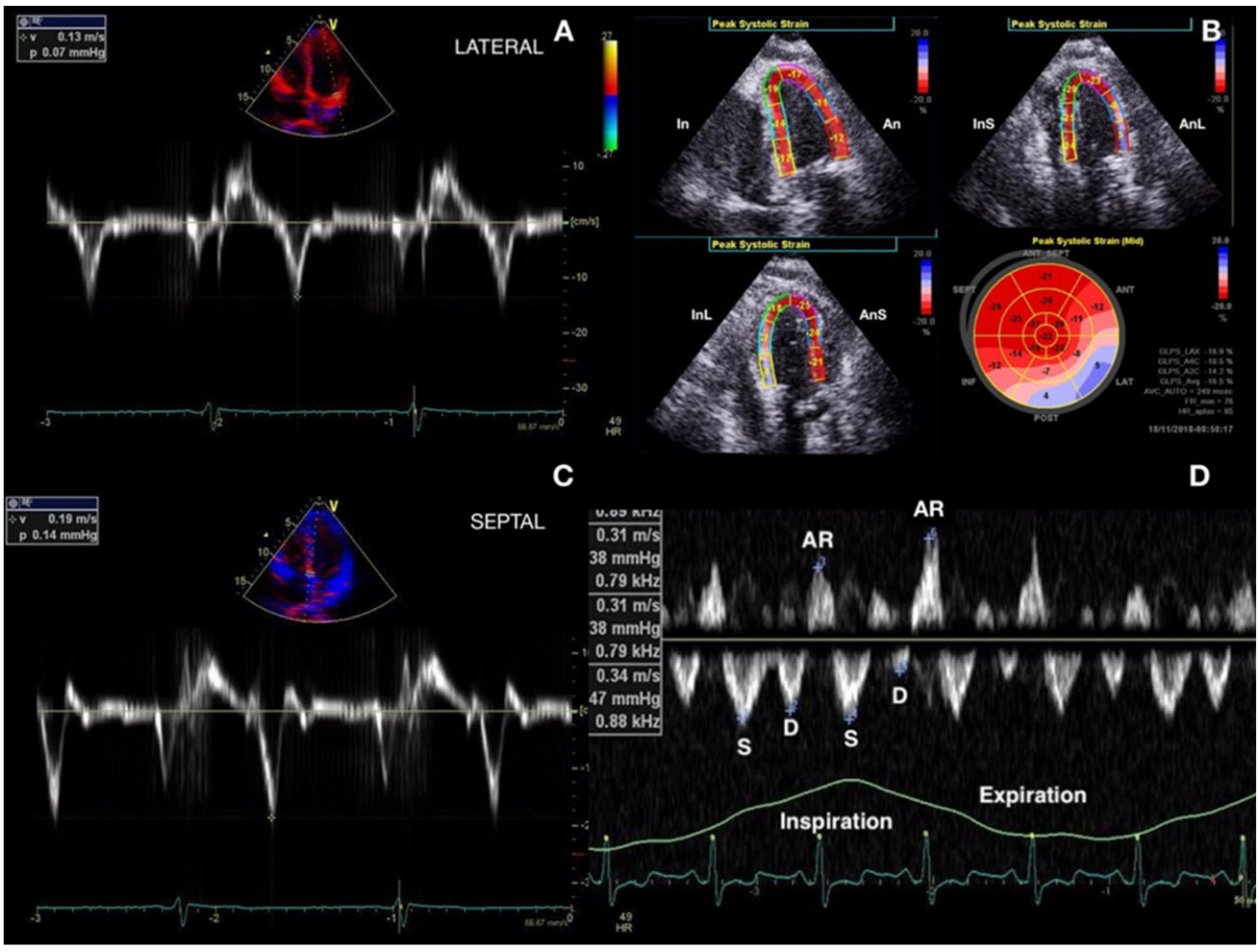

Figure 21 (*A*) Tissue Doppler velocity of the lateral mitral annular diastolic velocity (e′ of 13 cm/s) and (*C*) tissue Doppler velocity of the septal mitral annular diastolic velocity (e′ of 19 cm/s) demonstrating 'annulus reversus'. (*D*) Pulsed-wave Doppler of the hepatic veins with an end-diastolic reversal velocity of 0.34 m/s and a forward velocity of 0.31 m/s on expiration (ratio of 0.91). (*B*) Decreased peak LV longitudinal strain of the lateral wall from tethering with an increase in the septal peak longitudinal strain demonstrating 'strain reversus'. In, inferior; An, anterior; InS, infero-septal; AnL, anterolateral; InL, inferolateral; AnS, anteroseptal; S, systolic; D, diastolic; AR, atrial contraction-induced reversal.

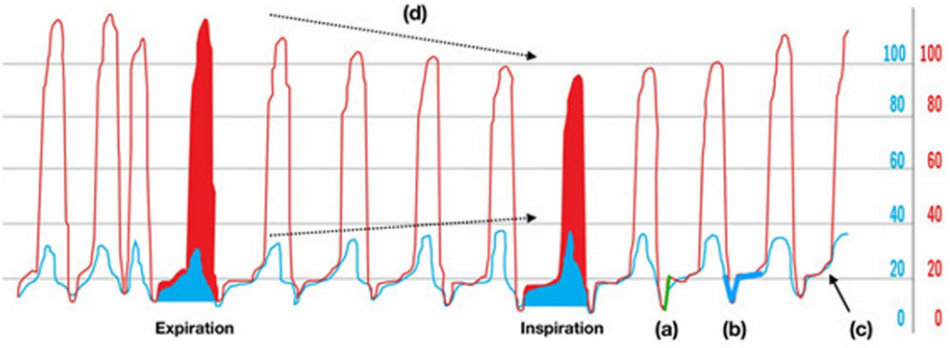

Figure 22 Simultaneous RV (blue tracing) and LV (red tracing) pressure tracings from an invasive hemodynamic study during cardiac catheterization. Both ventricles demonstrate a rapid rise in LV diastolic pressure >7 mmHg (*a*), diastolic filling demonstrating the square root pattern (*b*), and equalization of RV and LV end-diastolic pressures (<5 mm) (*c*). There is ventricular interdependence (*d*) and a systolic area index [(RV area/LV area on inspiration)/(RV area/LV area on expiration)] of 1.2 (blue/red tracings). The findings are suggestive of constrictive pericarditis.

delineation of pericardial thickening and calcification, confirming the diagnosis, and is useful in pre-operative planning, particularly in the setting of previous open-heart surgery.

When initial imaging is non-diagnostic and clinical suspicion lingers, right and left heart catheterization with haemodynamic assessment is the next step to confirm constrictive physiology (*Figure 22*). The presence of a rapid filling wave with a pressure increase of more than 7 mmHg (*Figure 22A*) coupled with near equalization of the LV and RV end-diastolic pressures (*Figure 22C*), is suggestive of constrictive physiology. The most salient finding, however, is demonstrating LV/RV interdependence, best shown by decreasing LV systolic and increasing RV systolic pressures on inspiration with the systolic area index ≥1.1 (*Figure 22D*).[108]

Ultimately, when the disease progresses and patients become symptomatic, radical pericardiectomy is warranted, a procedure that can reverse most of the salient findings of constrictive physiology.

In summary, in the setting of clinical right HF, the presence of preserved or increased septal e′ (>8 cm/s), once high output failure is excluded, with associated ventricular interdependence suggested by a respirophasic septal shift, and/or end-diastolic expiratory flow reversal within the hepatic veins can be used to diagnose constrictive pericarditis (*Figure 20*). Cardiac CT can accurately assess pericardial calcium burden, while pericardial characterization using CMR identifies active inflammation and can guide medical management.

Imaging markers of prognosis in HFpEF

Several clinical features and imaging markers have proven to provide clinical and prognostic relevance in patients with HFpEF. The presence and severity of CAD have an important prognostic role in

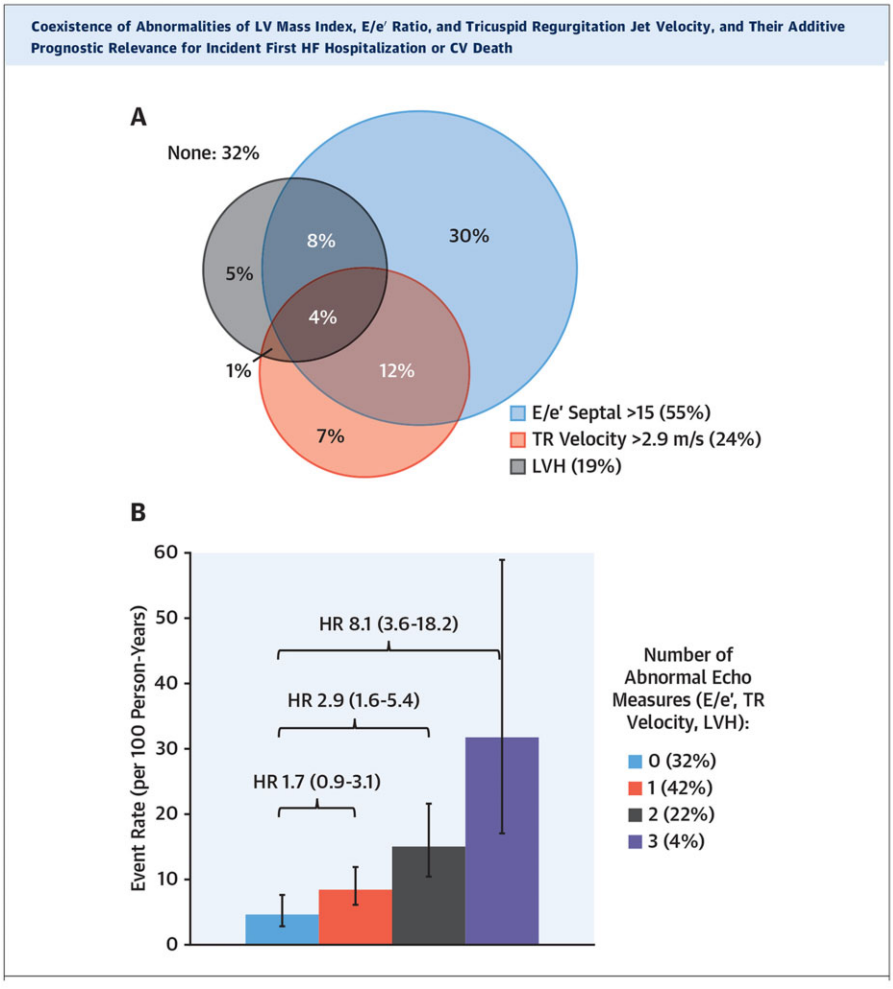

Figure 23 Risk in HFpEF patients ($n = 360$) when considering concomitant abnormalities of LV mass index, *E*/*e*′ ratio, and peak TR velocity. (*A*) Venn diagram demonstrating the overlap of these abnormalities. (*B*) Event rates (per 100 person-years) of incident heart failure hospitalization or cardiovascular death based on the number of abnormal echocardiographic findings, demonstrating their additive risk. HR, hazard ratio; LVH, LV hypertrophy. From the PARAGON-HF study.[41]

HFpEF.[117] Likewise, poorly controlled comorbidities, such as arterial hypertension, diabetes mellitus, chronic renal failure, and AF lead also to worse outcomes in HFpEF patients.[118–121] Thus, optimal control and treatment of these comorbidities is expected to improve the prognosis of HFpEF patients.[1]

Among the imaging markers of prognosis in HFpEF are LV hypertrophy, LA dilation, elevated *E*/*e*′ ratio, RV systolic dysfunction, and elevated RV systolic pressure (i.e. TR velocity >2.8 m/s). *Figure 23* shows the additive risk when more than one of these factors is present in HFpEF.

More recently, LV interstitial fibrosis (detected by ECV using CMR), as well as an abnormal GLS or abnormal LA reservoir strain, have demonstrated to be also important prognosticators for the outcomes of HFpEF patients.[33,122] Consequently, imaging parameters together with clinical risk markers could be used in risk stratification of HFpEF patients.

Future perspectives

A major challenge for HF diagnosis is that EF, which is the standard method to quantify LV pump function, fails to identify HF in about one-half of the patients. The introduction of LV strain imaging has partly solved the problem since LV systolic dysfunction can be identified by showing a reduction in GLS. However, about one-half of all HFpEF patients have normal GLS at rest. Since HF symptoms occur predominantly during exercise, studies at rest may not be sufficient to identify LV pump failure in all patients. This calls for more testing and imaging of LV pump function during exercise to measure peak LV systolic performance. Alternative measures of LV pump function should be explored. As shown in several studies, cardiac power is superior to EF as a measure of LV systolic function,[123] and as suggested in a recent study it may be applied successfully during exercise.[124] The approval of new therapies for HF will take into account the limitations of EF, and thus the clinical judgement of the whole context will be considered when deciding about treatment. In fact, recent data (EMPEROR-Preserved trial) indicate that patients with HF and EF > 40% could benefit from empagliflozin therapy, but with an attenuated response in patients with an EF ≥ 60%.[125,126]

Another area for further development is better phenotyping of HF patients. One recent success is the identification of cardiac amyloidosis, which also has specific therapy. Genetic testing is likely to make important contributions to phenotyping. Imaging of myocardial structure, including quantification of myocardial fibrosis and other features of remodelling by CMR is emerging as important diagnostic approaches in HF patients. Myocardial metabolism by CMR and by nuclear imaging should also be further explored. Furthermore, methods to quantify myocardial stiffness, such as elastography by shear wave imaging is promising.

With regards to echocardiography which provides many important parameters of cardiac structure and function, machine learning should be further explored. This should include a combination of risk markers of HF. Finally, the role of AF and preclinical markers of risk of developing AF should get attention.

Key points

- HFpEF is attributed to LV diastolic dysfunction, often combined with a degree of LV longitudinal systolic dysfunction.
- When evaluating patients with HFpEF, always consider specific cardiomyopathies, non-myocardial and non-cardiac diseases.
- Mechanisms of LV diastolic dysfunction include impaired relaxation, attenuated restoring forces, and increased passive elastic stiffness that leads to elevated LV filling pressure.
- The presence of LV hypertrophy and dilated left atrium provides support for the HFpEF diagnosis.
- Echocardiography is the first-line imaging modality in patients with suspected HFpEF as it provides in most cases accurate information about relevant structural cardiac changes and assesses EF, GLS, and LV diastolic function.
- CMR is the gold standard for imaging of cardiac structure and provides unique information about myocardial tissue characterization, such as the presence of scarring and fibrosis in the LV wall.
- Nuclear imaging is gold standard for diagnosing ATTR cardiac amyloidosis.
- A combination of several echocardiographic parameters differentiates between normal and elevated LV filling pressure with good accuracy.
- Since patients with HFpEF may have normal LV filling pressure at rest, a diastolic stress test or right heart catheterization is needed in some patients.
- Grading of LV diastolic dysfunction may be used for risk assessment.

Conclusions

HF with preserved EF may result from many different aetiologies. Multimodality imaging allows for differential diagnosis, determination of aetiology, and prognostication, being a cornerstone for the clinical management of this complex entity. Echocardiography is the first-line imaging modality in patients with suspected HFpEF as it provides in most cases accurate information about LV filling pressure and relevant structural cardiac changes.

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