

# Imaging in heart failure with preserved ejection fraction: insights into echocardiography and cardiac magnetic resonance imaging

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Heart failure with preserved ejection fraction (HFpEF) is increasingly prevalent and represents more than half of all heart failure cases. It is defined by the presence of heart failure signs and symptoms, identification of cardiac structural abnormalities leading to high left ventricular filling pressures, and an EF > 50%. Common imaging findings in HFpEF include left ventricular hypertrophy, diastolic dysfunction, left atrial enlargement, and elevated pulmonary artery pressure (> 35 mm Hg). Echocardiography is the primary imaging modality for diagnosing HFpEF. It can be complemented by cardiac magnetic resonance (CMR) when further characterization is needed. Advances like real-time 3-dimensional echocardiography and speckle-tracking derived strain, as well as tissue characterization by CMR, have furthered our understanding of the mechanisms and aided in making the diagnosis of a diverse group of conditions that can present as HFpEF. This review aims to touch upon the imaging methods of characterizing HFpEF and discuss their role in specific disease entities.

## Keywords

Heart failure; Ejection fraction; Left ventricular hypertrophy; Echocardiography; Cardiac magnetic resonance

## 1. Definition

The definition of heart failure with preserved ejection fraction (HFpEF) has evolved over the years. The American College of Cardiology defines HFpEF simply as heart failure symptoms in a patient with an EF > 50% where other non-cardiac causes of dyspnea and alternate established cardiopulmonary diseases had been excluded. However, the most recent definition is inclusive of (but not restricted to) cardiac structural abnormalities resulting from high filling pressures, diastolic abnormalities, elevated biomarkers, and elevated left heart filling pressures by invasive hemodynamic assessment [1].

Diastolic dysfunction was initially thought to be a diagnostic criterion for HFpEF [2]. However further studies demonstrated that diastolic dysfunction was not universally present in all HFpEF patients and other factors like systemic and pulmonary hypertension, chronotropic reserve, right heart function, and left atrial dysfunction can contribute to HFpEF

presentation [3]. Arterial hypertension is the leading risk factor for the development of HFpEF [4].

## 2. Diagnosis

HF symptoms can be non-specific so clinicians should maintain a high index of suspicion [5]. The first step is to exclude non-cardiac dyspnea and alternate cardiac causes like valvular heart disease, isolated right HF, and non-group 2 pulmonary hypertension [1].

The threshold to define preserved EF according to the American College of Cardiology and the European Society of Cardiology is > 50% [6, 7]. Once preserved EF has been documented the clinician should focus on determining if there is evidence of an altered cardiac structure and function to provide objective evidence of HF. Common imaging findings in HFpEF include LV hypertrophy (LVH), LV diastolic dysfunction, left atrial enlargement, increased pulmonary artery pressure (> 35 mm Hg), and right ventricular systolic dysfunction [5].

The LV end-diastolic dimension in HFpEF varies between studies with some reporting it as smaller than control patients while others reported more normal ranges [8, 9]. HFpEF patients have increased LV stiffness, impaired LV relaxation, and higher LV end-diastolic pressures. LVH is commonly seen in these patients, although it can also be seen in patients with chronic hypertension without HF [8].

Diastolic dysfunction is not a prerequisite for HFpEF and is present in approximately 70% of HFpEF patients [8–17]. A sub-analysis of the I-PRESERVE trial showed that 31% of HFpEF patients had normal diastology, 29% had mild, 36% had moderate, and 4% had severe diastolic dysfunction. Similarly, diastolic dysfunction determined by echocardiography can exist without clinical HF and may represent either pre-clinical HFpEF or simply isolated diastolic dysfunction [18].

The presence of atrial fibrillation can be part of the diagnostic workup for clinicians since it has been found to be progressively more common in HFpEF compared with reduced ejection fraction patients [19].

### 3. Echocardiographic assessment of diastology

Elevated LV filling pressure is the main consequence of diastolic dysfunction [20]. LV filling pressures include the mean pulmonary capillary wedge pressure (PCWP) or mean left atrial pressure (in the absence of atrioventricular obstruction), LV end-diastolic pressure, and pre-A LV diastolic pressure [21]. Increased LV filling pressure is defined as a PCWP > 12 mm Hg or an LV end-diastolic pressure > 16 mm Hg [22]. These filling pressures are determined mainly by the compliance of the LV wall and may be altered by incomplete myocardial relaxation and variations in diastolic myocardial tone [21].

Traditionally, cardiac catheterization has been the gold standard to measure LV filling pressures but being invasive, it can be impractical, especially for repeat measurements [23]. Currently recommended non-invasive methods to quantify filling abnormalities include the Doppler transmitral flow patterns, pulsed tissue Doppler of the mitral annulus, and the calculated left atrial volume index [24–26].

Different mitral inflow patterns can be determined by calculating the E/A ratio: normal, impaired LV relaxation, pseudonormal, and restrictive LV filling [26].

However, this method using inflow velocities alone to assess LV filling pressures has multiple limitations. It is not ideal to recognize pseudonormal filling patterns and restrictive LV filling in patients with normal LVEF. Electrophysiological abnormalities such as first-degree atrioventricular block and sinus tachycardia can cause partial or complete fusion of the mitral E and A waves, making the E/A ratio uninterpretable. In this context, the mitral DT cannot be measured either. Rhythms like atrial flutter, 3 : 1 or 4 : 1 atrioventricular block make the E/A and DT unmeasurable [26]. Further, mitral inflow velocities are highly sensitive to and may vary with changing preload conditions [27].

PW Doppler tissue imaging (DTI) uses Doppler principles to quantify high-amplitude and low velocity signals from myocardial motion and quantify mitral annulus displacement velocity during the cardiac cycle [27, 28]. DTI mitral measurements include early ( $\dot{e}$ ) and late ( $\dot{a}$ ) diastolic velocities from the septal and lateral sides of the mitral annulus. Unlike early mitral inflow velocity (E), early diastolic tissue velocity ( $\dot{e}$ ) can be interpreted as a preload-independent index of LV relaxation [29, 30]. Reduced  $\dot{e}$  velocities are indicative of diastolic dysfunction (Fig. 1). On account of intrinsic differences in the myocardial fiber orientation, lateral  $\dot{e}$  velocities are slightly higher than septal  $\dot{e}$  velocities [27]. In adults > 30 years old, lateral  $\dot{e}$  velocities > 12 cm/second reflect a normal diastolic function [31]. Late diastolic velocities ( $\dot{a}$ ) have a positive correlation with LA systolic function and a negative correlation with LV end-diastolic pressure (LVEDP) [30].

Calculations performed with these measurements can provide additional information regarding diastolic function [26]. The mitral E velocity measured through PW Doppler can be corrected for the influence of relaxation by divid-

ing it by  $\dot{e}$  (i.e., E/ $\dot{e}$  ratio), which correlates well with the mean PCWP and can be used to estimate LV filling pressures [28, 32]. E/lateral  $\dot{e}$  > 10 or E/septal  $\dot{e}$  > 15 correlates with an increased LV end-diastolic pressure, whereas, a E/ $\dot{e}$  < 8 is considered normal [27]. The average of lateral and septal  $\dot{e}$  should be used to estimate the E/ $\dot{e}$  ratio if there are regional wall motion abnormalities [33].

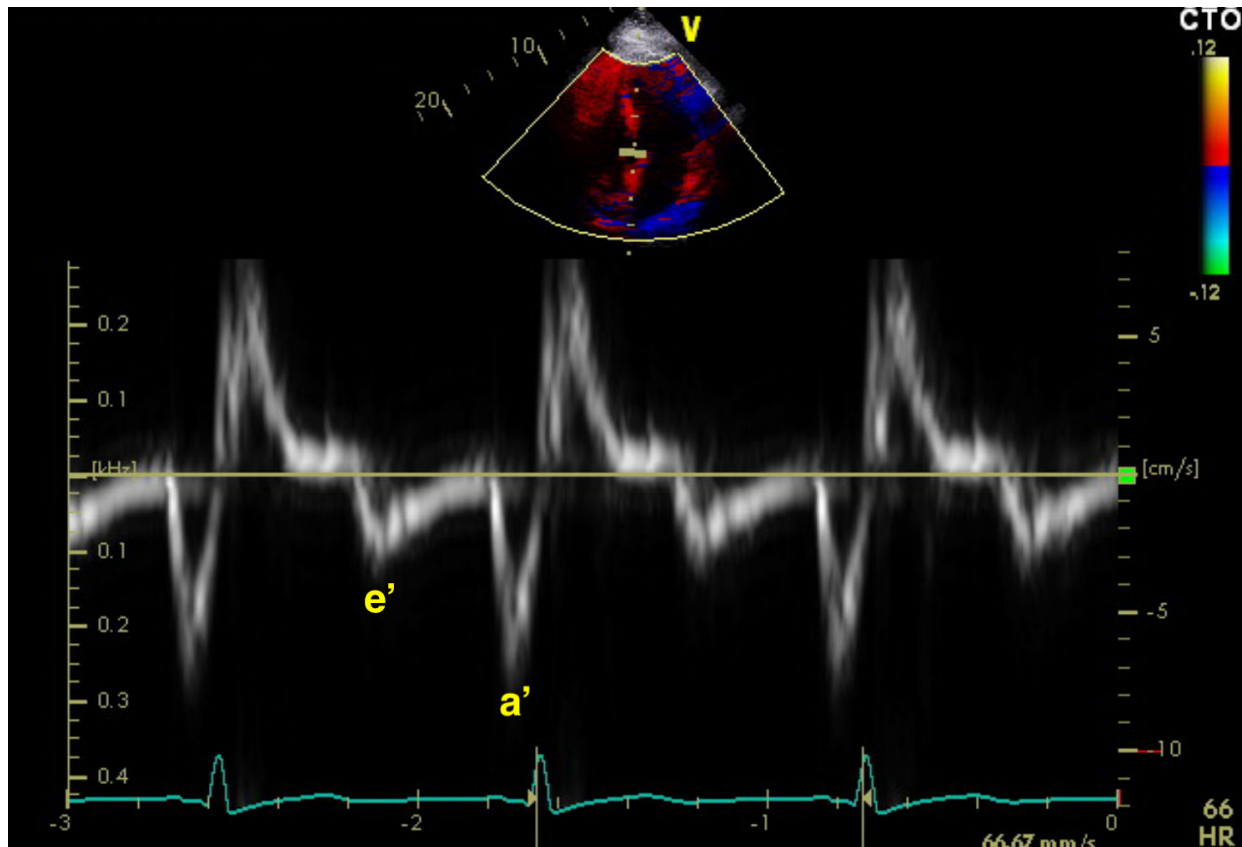
This method has limitations as well. DTI measures the absolute tissue velocity without the capacity to differentiate between active and passive motion (fiber shortening/lengthening vs translation/tethering) [27]. Moreover, there is significant variability depending on the location of the sample, angle-dependence, load-dependence, variability caused by the cardiac cycle, and low reproducibility [26, 34]. The E/ $\dot{e}$  ratios should not be used to determine diastolic dysfunction in subjects with significant annular calcification, surgical rings, mitral stenosis, prosthetic mitral valves, moderate to severe mitral regurgitation, or constrictive pericarditis [26].

A subset of patients with HFpEF can have normal resting hemodynamics with an elevation of filling pressures only after exercise. The evaluation of hemodynamics during exercise can reveal increased LV filling pressures and aid in making the diagnosis [35, 36]. This phenomenon is possibly explained by the fact that HFpEF patients are highly sensitive to volume shifts [37]. The combination of cardiopulmonary exercise testing with echocardiography and invasive PCWP measurement allows clinicians to identify hemodynamic changes during exertion. It can provide robust information in both HFrEF and HFpEF patients [38]. Invasive hemodynamic measurements during exercise can detect increased peripheral oxygen consumption in patients with heart failure and signs of systo-diastolic dysfunction and pulmonary congestion [39–44].

Exercise capacity can be significantly decreased in patients with HFpEF. An impaired left atrial compliance seems to be closely associated with a limited exercise capacity in these patients [45]. Left atrial strain, an indicator of atrial compliance, is impaired in patients with HFpEF. In the future, left atrial strain could be part of the diagnostic evaluation of diastolic function and aid in the diagnosis of HFpEF [45–49].

### 4. Left ventricular hypertrophy

Echocardiography is sensitive in diagnosing LVH (Fig. 2) and can aid in stratifying patients at a higher risk for cardiovascular and renal complications [50, 51]. LV mass can be measured more accurately by real-time 3D echocardiography based reconstruction techniques and compares favorably with CMR [52]. Foreshortening of the LV apex and poor acoustic windows limiting epicardial and endocardial visualization remains a challenge. CMR evaluation of LV mass is discussed in detail later.



**Fig. 1. Tissue Doppler velocity profile from the septum in a patient with HFpEF: Reduced septal early ( $e'$ ) velocity indicates diastolic dysfunction.** In normal hearts with preserved diastolic function, the  $e'$  velocity should be higher than  $a'$ .

## 5. Speckle tracking echocardiography

Speckle tracking echocardiography is a major advancement that allows the assessment of global and regional myocardial strain by tracking the displacement of acoustic markers placed on the myocardium through the cardiac cycle [53]. Global longitudinal strain (GLS) refers to the apex-base deformation measured from apical views, whereas global circumferential (GCS) and radial strains are measured from the parasternal short-axis views. Myocardial strain is more sensitive at picking up subclinical myocardial disease than 2D assessment alone [54] and can help distinguish underlying etiologies of HFpEF (Fig. 3). This is discussed in detail in the following sections.

## 6. Cardiac magnetic resonance imaging in HFpEF

CMR is not widely used as the first line imaging modality for diastolic assessment due to the ready availability, portability, and cost-effectiveness of echo. However, due to its volumetric coverage, it is the gold standard for measuring LV mass, LA and LV volumes, and LVEF (Fig. 4) [55]. It is free of geometric assumptions made by 2D echo and is not limited by acoustic windows.

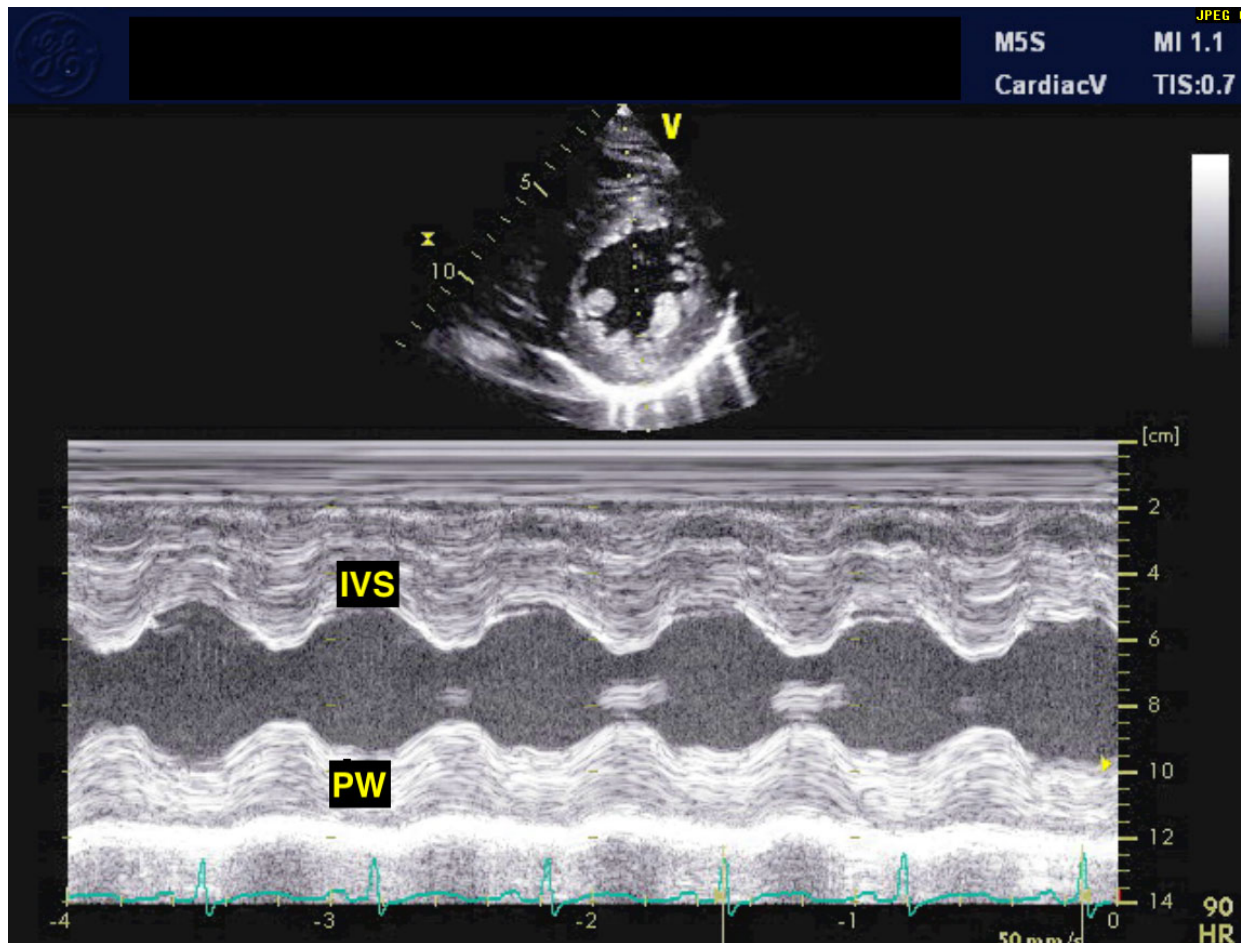
Phase-contrast CMR can provide measurements of mitral inflow and tissue velocities that correlate well with echo as

well as invasive PCWP [56–58]. but are limited by lower temporal resolution (30–40 ms compared to < 10 ms with echo) and image degradation with arrhythmias [59]. Moreover, such replication of echo techniques does not play to the strengths of CMR.

CMR derived tagging sequences can be used to evaluate LV strain. Tagged grids generated over the myocardium using radiofrequency pulses and tracked over the cardiac cycle can provide measures of myocardial deformation [60]. Speckle tracking echo was initially validated against this technique. Advances in CMR post-processing (Fig. 5) have enabled feature tracking on cine CMR images remitting the need for tagged sequences [60]. GLS and GCS with CMR feature tracking correlate closely with speckle tracking echo [61].

However, the most important contribution of CMR is non-invasive tissue characterization. Late gadolinium enhancement (LGE) imaging is the oldest and most well established method of tissue characterization. Intravenously administered gadolinium chelate accumulates and persists in areas of expanded extracellular matrix-like fibrous tissue. T1-weighted imaging performed 10–15 minutes after gadolinium administration can detect areas of replacement fibrosis which appear hyper-enhanced or bright against a background of normal dark myocardium [62].





**Fig. 2. M-mode echocardiography at mid papillary level on the short axis view showing concentric LVH.** There is increased thickness of the interventricular septum (IVS) and the posterior wall (PW).

The development of native T1 mapping and extracellular volume (ECV) measurements have further extended our ability to detect diffuse fibrosis [63, 64]. T1 or longitudinal relaxation time constant is a magnetic property of a tissue detectable by CMR. The difference in native myocardial T1 and post-gadolinium myocardial T1 can give a measure of the ECV since gadolinium primarily deposits in the extracellular space. Interstitial fibrosis can be detected by CMR as increased native T1 and ECV [63, 65].

In terms of cost-benefit, a 2010 analysis of Medicare data (361 patient sample) showed that the overall benefits of performing cardiac MRI scans outweigh its cost. This study showed that CMR imaging was capable of resulting in a new diagnosis in 27% of patients, avoidance of invasive procedures in 11% of patients, and prevented additional diagnostic testing in 7% of patients. A comparison of health care savings using CMR as more traditional standards of care showed a potential savings of costs overall [66].

A detailed list of advantages and disadvantages of both echocardiography and CMR is shown in Table 1.

## 7. Imaging for specific cardiomyopathies Causing HFpEF

### 7.1 Hypertensive heart disease

Hypertensive heart disease is perhaps the most common cause of diastolic dysfunction. Chronically elevated afterload in hypertension causes LV walls to thicken and cavity size to shrink. This change in LV geometry is an adaptive response to reduce wall stress (LaPlace's Law: wall stress = (pressure x radius)/(2 x wall thickness)) and results in concentric LVH/remodeling [67]. This is accompanied by an increase in the extracellular matrix as well. A thick ventricle with a small cavity impairs diastolic relaxation and over time adequate filling can only occur at elevated filling pressures.

Echocardiography is the primary imaging modality for evaluating hypertensive heart disease and protocols follow the general outline described above including morphological (LV wall thickness, LA size) and physiological assessments (mitral inflow, DTI, pulmonary vein flow, tricuspid regurgitation velocity, etc.) [68]. Accurate measurements of LV mass and LVEF can be obtained from 3D echo and CMR as discussed.

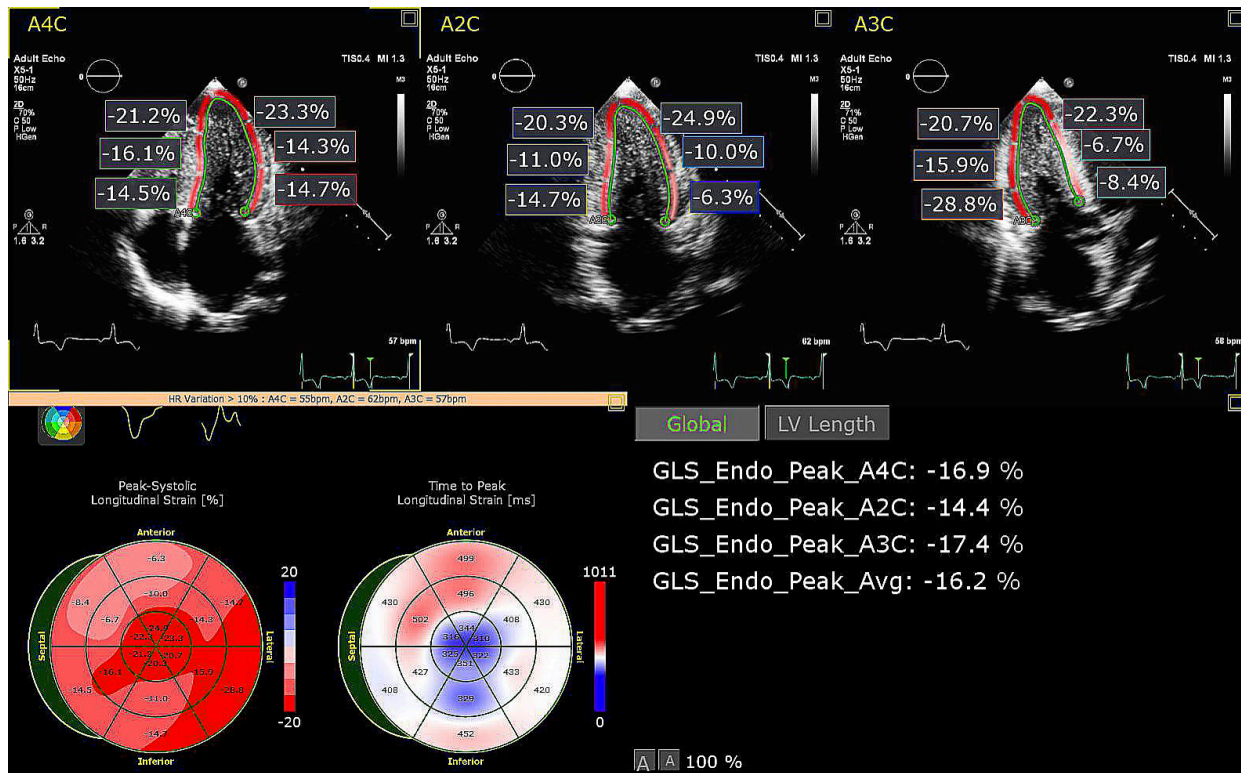


Fig. 3. Reduced global longitudinal strain (GLS) in hypertensive heart disease.

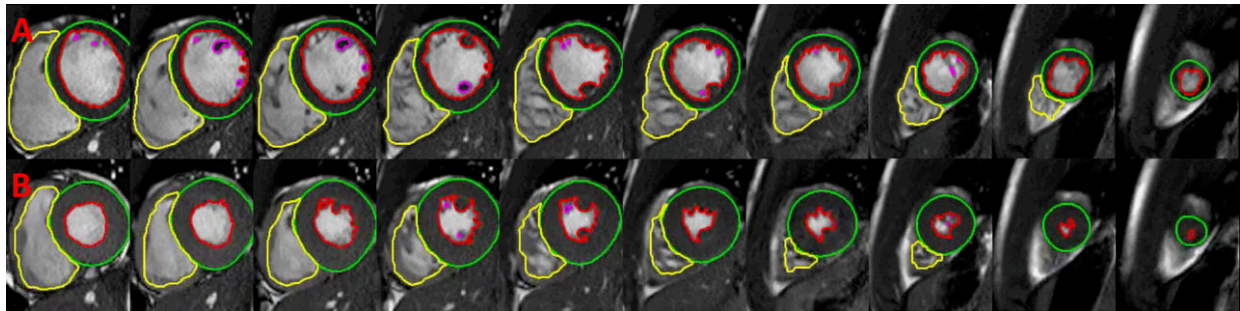


Fig. 4. Left ventricular mass on CMR is calculated as the area between epicardial (green) and endocardial (red) borders multiplied by the distance between slices and then multiplied by the specific gravity of myocardium (1.05 g/mL). Ejection fraction is similarly calculated as a ratio of end systolic (B) and end diastolic frames (A) calculated from the area within the endocardial (red) borders.

Global longitudinal strain (GLS) is reduced in hypertensive heart disease (Fig. 3). A study comparing hypertensive patients with preserved EF to control subjects found reduced GLS with hypertension even though the LVEF was comparable [69]. GLS was further reduced in hypertensive patients with clinical HFpEF [70]. In contrast, athletes with physiological hypertrophy have a higher GLS despite increases in wall thickness [71].

The mechanism of HFpEF has also been explored using strain. A very interesting study comparing 120 hypertensive patients with similar EF but higher relative wall thickness and LV mass index to age and gender-matched volunteers found that while global longitudinal strain was reduced in hypertension, global circumferential strain and LV twist were increased [72]. Thus, an increased circumferential strain may

counterbalance reduced longitudinal strain to maintain EF in hypertensive patients with diastolic dysfunction. Drop-in longitudinal strain in hypertension also correlates with tissue inhibitor of matrix metalloproteinase-1 [73], a serum marker of fibrosis, suggesting that increased wall thickness is a function of cardiomyocyte hypertrophy and interstitial fibrosis.

Chronic hypertension leads to the deposition of fibrous tissue, primarily type 1 fibrillar collagen, in the extracellular compartment, thereby increasing myocardial stiffness, and worsening diastolic dysfunction [74–76]. CMR can detect replacement fibrosis using LGE imaging. One study found up to 50% of hypertensive individuals to have some form of LGE without a specific pattern [77]. Another study showed an incremental increase in the prevalence of LGE with worsening diastolic dysfunction (13% in normal, 48% in impaired relax-

**Table 1. Advantages and disadvantages of echocardiography and CMR**

Modality	Advantages	Disadvantages
<b>Echocardiography</b>	Economic technology, readily available	Quality of images dependent on anatomy (e.g., obesity, thoracic deformations, emphysema)
	Accuracy and prognostic value extensively demonstrated	Lower resolution compared to CMR
	Accurate ventricular function assessment	Operator-dependent
	No radiation exposure	High inter-observer variability
	Ideal for emergent bedside evaluation	
	Allows comprehensive evaluation of strain and strain rate analysis. GLS measures are useful and reproducible in HFpEF	
<b>CMR</b>	High-quality image independent of patient anatomy	Certain relative contraindications such as: claustrophobia, end-stage renal disease, arrhythmias
	No radiation exposure	Absolute contraindications: non-compatible metallic material
	Accurate quantification of myocardial mass	Limited availability
	Evaluation of myocardial inflammatory disease	Higher cost compared with echocardiography
	Allows evaluation of scar with LGE. Further tissue characterization with T1 and T2 mapping	Longer scan times
		Strain analysis cumbersome

CMR, cardiac magnetic resonance imaging

GLS, Global Longitudinal Strain

LGE, Late Gadolinium Enhancement

ation, 78% in pseudonormal, and 87% in restrictive filling [78]. Despite a high prevalence, qualitative visualization of localized replacement fibrosis by LGE may, in fact, miss the majority of the diffuse interstitial fibrosis. Diastolic dysfunction in asymptomatic patients with hypertension predicts the eventual development of symptomatic HFpEF and its complications [79].

ECV using T1 mapping technique can detect interstitial fibrosis. Two studies showed ECV to be higher in hypertensive patients with LVH when compared to those with hypertension but without hypertrophy and with controls [80, 81]. A third study evaluating morphological variants in hypertension found interstitial fibrosis as detected by ECV to be the highest in eccentric hypertrophy, followed by concentric hypertrophy, concentric remodeling, and normal LV [82]. Elevated ECV also correlates well with strain [81].

### 7.2 Aortic stenosis

In aortic stenosis, LV systolic pressure increases, as the aortic valve orifice gets smaller. Chronic pressure overload leads to increased myocardial hypertrophy and interstitial fibrosis resulting in impaired early filling and poor compliance. Once fibrosis has become established further scarring accumulates rapidly [83]. In late stages, the LV can maintain diastolic volume only at elevated filling pressures. This mechanism of diastolic dysfunction is very similar to hypertensive heart disease. Reversal of diastolic dysfunction may take years after aortic valve replacement.

Initial echo based diastolic assessment of aortic stenosis is also similar to hypertensive heart disease. GLS goes down with increasing severity of aortic stenosis and is an independent predictor of mortality [84]. Among those with asymp-

tomatic severe aortic stenosis, lower GLS portends poorer exercise tolerance and worse prognosis [85].

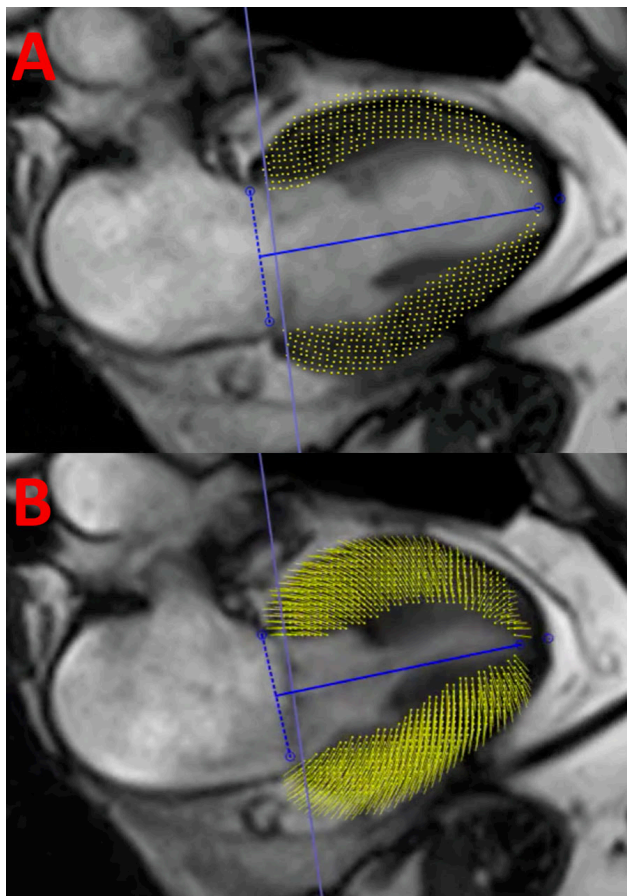
Mid-wall fibrosis is the most common form of LGE seen in aortic stenosis and predicts poor outcomes [86–89]. Native T1 and ECV are also elevated with aortic stenosis. Further, both ECV and intracellular volume (ICV) appear to decrease after aortic valve replacement suggesting a regression in interstitial fibrosis and cellular hypertrophy respectively [90, 91].

### 7.3 Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiomyopathy characterized by myocardial hypertrophy, myofibril disarray, fibrosis, and mitral valve abnormalities. Both American and European guidelines suggest a wall thickness > 15 mm in the absence of other underlying causes as the diagnostic threshold for HCM [92, 93]. Hypertrophy in HCM is often localized with asymmetric septal hypertrophy being the most common phenotype. Other morphological variants include concentric hypertrophy, mid-ventricular hypertrophy, apical hypertrophy, and focal hypertrophy [94]. Systolic anterior motion of the mitral leaflet and mid-cavitary obliteration causing dynamic outflow obstruction are other known perturbations. Mitral regurgitation and left atrial enlargement are also commonly seen.

The mechanism of diastolic dysfunction in HCM is complex and includes 1. altered global and regional relaxation from hypertrophy and myofibril disarray; 2. smaller LV cavity size; 3. reduced compliance due to fibrosis; 4. pressure overload from dynamic obstruction; and 5. ischemia from demand-supply mismatch [95]. This complex interplay explains why parameters like E/A, DT, IVRT correlate poorly





**Fig. 5. Feature tracking is a novel method for the assessment of diastolic function on CMR.** It measures regional and global LV strain. Panel A shows a diastolic frame and Panel B shows a systolic frame.

with filling pressures in HCM [57].  $E/\dot{e}$  has a modest correlation with invasive left atrial pressure [96, 97] and predicts adverse outcomes [98].

GLS reduction in HCM is typically greater than the hypertensive heart [71] and is associated with poor prognosis and increased hospitalization [99, 100]. Regional depression in strain correlates well with fibrosis seen on CMR [101, 102]. Low GLS, higher mechanical dispersion (calculated as the standard deviation of time from Q/R on ECG to peak longitudinal strain), and LGE on CMR are all associated with higher rates of ventricular tachyarrhythmia [101].

CMR can help distinguish morphological variants of HCM where acoustic windows are poor and also facilitate accurate measurement of LV mass. But the strength of CMR lies in the identification and quantification of fibrosis. Replacement fibrosis in HCM, as detected by LGE, has a patchy and mid-wall distribution and primarily affects the right ventricular insertion points and areas of maximal wall thickness (Fig. 6). LGE in HCM is an independent predictor of all-cause mortality and cardiac mortality [103, 104]. LGE involving > 15% of the myocardium doubles the risk of sudden cardiac death. The addition of LGE increases the performance of risk prediction models in HCM (net reclassification index

13%) [105]. Studies with T1 mapping have aimed at detecting interstitial fibrosis missed with LGE. Both native T1 and ECV tend to be higher in HCM compared to hypertensive patients and controls [106]. T1 and ECV elevation in genotype (+) phenotype (-) individuals suggests their possible utility in early detection of disease [107].

#### 7.4 Infiltrative cardiomyopathies – cardiac amyloidosis

Infiltrative heart disease includes conditions like cardiac amyloidosis, sarcoidosis, and Anderson-Fabry disease.

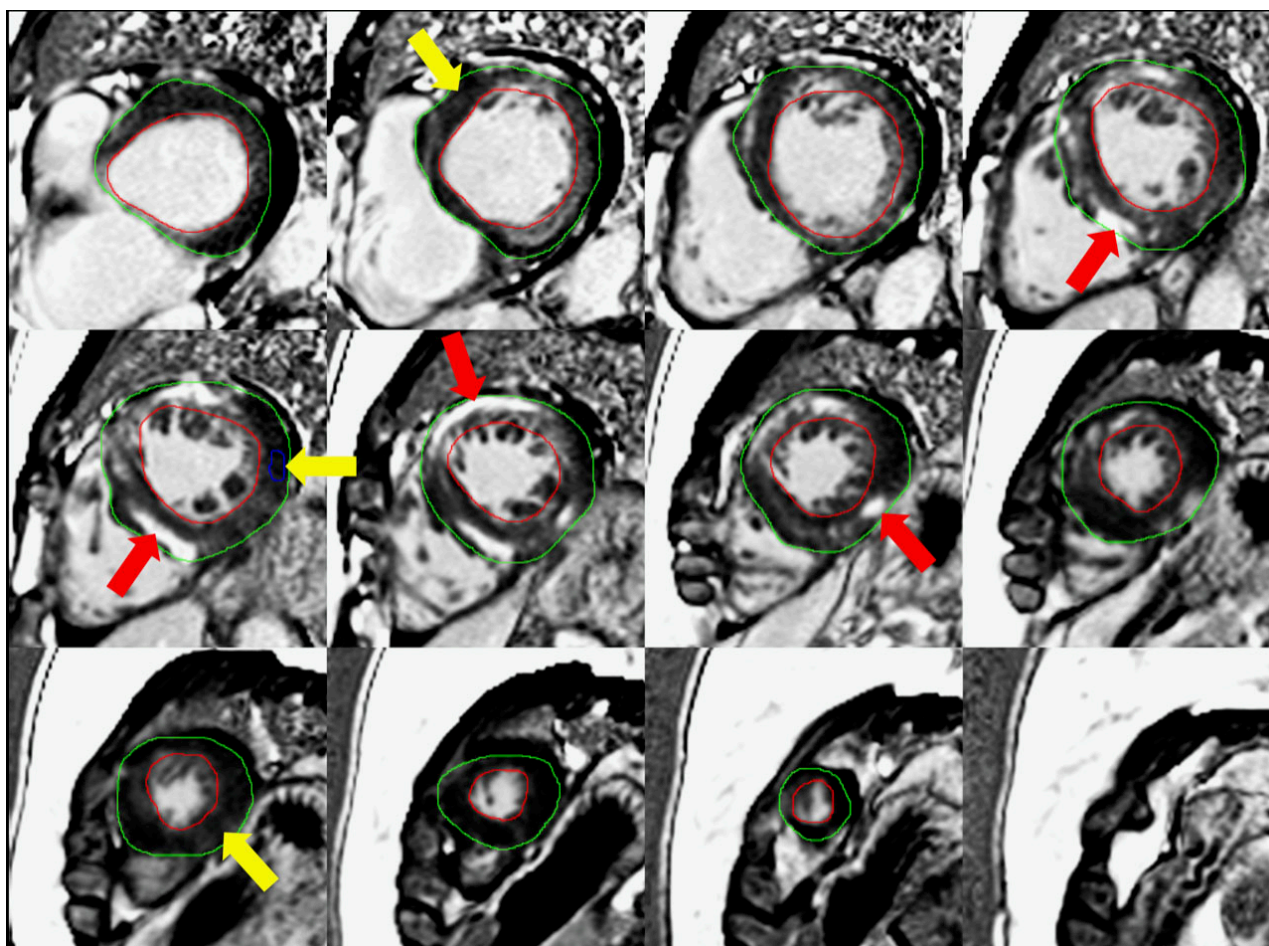
Cardiac amyloidosis is characterized by amyloid protein fibril (immunoglobulin light chain in AL and transthyretin in ATTR type) deposition in the extracellular space. This extracellular expansion gives the appearance of LVH on echocardiography. The classical “speckle appearance” of amyloid on 2D echo is less reliable in the age of harmonic imaging. Low voltage on ECG (in contrast to hypertension and HCM) and renal dysfunction are other clues that can point towards amyloid.

Diastolic dysfunction worsens with the progression of amyloid with grade 1 in initial stages and grade 3 in late stages [108]. Advanced stages show restrictive physiology with mitral  $E/A > 2.5$ ,  $DT < 150$  msec,  $IVRT < 50$  msec, decreased septal and lateral  $\dot{e}$  velocities (3-4 cm/sec), and  $E/\dot{e} > 14$  [68]. Lateral  $\dot{e}$  remains higher than septal  $\dot{e}$  which helps to distinguish this restrictive cardiomyopathy from constrictive physiology [109].

Cardiac amyloid reduces both longitudinal and circumferential strain more profoundly than HCM and hypertensive heart disease [110]. A study found EF/GLS ratio (normally 3) to be higher in amyloid (5.7) compared to HCM (3.7) and normal healthy controls (3.2) [111]. The authors suggested an EF/GLS ratio of 4.1 be used as a threshold to distinguish amyloid from HCM. However, differences in severity and regional involvement are bound to cause fluctuations.

Regional strain is perhaps the most useful to distinguish amyloid from other causes of LVH. Amyloid deposition affects the basal segments more than the apex in both AL and TTR forms of amyloid such that there is an “apical sparing” pattern is seen on strain mapping [112, 113]. Apical sparing picked up visually on polar maps [114] or quantified by a relative regional strain ratio (average apical strain/(average basal strain + average mid strain)) [115, 116] can be a sensitive and specific echo marker for cardiac amyloidosis. Both GLS and regional strain have prognostic implications for amyloid [117].

Amyloid, especially in advanced disease, has a characteristic CMR appearance (Fig. 7). Due to its rapid accumulation in the expanded extracellular compartment, gadolinium contrast clears rapidly from the blood pool. On LGE imaging, it is difficult to “null” the normal myocardium which is diffusely involved. Global subendocardial and diffuse patchy LGE patterns are typically seen [118]. LGE also predicts prognosis in cardiac amyloid [119] but may miss the early stages of disease. Native T1 mapping and ECV are quantifiable [120] and are elevated even in early disease. ECV is typically higher and T1



**Fig. 6. Late Gadolinium Enhancement (LGE) on CMR.** This represents replacement fibrosis. This can be assessed qualitatively as well as quantitatively - as a percentage or grams of myocardial tissue. Red arrows show area of fibrosis (bright) while yellow arrows denote normal myocardium (dark).

lower in TTR compared to AL amyloidosis [121]. Changes in these values can potentially be used as biomarkers for treatment response.

#### 7.5 Infiltrative cardiomyopathies - Anderson Fabry Disease

Anderson Fabry Disease (AFD) is a X-linked lysosomal storage disease that results in glycosphingolipid accumulation within lysosomes. Increased wall thickness is the most common echo finding, while atrial enlargement, right ventricular hypertrophy, mitral valve thickening and prolapse, and sinus of Valsalva dilatation have also been described [122]. The “binary sign”, referring to hyperechoic endocardium adjacent to a hypoechoic sub-endocardium due to selective deposition of sphingomyelin does not appear to be a consistent finding [55]. Thickened papillary muscles have also been reported. Due to morphological similarity, up to 10% of HCM and undifferentiated LVH turn out to be AFD [123, 124].

Diastolic dysfunction is a consistent feature of AFD and worsens with increasing wall thickness and fibrosis [122]. Genotype (+) patients without LVH have lower tissue Doppler velocities and higher  $E/e'$  compared to controls suggesting that these could be used as early markers of disease [125]. Longitudinal and radial strain, and peak systolic strain

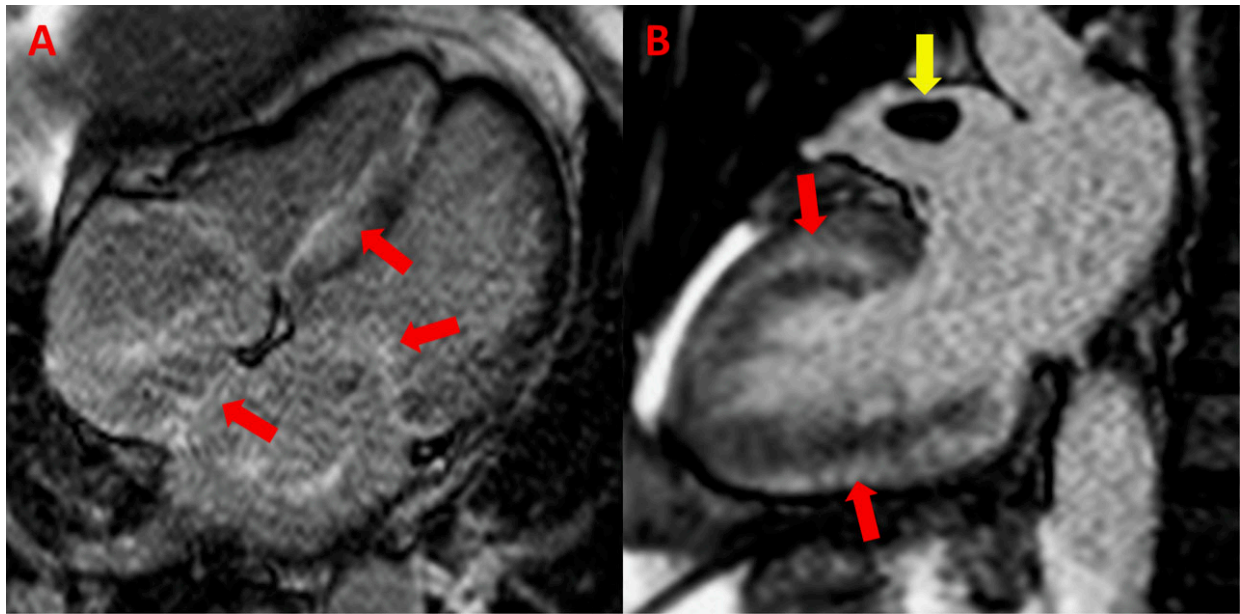
rate are significantly reduced in AFD compared with controls and appear to reverse with enzyme replacement therapy [126]. Strain is reduced the most in the basal inferolateral and anterolateral segments and correlates with LGE on MRI [127].

LGE is present in up to 50% of AFD and primarily involves the inferolateral wall in a mid-wall distribution [128]. Myocardial T1 characteristically goes down in AFD since fat (sphingolipid in AFD) is known to decrease T1 [129, 130]. This finding can be used to distinguish AFD from other causes of LV thickening.

#### 7.6 Endomyocardial fibrosis

Endomyocardial fibrosis manifests as diffuse fibrosis of the endocardial surfaces of one or both ventricles and is often associated with ventricular thrombus formation. It causes a restrictive pattern of myocardial relaxation on echocardiography. Typical appearance of endomyocardial fibrosis on late gadolinium enhanced CMR is described as a “double V” sign signifying dark normal myocardium outside, bright layer of fibrosis in between and dark layer of thrombus in the LV cavity [131].





**Fig. 7. Late gadolinium enhancement on CMR in a case of cardiac amyloidosis.** Panel A shows rapid clearing of contrast from the LV cavity and diffuse delayed enhancement of the myocardium, valves and inter-atrial septum (red arrows). Panel B shows a 2 chamber view with diffuse delayed enhancement of the myocardium. A left atrial appendage thrombus is incidentally noted (yellow arrows).

### 7.7 Myocarditis

The American Heart Association defines myocarditis as inflammation of the myocardium identified through clinical, imaging, and microscopic findings. An inflammatory cardiomyopathy can be defined as myocarditis associated with cardiac dysfunction [132]. Due to the nonspecific clinical, echocardiographic, and electrocardiographic findings in myocarditis, multimodality imaging is critical for diagnosis. TTE can be used for initial workup and determine presence of cardiac dysfunction. CMR is the noninvasive reference standard for assessing myocarditis. CMR, through a combination of T2- and T1-weighted imaging, has a sensitivity and specificity of 80% for its diagnosis. T2-weighted imaging can identify edema with a sensitivity of up to 81%. Late delayed gadolinium enhancement can identify inflammation or fibrosis with different patterns suggestive of distinct etiologies. CMR can further guide clinicians to identify patients who should undergo an endomyocardial biopsy [133].

The following are the diagnostic CMR criteria for myocarditis, the Lake Louise Consensus Criteria. CMR findings are consistent with myocardial inflammation if two or more of the following are found:

- i. Regional or global myocardial signal intensity increase in T2-weighted imaging.
- ii. Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in T1-weighted imaging.
- iii. There is at least one focal lesion with non-ischemic regional distribution in inversion-recovery prepared gadolinium-enhanced T1-weighted images. Characteristics consistent with myocyte injury and/or scarring.

It is recommended to repeat a CMR between 1-2 weeks if none of the criteria are present but there is sufficient clinical suspicion or if only one of the criteria is present. In addition, LV dysfunction and/or pericardial effusion provide additional, supportive evidence for myocarditis [134].

### 7.8 Pericardial disease

Disease of the pericardium like constrictive pericarditis can mimic the clinical presentation of restrictive cardiomyopathy and HFpEF [135]. Echocardiography can help assess pericardial effusion size and location, increased pericardial thickness (> 3 mm), and hemodynamic consequence (chamber collapse, respiratory variation). CT and CMR can be used to better define pericardial thickness, calcification, inflammation and enhancement. Better delineation of pericardial pathology can help distinguish it from HFpEF since treatment of the two conditions differ [136, 137].

## 8. Future direction

HFpEF remains a challenging clinical syndrome however the field is evolving rapidly. Radiomic texture analysis of CMR derived T1 images has been shown to distinguish hypertrophic cardiomyopathy from hypertensive heart disease [138]. A recent publication shows the utility of cardiac CT derived ECV to help diagnose cardiac amyloidosis in up to 15% of patients with aortic stenosis undergoing transcatheter aortic valve replacement (TAVR) evaluation [139]. High clinical suspicion and targeted testing is critical to early diagnosis and management. Advanced multi-modality imaging can help with accurate diagnosis and initiation of specific therapy.

## Author contributions

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## Conflict of interest

The authors declare that they have no conflict of interest.

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