Comprehensive Assessment of Heart Failure with Preserved Ejection Fraction Using Cardiac MRI

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Comprehensive Assessment of Heart Failure with Preserved Ejection Fraction Using Cardiac MRI

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KEYWORDS

• Heart failure with preserved ejection fraction • Diastolic dysfunction • Cardiac magnetic resonance • Cardiac filling pressures

KEY POINTS

- The diagnostics process of heart failure with preserved ejection fraction (HFpEF) is complex and generally imprecise.
- Allocating heart failure phenotypes based on a discrete marker of cardiac function as the ejection fraction by the Simpson biplane method can be misleading.
- Echocardiography is a first-line imaging technique to characterize HFpEF but suffers inherent limitations related to ultrasound capabilities.
- Cardiac magnetic resonance (CMR) provides superior anatomic and functional assessment and enables tissue characterization, providing unprecedented diagnostic precision.
- CMR refinements that incorporate advanced cardiac mechanics and tissue characterization will redefine the imaging boundaries in HFpEF.

INTRODUCTION

Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for nearly half of the HF burden and its prevalence is increasing because of population aging. Its diagnostic process is challenging and generally imprecise because of the absence of a single diagnostic marker to adjudicate this condition, the complex and multiparametric echocardiography evaluation involved, and the broad spectrum of causes encompassed in HFpEF.[1]

Guidelines have historically referred to this condition as diastolic HF because of the frequent associated diastolic dysfunction (DD). However, the presence of DD does not imply HFpEF, so these 2 conditions do not always go together.

In 1998, the European study group on "diastolic heart failure" suggested diagnostic criteria detaching this entity from systolic or congestive HF.[2]

Regarding the ejection fraction (EF) criteria, a pragmatic and arbitrary approach divided HF with preserved left ventricular ejection fraction

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(LVEF) more than 50% and reduced LVEF less than 40%, leaving in between an awkward mid-range phenotype of HF.[3] This snapshot approach's main problem is that it generates an artificial division of a likely continuous phenomenon based on a very discrete ventricular function marker, such as the LVEF by Simpson's biplane method.

Current diagnostic criteria give a central role to imaging (mainly echocardiography), demonstrating LVEF more than 50% and relevant structural heart disease to which the symptoms could be attributable. However, it also incorporates clinical features, such as HF signs and symptoms, and biomarker evidence of elevated intracardiac pressures represented by increased brain natriuretic peptide.

The caveat with this definition is that it only encompasses symptomatic patients (stages C and D of ACC/AHA classification), excluding patients at risk of HF (stage A) or asymptomatic patients with structural alterations, such as left ventricular hypertrophy (LVH) (stage B), which is precisely the most frequent scenario to encounter in clinical practice.

Furthermore, recent diagnostic scores systems, such as the H2FPEF and the HFA-PEFF, intend to solve the diagnosis challenge by giving distinct consideration to clinical data, biomarkers, and imaging, but with large discrepancies in adjudicating this condition,[4] highlighting the complexities in HFpEF diagnosis and underscoring the need for a robust imaging technique to characterize this disease.

This review describes cardiac magnetic resonance (CMR) capabilities in HFpEF, focusing on differential diagnosis, and portrays CMR as a one-stop shop for HF.

Considerations in Heart Failure with Preserved Ejection Fraction Imaging

Echocardiographic evaluation of the heart cavities was mainly anatomic and static until Nishimura's publications on left ventricular (LV) diastolic function in 1997, portraying the diastolic evaluation as the clinicians' "Rosetta Stone."[5] Since then, echocardiography has come a long way, implementing an algorithmic evaluation that grades DD into stages and incorporates cardiac mechanics (strain).[6] Recently arising are advanced cardiac work indexes assembled from the LV pressure-strain loops, such as global work, index, waste, and efficiency. Notwithstanding all these refinements, inadequate acoustic windows and the impossibility of performing tissue characterization are the main limiting factors for this widespread technique.

In contrast, CMR is a comprehensive diagnostic tool that combines anatomic, functional, and tissue characterization capabilities, being better suited for evaluating a broad disease, such as HFpEF. CMR is the gold standard for size and function in cardiac chambers, providing functional information using flow sequences (2-dimensional [2D] or 4-dimensional [4D]). Most remarkably allows performing tissue characterization via parametric mapping (T1, extracellular volume [ECV], T2) and gadolinium (GAD) enhancement. Furthermore, novel CMR sequences, such as fast strain-encoded CMR (fast SENC), and postprocessing techniques, such as feature tracking, enable accurate cardiac mechanics evaluation. Moreover, on the immediate horizon is high-quality coronary angiography with flow acquisition, automatic quantitative stress myocardial perfusion, and fingerprinting CMR that allows for nongated real-time simultaneous acquisition of mapping and CINE images,[7] enhancing detection of underlying alterations that could ultimately be a game-changer in cardiac imaging.

HEART FAILURE WITH PRESERVED EJECTION FRACTION IMAGING

HF with reduced ejection fraction frequently presents with LV dilatation and ejection fraction (EF) less than 40% to 50%; on the other side, gross imaging characteristics of HFpEF include normal or near-normal systolic LV function (LVEF >50%), cardiac structural alterations, mainly in the form of LVH or left atrial enlargement (LAE) and variable degrees of DD. Unfortunately, these features are common to a conundrum of disorders,[8] such as arterial hypertension, myocardial ischemia, obstructive sleep apnea, diabetes, chronic kidney disease, obesity, early stages of hypertrophic cardiomyopathy (HCM), and the broad spectrum of restrictive cardiomyopathies, including storage and infiltrative that present LV thickening.

The main advantage of CMR over echocardiography is the ability of CMR to integrate anatomic, functional, and tissue characterization, offering unprecedented diagnostic precision. Notwithstanding CMR capabilities, echocardiography, because of its widespread access and well-validated features, is the first-line imaging technique in HFpEF.

Imaging Objectives

Aiming to improve patient prognostic imaging in HFpEF, should provided:

a. Cardiac chamber size and systolic function

b. Diastolic function, cardiac filling pressures, and pulmonary hypertension (PH)
c. Likely cause of HF
d. Associated findings

Cardiac chamber size and systolic function

Left ventricle LV wall thickness magnitude and distribution using 2D mode (or B mode) are generally reliably. Common echocardiography pitfalls are missing apical lateral hypertrophy because of poor visualization and overestimating basal septum thickness by including in the measurement the right ventricle (RV) moderator band's insertion. Because of its high in-plane spatial resolution, CMR can accurately measure wall thickness in a short-axis plane, reassuring that the measure is orthogonal to the long-axis plane.

Regarding echocardiography LV mass calculation, its assessment is quite deficient because echocardiography indirectly assesses the mass by sampling one point of the anteroseptal septum and the posterior wall, extrapolating it and assuming an ellipsoid shape. In contrast, CMR calculates LV mass directly without geometric assumptions by tracing the epicardial and endocardial contours in a complete short-axis stack of the heart.

LV systolic function is calculated in echocardiography by the modified Simpson's biplane method of disk summation, which is a marker of how much blood is retained and expelled in the LV systole. In preserved EF, the LV should eject at least half of its filling volume. This simplistic approach for evaluating LV function has stood over time, but it is insufficient and limited to comprehensively assess LV function. Furthermore, significant LVH can be associated with severely reduced LV longitudinal excursion, a scenario in which Simpson's methods do not reflect the real LV systolic function, overestimating EF because of geometric confounders.[9] Another shortcoming is the presence of limited acoustic windows and the foreshortening of the LV, which causes a dramatic underestimation of LV volumes. These issues portray some of the serious limitations of Simpson's EF in adjudicating LV function.

Deformation imaging, such as strain, partially overcomes these limitations. Still, it is highly dependent on acoustic windows, adequate temporal resolution, and operator experience, not to mention it is time-consuming and presents significant variabilities depending on the vendor's software. Consequently, in daily practice, LVEF by Simpson's method is an imperfect best choice.

Regarding CMR, evaluation of LV volumes uses a short-axis cine stack that covers the entire heart. Modern cine sequences use breath-hold, electrocardiographic-gating, and segmented steady-state free precession (SSFP), delivering images with a high spatial and temporal resolution, which are far superior to other cardiac imaging modalities.

Left atrium Left atrium (LA) enlargement is the chronic expression of LV diastolic function. As DD progresses, LA filling pressure increases, affecting its reservoir, conduit, and pumping or contractile properties.

Atrial volume and function constitute reliable indicators of the duration and severity of DD independent of loading conditions and provide prognostic information.

There is a large amount of data supporting maximal LA volume use at LA end-diastole, but also minimal LA volume at end-systole has prognostic significance.[10]

Regarding LA volume estimation by echocardiography, it is performed in a 2-chamber and 4-chamber view and then indexed by body surface area. This variable, termed left atrium volume index (LAVI), is presented as the standard. However, this method is known to underestimate LA volume, and also its normal limit that started at 28 mL/m^2 and is now on 34 mL/m^2 may be still a moving target.[10]

CMR evaluation of LA volume is the gold standard (**Fig. 1**). This calculation is performed in a short-axis stack of the whole LA (see **Fig. 1**B), contouring the end-diastolic area of the LA for each slice. As slice thickness and gap are known, an accurate anatomic 3-dimensional (3D) model of the LA can be constructed (see **Fig. 1**C). The pitfalls of this approach are it is time consuming, and cumbersome. A more practical but less academic approach calculates the LAVI using a biplane (see **Fig. 1**A) or triplane view, which yields significantly higher values than echocardiography.

In addition, CMR enables advanced mechanical assessment of the LA, using feature tracking to measure LA strain and strain rate, variables that are impaired in HFpEF and associated with exercise intolerance,[11] whereas on the other end, endurance athletes' evidence increased LA contractile function evaluated by strain,[12] highlighting the central role of LA function besides its size.

LA enlargement in HFpEF is the hallmark of the disease. It should be proportionate to the rest of the cardiac anatomic and functional findings. For example, mild LVH generally goes with type I DD and with mild or moderate LA enlargement. If severe LA enlargement is identified in this setting,

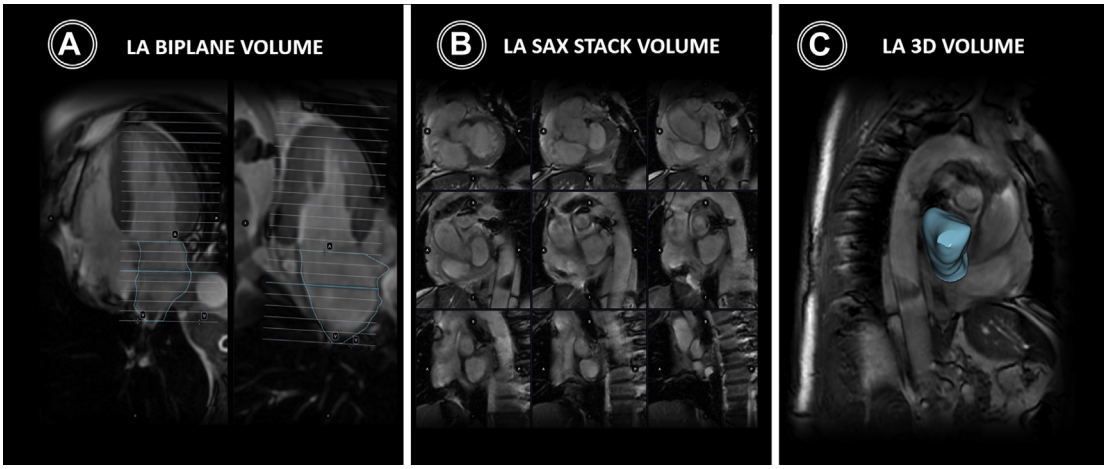

Fig. 1. Quantification of left atrial volume using CMR. (*A*) The biplane method measures the LA area in 4-chamber and 2-chamber view and integrates a volume by using a disk or mesh method. (*B*) Standard procedure for LAV assessment in CMR. The LA area is traced at each slice of a short-axis stack covering it entirely. (*C*) LA 3D volume. Because slice thickness and gap are known, an accurate 3D model is constructed using panel B information.

other causes of LA dilatation should be considered (atrial fibrillation or mitral valve disease). Conversely, it is not advisable to pursue an HFpEF diagnosis in the presence of confirmed normal size LA, suggesting other causes of dyspnea, such as pulmonary disease, be addressed (Table 1).

Right ventricle RV function is a crucial prognostic element in HF and relevant to assess in the presence of advanced DD causing PH.

The RV is a crescent-shaped structure with 3 distinct sections, an inlet, a trabeculated apex, and an outlet. Because of this particular shape, LV evaluation parameters, such as Simpson's biplane, are not applicable.

Echocardiography has traditionally settled for surrogate markers of right ventricular ejection fraction (RVEF), such as markers of regional and longitudinal function. These markers are measure at the lateral tricuspid annulus, and consist on the tricuspid annular plane systolic excursion (TAPSE) and the systolic annular velocity using tissue Doppler index (TDI).

Serious limitations of these local parameters are as follows: being dependent on volume changes and pericardial integrity and reflecting a small portion of the RV function. Other so-called global indexes, such as fractional area change and myocardial performance index by TDI, are also discrete surrogates for RVEF.

CMR is the only technique that can directly and confidently estimate RVEF without surrogate markers or geometric assumptions. Furthermore, CMR can also evaluate DD using the RV filling curve and flow parameters and perform strain analysis.

Table 1
Differentials of heart failure with preserved ejection fraction (mimics of heart failure with preserved ejection fraction)

Group	Etiology	Tests
Respiratory	Pulmonary hypertension primary or secondary (obstructive sleep apnea, chronic obstructive pulmonary disease)	Pulmonary function test, 6-min walking test, high-resolution computed tomography, overnight respiratory polygraphy
Extracardiac volume overload	Liver and kidney disease, nephrotic syndrome	Liver and kidney ultrasound and MRI, liver fibroscan
High-output state	Anemia, hyperthyroidism, extracardiac shunts	Laboratory test, echocardiography bubble test with late acquisition
Others	Obesity, physical deconditioning, venous insufficiency	6-min walking test, treadmill, Lower extremity Doppler ultrasound

Diastolic function, filling pressures, and pulmonary hypertension

Diastolic function is a complex process that requires the orchestrated contribution of ventricular relaxation and suction in the early phase and a brisk atrial contraction and filling in the later stage. Noninvasive evaluation of diastolic function is performed by echocardiography using a series of different parameters, mainly pulsed-wave Doppler measurements that assess the filling of the LA and LV, and tissue Doppler that interrogates myocardial velocities.

DD initiates classically as an LV relaxation impairment condition associated with normal filling pressures, DD progress elevating LV and LA filling pressures, and finally, severely compromising left atrial function and its contribution to LV filling.

Echocardiography evaluation of DD specifically uses Doppler to evaluate transmitral inflow, pulmonary veins flow, and mitral annular velocities (E′), among other more complex indexes. The main caveat of echocardiographic DD evaluation is that it uses elements that occur late in diastole, such as parameters of LV filling or atrial contraction, therefore, not accounting for the isovolumetric LV relaxation occurring in early diastole, which is one of the earliest and essential determinants of diastolic function.

Adding more complexity, flow-derived variables, such as mitral inflow, are subject to a phenomenon known as "pseudonormalization," which generates a normal aspect of the mitral inflow pattern with increasing LA pressure.

Finally, the mitral inflow pattern is more reliable in the presence of reduced LVEF and should not be interpreted solely in preserved LVEF.[6]

Diastolic function assessed by cardiac magnetic resonance CMR using flow sequences accurately provides flow information averaged over numerous cardiac cycles, delivering curves that resemble Doppler echocardiography. Moreover, CMR can also measure mitral annular velocities (e') using low-speed phase-contrast sequences, but it is far more practical to rely on echocardiography in this arena.

An interesting approach to assess LV function via CMR is calculating volume-time curves (**Fig. 2**), which is done by tracing LV volume in the short axis (see **Fig. 2**A), ideally with full heart coverage (see **Fig. 2**C, D). For each slice, contours are traced throughout the cardiac cycle (typically, 1 RR interval includes 30 frames per slice). This LV volume-time curve (see **Fig. 2**E) allows calculating a myriad of parameters representing systolic and diastolic function, such as systolic indexes: peak ejection rate (PER), peak ejection time, and diastolic indexes: peak filling rate (PFR), peak filling time (PFT). Both PER and PFR can be normalized to end-diastolic volume (EDV), giving 2 other derived indexes PER/EDV and PFR/EDV, that can also be calculated for the RV (see **Fig. 2**F).

The classic drawback with this approach is that it requires manual tracing of a massive set of images that could easily exceed 500 images for both ventricles.

To overcome this challenge, state-of-the-art dedicated CMR software that incorporates artificial intelligence can deliver fully automatic whole-heart biventricular contour tracing throughout the cardiac cycle, thus rendering this method attractive (see **Fig. 2**).

Moreover, dedicated advanced cardiac software that processes a whole-heart 4D flow can semiautomatically track the 4 cardiac valves, thus performing a comprehensive quantitation of intracardiac flow, providing automatically classical indexes of diastolic function for both atrioventricular valves, such as E- and A-wave velocity, E/A ratio, e' velocity, and E/e' ratio (**Fig. 3**); however, this module is currently for research only.

Filling pressures LV filling pressure is assessed based on the early mitral inflow wave (E) in relation to the mitral annulus early velocity (e') at the lateral and septal locations. The general concept is that myocardial disease reduces e' velocities, and a stiff LV has diminished early filling time, augmenting the E velocity because the same amount of volume has less time to transit from the LA to the LV. These changes increase the E/e' ratio; in echocardiography, an average of the septal and lateral E/e' over 14 reflects LV augmented filling pressures.

Other useful elements indicating augmented LV and LA filling pressures that CMR identify include the following:

- High-velocity flow during diastasis (termed L wave), which reflects elevated LA pressure forcing flow to enter the LV in middiastole
- Pulmonary vein flow pattern with a marked diastolic predominance and an augmented atrial reversal wave, denoting a vigorous LA contraction to overcome increased LV pressure
- Mitral regurgitation with a diastolic component (in the absence of electric conduction abnormalities), evidencing elevated LV pressure at end-diastole, that overcomes LA pressure, producing premature mitral regurgitation

Pulmonary hypertension Regarding PH, besides calculating pulmonary arterial pressures (PAP), imaging techniques should address its source as

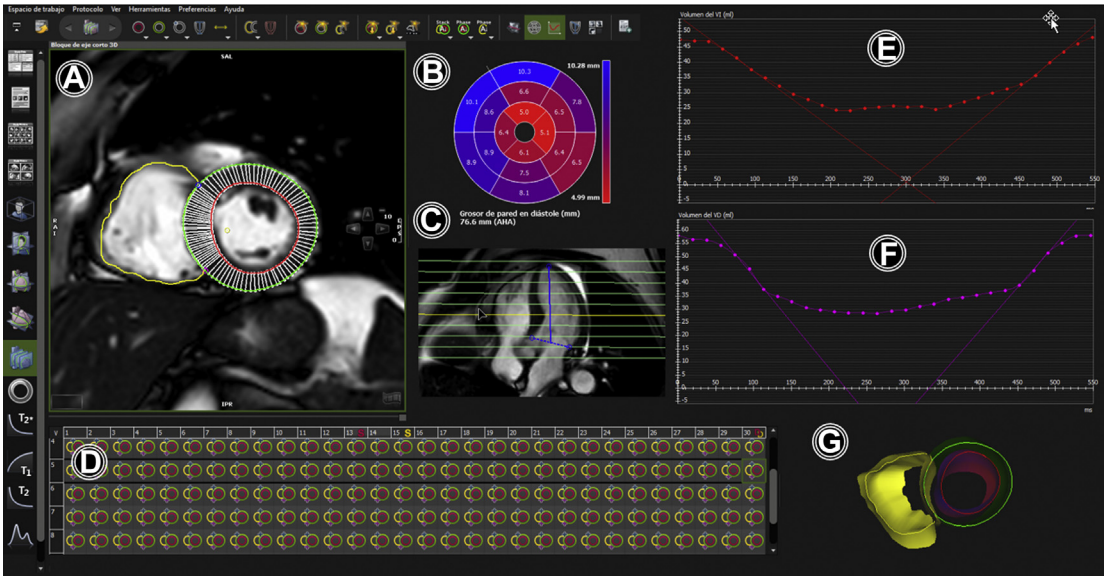

Fig. 2. Ventricular volume-time curves. Volume-time curves are obtained by analyzing a short-axis stack of images with complete coverage of both ventricles. (*C*) A 4-chamber view of the heart that demonstrates full coverage of the short-axis stack containing 10 slices. (*A*) One slice of this stack (slice 5/10) located at the midlevel of the ventricles. In this slice, endocardial contours for the right and left ventricle are traced, repeating this procedure throughout the entire cardiac cycle (typically involving 30 frames inside 1 RR interval) (*D*). This manual process is incredibly enhanced by CMR dedicated software with artificial intelligence border detection. This software accurately and rapidly (in <10 seconds) traces more than 800 images, including contours of the LV endocardium and epicardium and the RV endocardium, a process that would be manually unbearable. With this information, volume-time curves are constructed for the LV (*E*) and the RV (*F*), providing systolic and diastolic indexes of cardiac function, such as systolic PER, systolic PFT, diastolic PFR, and diastolic PFT. Of note, PER and PFR need to be indexed by EDV. Also, this software performs automatic thickness measurement of each LV myocardial segment (*B*) and provides a live 3D model of the whole heart over the entire cardiac cycle (*G*).

cardiac or extracardiac. In the former, echocardiography using Doppler is far superior to CMR in estimating PAP because CMR estimation of PAP uses cumbersome indirect formulas applied to pulmonary flow. What CMR can offer in this area is a better anatomic and functional evaluation of the pulmonary vasculature, including advanced flow dynamics (vortexes, energy loss, branches flow asymmetry, among others) and assessment of extracardiac causes of PH, such as shunts and pulmonary and vascular diseases.

Likely cause of ventricular thickening and heart failure

In the presence of LVH, the imaging goal is to pinpoint its cause at an early stage. An ideal imaging technique should distinguish between adaptation or load-related LVH, such as in hypertensive cardiomyopathy, aortic stenosis, and athletes' hearts, versus a pathologic LV thickening not associated with loading conditions, for example, infiltrative cardiomyopathy or HCM.

Echocardiography provides clues regarding LVH patterns and some red flags (**Table 2**), suggesting pathologic LVH. Unfortunately, most of these red-flag features are only evident at later stages of the disease. Thus, echocardiography cannot confidently distinguish between the mentioned scenarios.

Conversely, because of its tissue characterization capabilities, CMR can identify distinct LV wall-thickening phenotypes and depict myocardial fibrosis and other features, such as lipid and iron deposition, providing unmatched diagnostic precision.

Table 3 summarizes the imaging objectives in HFpEF and compares the performance of echocardiography versus CMR.

Associated alterations and findings

CMR can provide clues of extracardiac findings that can be a valuable piece in solving the diagnostic puzzle. For example, CMR can accurately quantify hepatic iron overload and confirm the diagnosis of iron overload cardiomyopathy. In amyloidosis, besides LVH (**Fig. 4**A) associated with myocardial T1 and ECV elevation (**Fig. 4**B), marked renal T1 and ECV elevation (**Fig. 4**C) could link renal failure and HF together, whereas mediastinal pathologic lymph nodes or axillary lymph

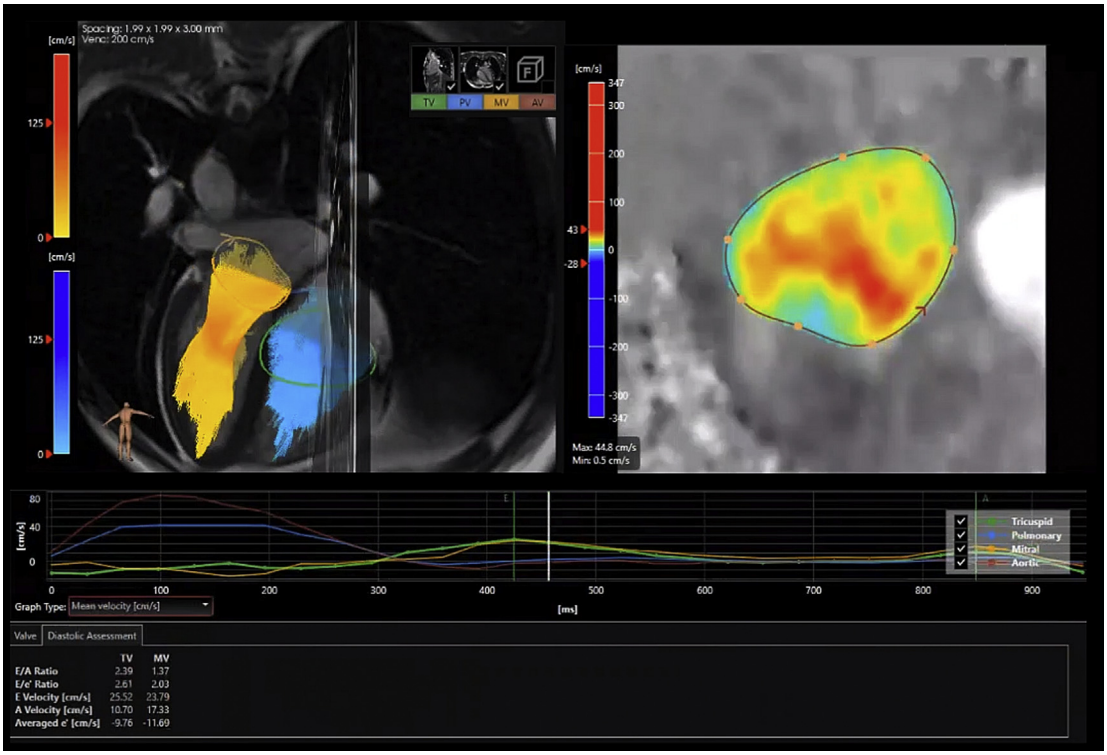

Fig. 3. Comprehensive automatic biventricular diastolic assessment by 4D flow CMR. 4D flow analysis depicting biventricular inflow; flow patterns are analyzed in the 4 cardiac valves with the aid of valve tracking, obtaining accurate biventricular time-volume curves, filling velocities early (E), and late (A) for mitral and tricuspid inflow along with annular velocities (e'). Also, E/A and E/e' ratios are given, delivering an automatic integral evaluation of diastolic function.

nodes, especially when more than 3 cm, may suggest sarcoidosis.

Other useful extracardiac findings are signs of chronic liver and kidney disease that can produce volume overload and thus mimic or contribute to the HFpEF pathophysiology.

Cardiac Magnetic Resonance Evaluation in Heart Failure with Preserved Ejection Fraction

Gross basic concepts

MRI uses the potential body magnetism related to the hydrogen molecule abundant in the human body. To do so, the patient is position inside a powerful static magnetic field (MF), generally with a strength of 1.5 or 3.0 T, which corresponds to nearly 30,000 times the earth's MF. This basal MF (M_z) aligns hydrogen atoms that start swirling around the main axis, phenomena termed precession, and the cornerstone of CMR, which is very similar to a spin rotating. This basal and resting magnetization needs to be manipulated in order to be measured. Manipulation of hydrogen molecules or spins uses intermittent radiofrequency pulses (RF) that are rapidly switched on and off in sequence (producing a periodic loud and awkward sound). Every time the RF pulse is turned off, spins return to their basal precession condition, exhibiting 2 main components, namely the longitudinal relaxation (T1) and the transverse relaxation (T2), each of these components is measured at a specific time-point, giving the known T1 and T2 relaxation times in milliseconds.

T1 and T2 times are unique for each tissue and depend on the size of the molecule and its relation to surrounding structures (lattice).

CMR uses 2 basic types of sequences, spin echo sequences that provide morphologic and anatomic assessment, and gradient echo sequences that give functional information. GAD-based contrast agents allow scar or fibrosis detection and are also used for myocardial perfusion.

CMR is a method with high reproducibility and good spatial and temporal resolution, and because of its nonionizing nature, it is incredibly safe and green.

On the downside, CMR requires expertise in scanning and reporting and presents patient limitations, such as claustrophobia, poor breath holders, irregular heart rhythm, tachycardia, glomerular

Table 2
Red flags for specific cardiomyopathies

	Feature
Clinical	• Young age at presentation • Extracardiac clinical findings, such as speech or intellectual impairment, muscle weakness • Visual impairment (retinitis pigmentosa) • Evidence of multisystemic affection
Auxiliary examinations and laboratory tests	• ECG with short PR or Wolff • High liver enzymes • High skeletal muscle creatine kinase owing to myopathy
Echocardiography	• Atrial septal thickening • Diffuse valvular thickening • Presence of thrombus without wall motion alteration • Marked reduction of longitudinal function with apparent preserved LVEF • Pericardial effusion • Advanced systolic or diastolic dysfunction at young age

Table 3
Imaging objectives in HFpEF and comparison of the performance of echocardiography versus CMR

Variable	CMR	Echo
Cause of HF	+++	–
LV volume and function	+++	++
RV volume and function	+++	+
Valvular alterations	+++	++
Estimating filling pressures	+	++
Grading DD	+	++
Pulmonary hypertension	+	++
Extracardiac findings	++	–

(+++), optimal; (++), adequate; (+), discrete; (–), insufficient.

filtration rate less than 30 mL/min, which precludes GAD administration and the presence of incompatible implanted metal objects (brain clips, cochlear implants, external bone tutors).

Cardiac magnetic resonance basic protocol for heart failure with preserved ejection fraction

A basic CMR protocol is detailed in **Table 4** and includes anatomic, functional, and tissue characterization information; this protocol can be accomplished in 45 minutes of magnet.

Specific sequences and uses

Flow patterns by cardiac magnetic resonance

CMR evaluates flow using 2 distinct sequences: the traditional one is called phase contrast, consisting of a 2D flow acquisition at a specific point, with the inherent anatomic and plane orientation limitations. The second alternative is an advanced sequence called 4D flow, which constructs a volumetric image with 3D flow information attached. Both sequences need an input of maximum velocity to analyze (called velocity encoding or VENC), which behaves exactly as the Nyquist limit in echocardiography. Notably, the well-validated Doppler velocity criteria for grading DD should not be used in CMR, as these velocities are underestimated by phase-contrast CMR.[13] Nevertheless, flow curve morphology, flow direction, and velocities ratios (such as E/A ratio) are reliable and validated and in line with echocardiography flow patterns.[13]

For example, a mitral inflow pattern with an early velocity (E wave) less than three-quarters of the atrial filling (A wave) is consistent with a typical Doppler pattern of impaired relaxation (type I) and thus concordant with normal filling pressures. Opposite to this, a triphasic mitral inflow pattern with a high-velocity middiastolic (diastasis) filling flow, termed L wave, is diagnostic of elevated LV and LA - filling pressures

Regarding RV DD, the tricuspid filling is highly variable depending on the respiratory cycle and the loading conditions. Hence, tricuspid inflow pattern is not as reliable as mitral inflow for evaluating DD. So other elements must be used to assess RV DD, such as antegrade pulmonary arterial flow in late diastole throughout the respiratory cycle and an increase in atrial reversal at the superior vena cava. Elements that are superiorly appraised by 4D flow CMR, enabling infinite flow measurements in any plane or orientation, providing comprehensive simultaneous flow and functional analysis.

Respective to CMR flow information, it is displayed as flow over time in milliliters per second; but, maximum and mean velocities and gradients can also be displayed.

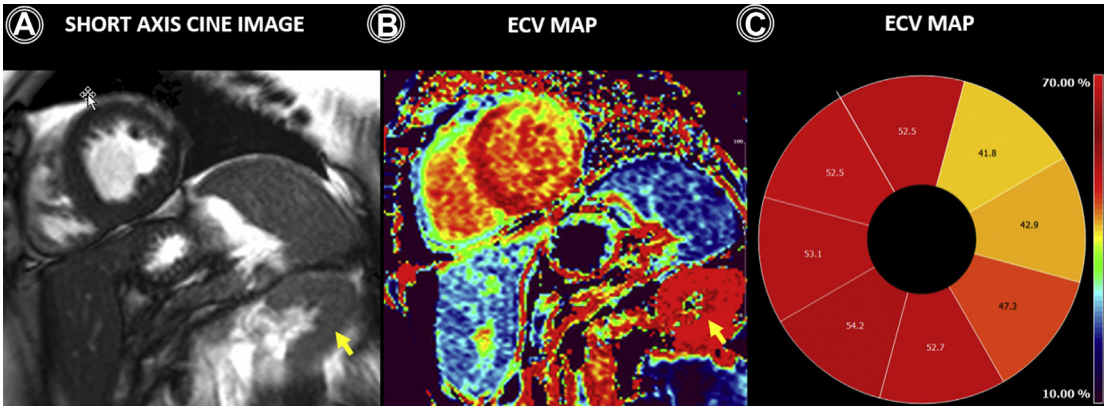

Fig. 4. Extracardiac findings in HFpEF. Extracardiac finding linking renal and cardiac failure. (*A*) A short axis of the heart showing moderate LVH. (*B*) The ECV map depicting extremely high EVC values in the LV septum and inferior walls and the left kidney (*arrow*). (*C*) The numerical value of the ECV in a bull's-eye plot. The final diagnosis was cardiac and renal amyloidosis.

Figs. 5 and 6 portray LV and RV diastolic restrictive physiology analyzed using 4D flow.

Tissue characterization and fibrosis assessment

Although different pathophysiological mechanisms are involved in HFpEF, including myocyte, interstitium, microvascular, and metabolic causes, it remains unclear whether HFpEF is a separate clinical entity, a result, or a part of a clinical syndrome. Adding more complexity is the fact that various pathologic conditions accompany HFpEF.[8] The most crucial benefit of CMR is

Table 4
Standard cardiac magnetic resonance imaging protocol in heart failure with preserved ejection fraction

CMR Sequence	Objective
1. Localizers	Study planning
2. Bright blood and black blood anatomic axial stacks	Thoracic anatomic evaluation
3. Fast-speed, low-quality SFFP CINE pilots	Study planning
4. Long-axis SSFP CINE (4C, 2C, 3C)	Visual assessment of size and function and longitudinal strain analysis
5. T1 map native	Interstitial fibrosis evaluation
6. T2 map	Edema evaluation
Contrast Administration	
7. First-pass perfusion imaging	Resting perfusion defect
8. Short-axis CINE stack	Measurement of ventricular wall thickness, function, volumes, and mass. Radial and circumferential strain
9. Phase contrast pulmonary vein flow	Grading of diastolic function and estimated filling pressures
10. Phase contrast mitral inflow (ideally analysis performed with valve tracking)	Grading of diastolic function and estimate filling pressures
11. Other flow sequences according to specific pathologic condition	Evaluation of valvular alterations
12. T1 map post-GAD	Estimation of extracellular volume
13. Late gadolinium enhancement (single shot and segmented in short and long axis)	Detection of replacement fibrosis
14. Whole-heart 4D flow optional (if 4DF is performed phase contrast sequences are skipped)	Comprehensive analysis of cardiac and vascular flow

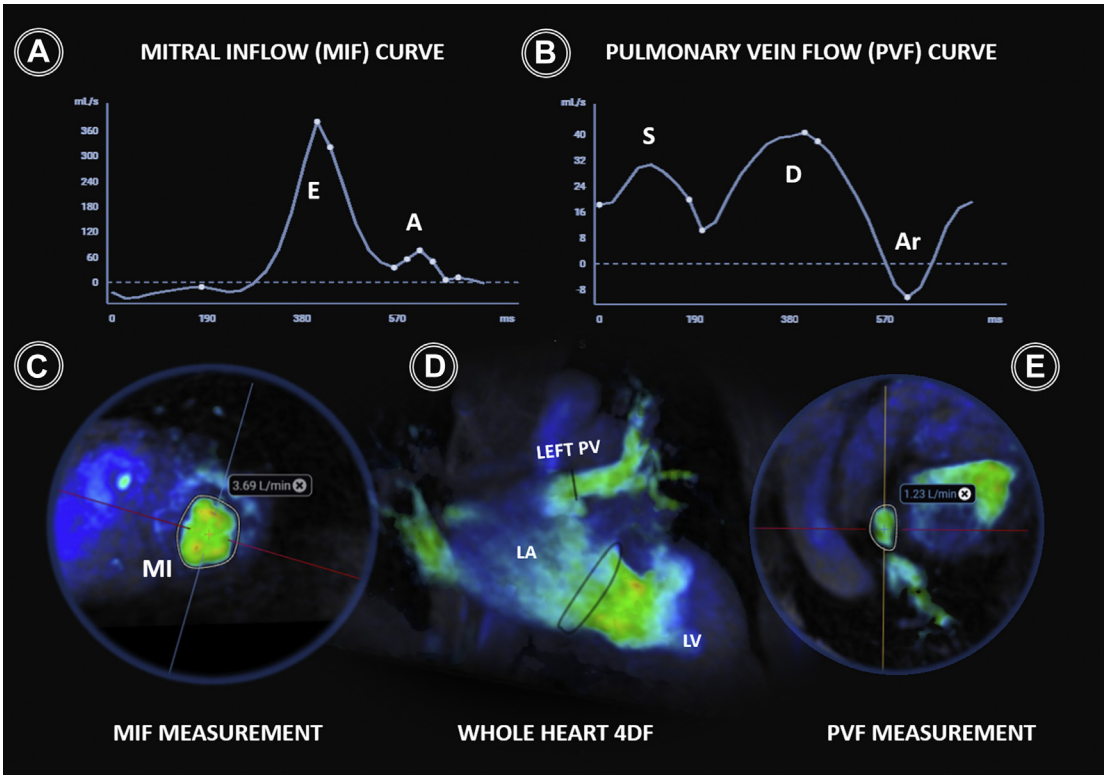

Fig. 5. LV restrictive filling by 4D flow. Severe LV DD is displayed using 4D flow CMR. (*A*) Mitral inflow with marked E-wave predominance over A wave. (*B*) Pulmonary venous flow with diastolic predominance and marked atrial reversal (Ar). (*C*) Mitral inflow measurement in multiplanar reconstruction (MPR). (*D*) The 4D flow volume center in the LV and LA. (*E*) Flow assessment of the left pulmonary trunk in MPR.

detecting the underlying pathologic condition of DD and revealing structural changes. Several diseases with similar clinical presentations may have the same clinical phenotype as the HFpEF condition, termed phenocopy, beclouding the diagnostic process.

GAD is a paramagnetic contrast agent that is rapidly washed out from normal myocardium. In the presence of replacement fibrosis, which corresponds to a scar with high collagen content, GAD is retained inside this scar, presenting a slow and late washout, reducing T1 relaxation time in this area and generating a bright or hyperintense signal in inversion recovery sequences. GAD distribution can be easily detected in the LV myocardium but is more challenging to see in thinner structures, such as the RV free wall or the atrias, where a 3D late gadolinium enhancement (LGE) high-resolution sequence is preferred.

Patterns of LGE can be separated into the following 2 groups (Fig. 7):

1. **Ischemic pattern** is the LGE pattern that follows anatomic coronary distribution, starting from the subendocardium and progressing in transmurality from endocardium to epicardium. LGE involving less than 50% of wall thickness is termed subendocardial and is deemed viable. Conversely, LGE comprising more than 50% of wall thickness is termed transmural and is reckoned not viable, meaning that those segments have a very low probability of recovering contractile function following revascularization. Sometimes small focal and subendocardial infarctions could be spotted in patients with HFpEF and are considered a "bystander" myocardial infarction not responsible for the clinical picture.
2. **Nonischemic pattern** is a group of distinct LGE patterns that include midwall, epicardial, and global endocardial (not corresponding to a coronary artery segmentation). In addition, its distribution could be patchy, focal, or diffuse. Specific pathologic conditions tend to affect the myocardium differently, thus presenting distinctive LGE patterns that are key to the differential. For example, amyloidosis can give a global endocardial or a patchy midmyocardial pattern; Anderson-Fabry disease generally presents basal inferolateral epicardial or mid-wall LGE.

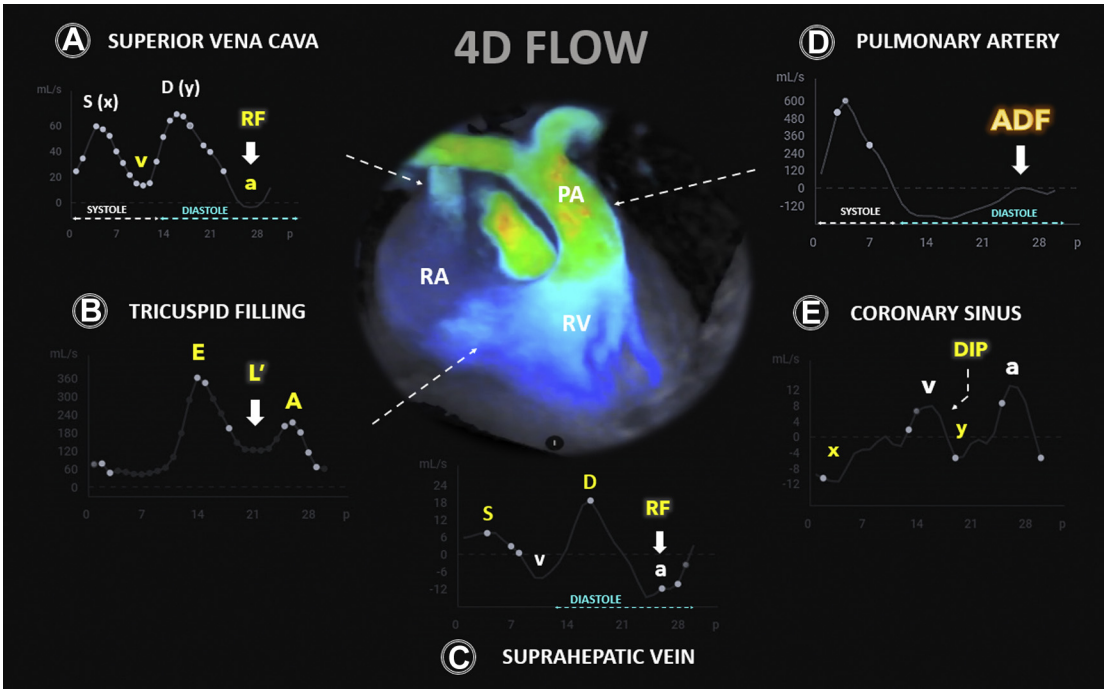

Fig. 6. RV restrictive filling. RV advanced DD, evaluated by a comprehensive set of parameters. Main findings. (*A*) superior vena cava with prominent reversal of flow (RF) corresponding to the "a" wave of the venous pulse. (*B*) Tricuspid inflow with E wave predominance and presence of an L wave, indicating flow from RA to RV during diastasis (hypertensive RA). (*C*) Flow in the suprahepatic vein displaying similar findings to SVC flow. (*D*) The hallmark of restrictive RV physiology evidencing anterograde diastolic flow (ADF) mainly at end-diastole, evidencing increased RV end-diastolic pressure generating premature pulmonary valve opening and ADF. (*E*) Flow in the coronary sinus depicting a DIP and steep curve corresponding to the "y" wave of the venous pulse.

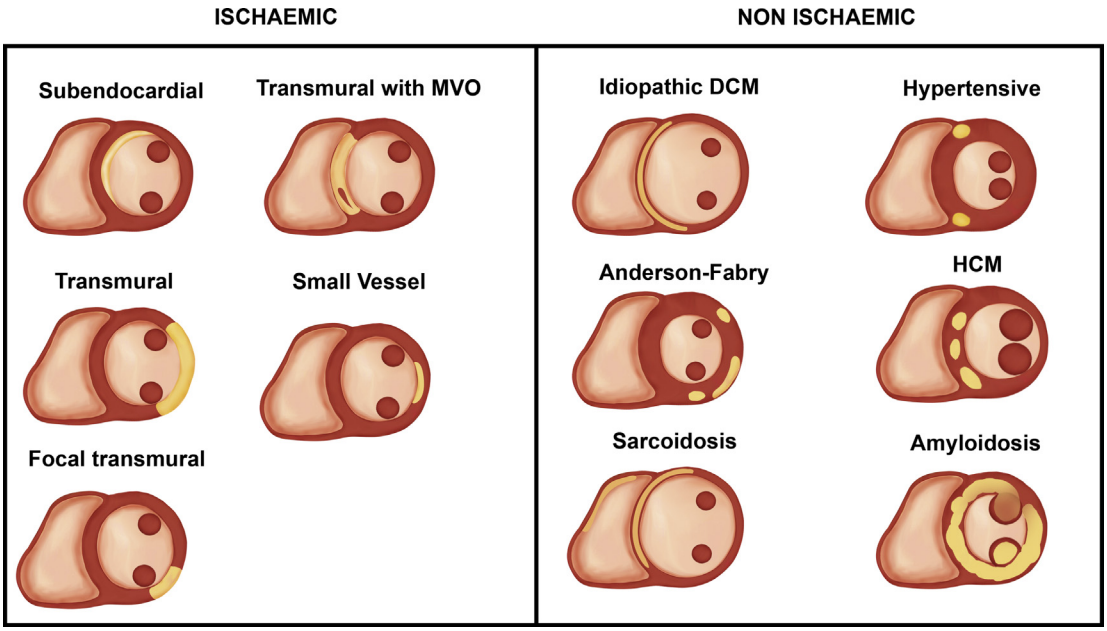

Fig. 7. LGE patterns. Representative LGE patterns in various conditions. In this scheme, 2 main groups are presented: ischemic LGE pattern and no ischemic LGE pattern. These LGE patterns are essential to the differential diagnosis process.

Unspecific patterns, another pattern frequently encountered but highly unspecific, is the affection of RV insertion points (inferior and superior) in the basal and midseptum, which is an expression of cardiac overload and is observed in various conditions, such as hypertensive cardiomyopathy, PH, HCM, and dilated cardiomyopathy.

Late gadolinium enhancement involvement in hypertensive cardiomyopathy Hypertensive cardiomyopathy or hypertensive heart disease (HHD) is among the most frequent conditions associated with HFpEF, so accurate imaging portrayal is crucial. HHD presents a broad spectrum of cardiac involvement ranging from mild LVH with normal systolic function, grade I DD (normal filling pressures), and mild LA enlargement. In this scenario, CMR reveals normal T1 and ECV and the absence of LGE.

In advanced stages, HHD can present moderate to severe LVH, advanced DD (grade II or III) with associated PH, and severe LA enlargement leading to atrial fibrillation. In this latter situation, CMR depicts elevated T1 and ECV and the presence of LGE that can range from the frequent focal involvement of both RV insertion points to the rare case of intense midwall LGE patches; Fig. 8 portrays evolving stages in HHD summarizing anatomic, functional, and tissue characteristics at each stage.

HCM can present with diverse LVH phenotypes (Fig. 9), which could be challenging to differentiate from HHD in the absence of LGE.

Some clues to differential are that HCM can present as follows:

- LVH generally follows a spiral anticlockwise pattern going from base to apex
- Mitral valve and papillary muscle abnormalities (elongated leaflets, accessory valvular tissue, anterior displacement, or apical insertion of papillary muscles)
- Typically has a type I transmitral inflow pattern
- Can present RV outflow tract obstruction
- Presence of myocardial crypts
- When LGE is present in half of the cases, it correlates with the thicker segments

As stated, LGE pattern is central to diagnosis, but the amount of LGE is crucial in terms of prognosis and to predict response to therapy. Because the presence of a higher percentage of LGE (ie, 15% in HCM) relates to worse outcomes in HF, worse DD, sudden cardiac death, and arrhythmias, furthermore higher LGE presence is related to fewer reverse remodeling following medical therapy.

Parametric mapping (T1, ECV, T2 and T2*), relies on each tissue inherent and unique magnetic relaxation properties, allowing CMR tissue characterization by measuring relaxation times (T1 and T2), also known as parametric mapping.

T1 mapping is acquired before contrast (native) and after contrast administration, to estimate ECV, which ideally needs a same-day hematocrit to subtract red blood cell volume. Elevated native T1 values reflect interstitial or microscopic fibrosis that is not visible by LGE. It is essential to mention that native T1 values must be measured in regions without LGE because the objective is to identify microscopic fibrosis. There is no practical point in measuring native T1 in LGE zones where the value is extremely high. Conversely, very low native T1 values suggest lipid infiltration, as seen in Anderson-Fabry disease, fatty metaplasia, or iron deposits.

T2 mapping allows the detection of water and edema, and T2* is used to detect iron overload mainly in the liver when iron deposit is suspected. Both of these sequences only need acquiring native maps (without use of GAD).

In addition, when GAD is contraindicated, a contrast-free CMR can still give tissue characterization by using native T1, T2, and T2*.

Cardiac mechanics (strain)

Strain imaging, which quantitatively assesses myocardial deformation in longitudinal, radial, and circumferential planes, is considered a less load-dependent index of systolic function than LVEF.[14] Strain is a robust deformation marker with a diagnostic and prognostic role for both global and regional LV function. The subendocardial layer of the myocardium is responsible for the long-axis function of the LV, so strain abnormalities may indicate early myocardial dysfunction in the setting of ischemic heart disease, which first affects the endocardium. Also, a reduced longitudinal strain despite an apparent preserved LVEF is predictive of worse outcomes in HFpEF.[15]

Myocardial strain and torsion can be acquired by CMR using dedicated sequences (FAST SENC, or DENSE) or the traditional SSFP CINES using feature tracking, similar to echocardiographic speckle tracking but yielding values not directly comparable. Nonetheless, CMR strain is not routinely performed.

Fig. 10 depicts an HHD with LVH associated with a septal bulge, peak systolic global longitudinal strain is preserved (see Fig. 10A, C), but is reduced in the basal anteroseptal segment (see Fig. 10B), segments that also have a slight elevation of native T1 (see Fig. 10D).

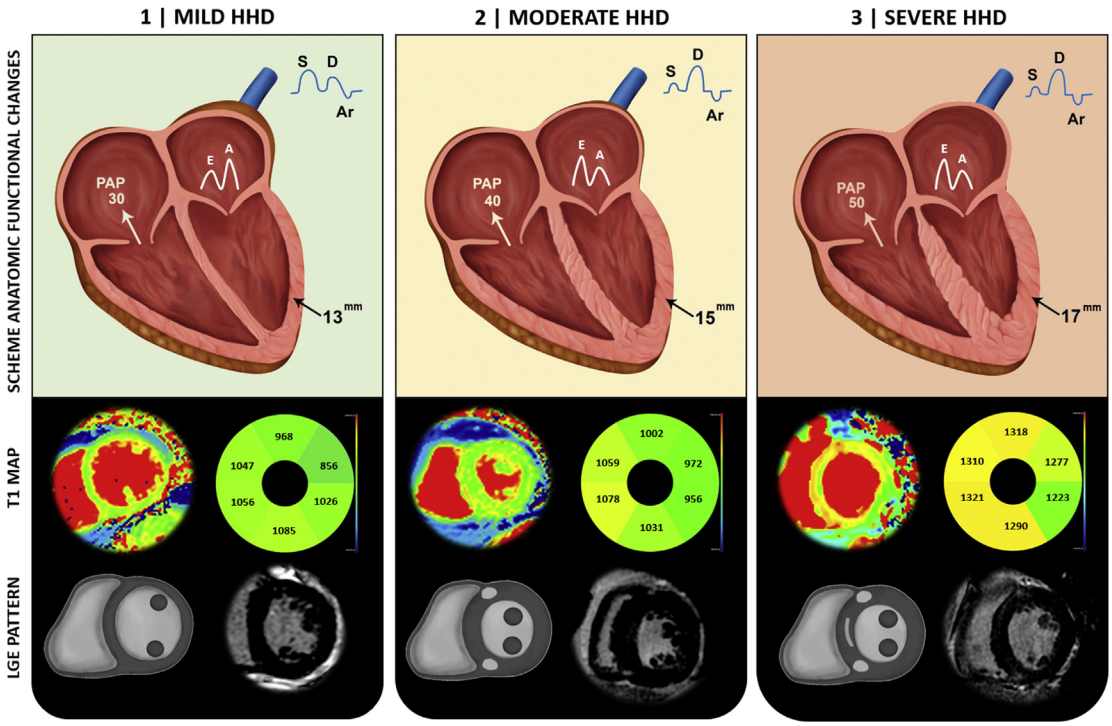

Fig. 8. Stages of HHD. Evolving stages of HHD. (1) Mild HHD, characterized by mild LVH and LAE, frequently presents with type I mitral filling pattern and normal pulmonary venous flow, concordant with normal filling pressures. In this scenario, CMR usually reports average T1 values and absence of LGE. (2) Moderate HHD, usually presents moderate LVH, more LA enlargement, and mitral inflow can be pseudonormalized. Pulmonary venous flow depicts diastolic predominance related to increased LA pressures retrogradely augmenting PAP. CMR, in this case, shows a slight elevation of T1 maps, especially in the thicker segments (septum) and LGE at a single or both insertion points. (3) Severe HHD. In this advanced and less frequent scenario, LVH and LAE are more severe; the mitral filling pattern is restrictive, and pulmonary venous flow shows a deep A-wave inversion. Elevated LV and LA filling pressures generate increasing PAP. CMR evidence of diffuse and higher native T1 elevation and LGE extends beyond insertion points into the LV septum.

Differential diagnosis

A first diagnostic step is to exclude conditions that can mimic HFpEF by causing dyspnea, exercise intolerance, and ankle edema, and are very prevalent, such as obesity, physical deconditioning, lung disease, and venous insufficiency.

A second differential objective should be to rule out specific cardiomyopathies that at early stages could be difficult to tell apart from a pure form of HFpEF. These cardiomyopathies include HCM, amyloidosis, and storage diseases, such as Anderson-Fabry, as previously commented.

Some extracardiac conditions that mimic HFpEF, such as high-output states caused by hyperthyroidism, anemia, extracardiac shunts, and arteriovenous (AV) fistulas, should also be considered.

Finally, any cause that generates extracardiac volume overload can mimic HFpEF, for example, chronic liver and kidney disease and nephrotic syndrome.

NOVEL METHODS AND FUTURE DIRECTIONS

Although increased myocardial stiffness plays an essential role in DD, there is no conventional imaging method to directly measure myocardial stiffness in vivo, as in the liver, where it is measured by transient elastography (Fibroscan). Fibroscan measures shear wave velocity, which corresponds to the sound wave velocity passing through tissues. The more fibrosis, the greater stiffness is present, which enhances sound-wave transmission reaching higher shear wave speed.

The same principle can be performed using 2D and 3D high-frequency magnetic resonance elastographies, which are novel techniques that generate a stiffness map using the same basics of shear wave velocity within tissues. Arani and colleagues[16] demonstrated the feasibility of 3D high-frequency CMR elastography as a contrast agent–free diagnostic imaging technique for quantitatively measuring myocardial stiffness in vivo.

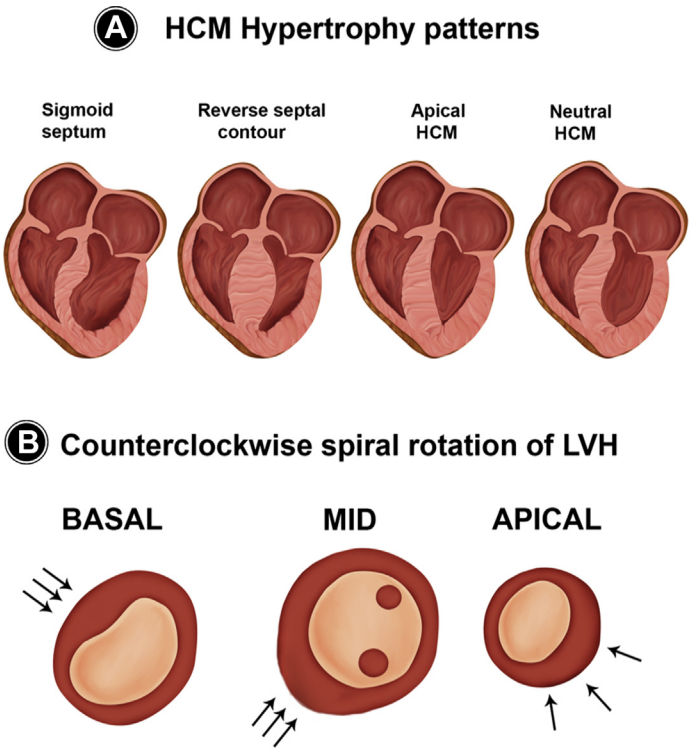

Fig. 9. LVH characteristic in HCM. LVH phenotypes and characteristics can aid in differentiating HCM from HHD. (*A*) LVH phenotypes in HCM. Neutral phenotype can be challenging to differentiate from HHD, especially when no LGE or T1 map alterations are present. (*B*) Counterclockwise spiral rotation of LVH in HCM. Starting from the base to apex, this clue suggests HCM assisting in discriminating between HCM and HHD.

Other feature is obesity, which is common in HFpEF and has numerous cardiovascular effects. Obokata and colleagues[17] showed that epicardial adipose tissue has a direct mechanical effect caused by increased pericardial restraint and enhanced ventricular interdependence. Also, a correlation exists between DD and increased epicardial adipose tissue, adding to its classic inflammatory role a potential pathophysiologic one in HFpEF.

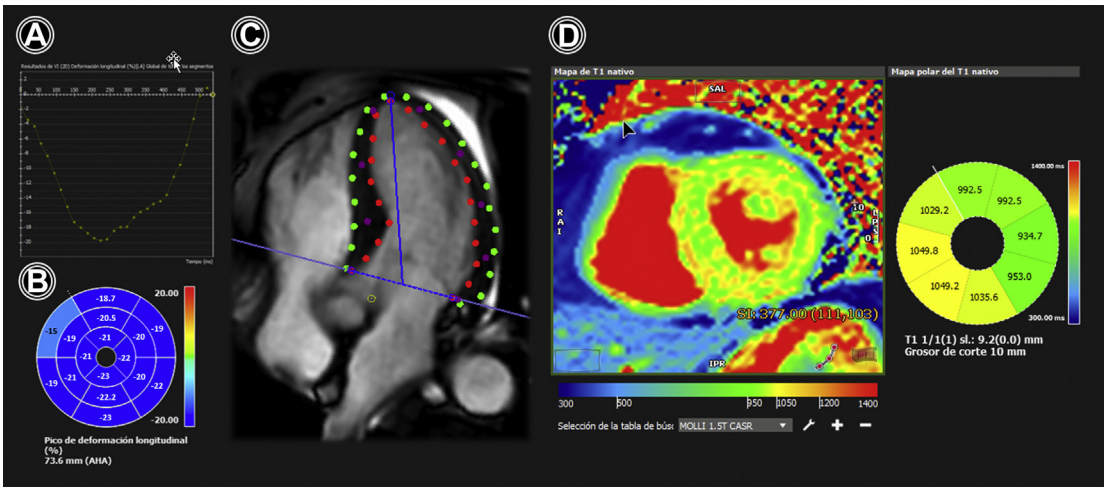

Fig. 10. Cardiac mechanics and tissue characterization in HHD. Global longitudinal strain in a patient with HHD. (*A*) Global strain curve with a preserved peak systolic value at 19.5%. (*B*) A bull's-eye representation of the AHA 17 segment model, evidencing a localized reduction of strain in the basal anteroseptal segment, which corresponds to the thicker segment (septal bulge). (*C*) The boundary points that are traced in the CINE images to estimate strain. (*D*) The native T1 map and its absolute values portraying a slight elevation of T1 values in the thicker segments (septum).

Finally, advanced cardiac flow parameters, such as energy loss index, shear stress, pressure drop, and vortex analysis, are promising elements that can be readily obtained with 4D flow sequences delivering next-level cardiac dynamics assessment.

Machine learning and artificial intelligence are gaining importance in the medical imaging field and are expected to transform clinical practice in the following years. CMR can use machine learning to help guide diagnosis and therapy management. Artificial intelligence is associated with radiomics, which is a novel image analysis technique. In which digital images are converted into numeric data that are analyzed to obtain several numerical quantifiers of shape and tissue characteristics. This radiomics process, when applied to large amounts of cardiac imaging data (as CMR studies store in Biobanks), can automatically identify pathologic clusters of disease that require further workup.[18]

SUMMARY

HFpEF is an etiologically, phenotypically, and clinically heterogeneous syndrome that poses a massive burden on health care systems worldwide. It diagnostic process is challenging; current consensus and guidelines denote the crucial role of cardiac imaging. CMR has emerged as a robust technique in patients with HFpEF, as it provides comprehensive information on most parameters recommended in guidelines. Moreover, CMR integrates anatomic, functional, and tissue characterization capabilities, thus enabling accurate distinction of different phenocopies from a pure form of HFpEF. Classic sequences outperform echocardiography in most aspects, and novel sequences with the aid of artificial intelligence could redefine the imaging boundaries in HFPEF.

CLINICS CARE POINTS

- Heart failure with preserved ejection fraction requires relevant structural heart disease to which the symptoms could be attributable.
- Echocardiography, because of its widespread access and well-validated features, is the first-line imaging technique in heart failure with preserved ejection fraction.
- The diagnostic process is challenging because of the absence of a single diagnostic marker, the complex echocardiography evaluation, and the broad spectrum of entities that cause heart failure with preserved ejection fraction.
- A robust and comprehensive imaging technique, such as cardiac magnetic resonance, is the ideal method to characterize this condition.
- The main advantage of cardiac magnetic resonance over echocardiography is the integration of anatomic, functional, and tissue characterization capabilities, offering unprecedented diagnostic precision.
- Late gadolinium enhancement is central in categorizing heart failure with preserved ejection fraction and has multiple roles, such as aiding diagnosis, by identifying typical late gadolinium enhancement patterns of distinct disease.
- Late gadolinium enhancement patterns are grossly divided into ischemic and nonischemic patterns.
- Total late gadolinium enhancement burden can be quantified, thus providing prognosis information and aiding in predicting response to therapy.
- Hypertensive heart disease presents a broad spectrum of cardiac involvement. Cardiac magnetic resonance findings range from normal T1, extracellular volume, and no late gadolinium enhancement presence, to markedly elevated T1 and extracellular volume and late gadolinium enhancement presence that can go from focal involvement of RV insertion points to intense midwall LGE patches, posing a tremendous diagnostic challenge in differentiating from hypertrophic cardiomyopathy.
- Cardiac magnetic resonance is key to differential diagnosis, separating causes that can mimic heart failure with preserved ejection fraction termed "phenocopies" to a more "pure" form of heart failure with preserved ejection fraction and also identifying extracardiac findings that can orient diagnosis.
- Finally, novel sequences that analyzed cardiac mechanics and advanced intracardiac flow features could reshape the understanding of heart failure with preserved ejection fraction.

DISCLOSURE

The authors have nothing to disclose.

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