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REVIEW

Cardiac magnetic resonance in heart failure with preserved ejection fraction: myocyte, interstitium, microvascular, and metabolic abnormalities

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Heart failure (HF) with preserved ejection fraction (HFpEF) is a chronic cardiac condition whose prevalence continues to rise, with high social and economic burden, but with no specific approved treatment. Patients diagnosed with HFpEF have a high prevalence of comorbidities and exhibit a high misdiagnosis rate. True HFpEF is likely to have multiple pathophysiological causes – with these causes being clinically ill-defined due to limitations of current measurement techniques. Myocyte, interstitium, microvascular, and metabolic abnormalities have been regarded as key components of the pathophysiology and potential therapeutic targets. Cardiac magnetic resonance (CMR) has the capability to look deeper with a number of tissue characterization techniques which are closer to the underlying specific abnormalities and which could be linked to personalized medicine for HFpEF. This review aims to discuss the potential role of CMR to better define HFpEF phenotypes and to infer measurable therapeutic targets.

Keywords Cardiac magnetic resonance • Heart failure with preserved ejection fraction

Introduction

Heart failure (HF) with preserved ejection fraction (HFpEF) is a chronic cardiac condition whose prevalence continues to rise.[1,2] Yet, no specific approved treatment exists for this disease, with disappointing clinical trial results to date.[3–7] Patients diagnosed with HFpEF have a high prevalence of comorbidities and exhibit a high misdiagnosis rate.[8] True HFpEF is likely to have multiple pathophysiological causes – with these causes being clinically ill-defined due to limitations of current measurement techniques.[9] Myocyte, interstitium, microvascular, and metabolic abnormalities[10–14] have been regarded as key components of the pathophysiology and potential therapeutic targets. Echocardiography is the most commonly used imaging modality for HFpEF, and provides important information regarding cardiac function (including diastolic) and structure.[15] Cardiac magnetic resonance (CMR),

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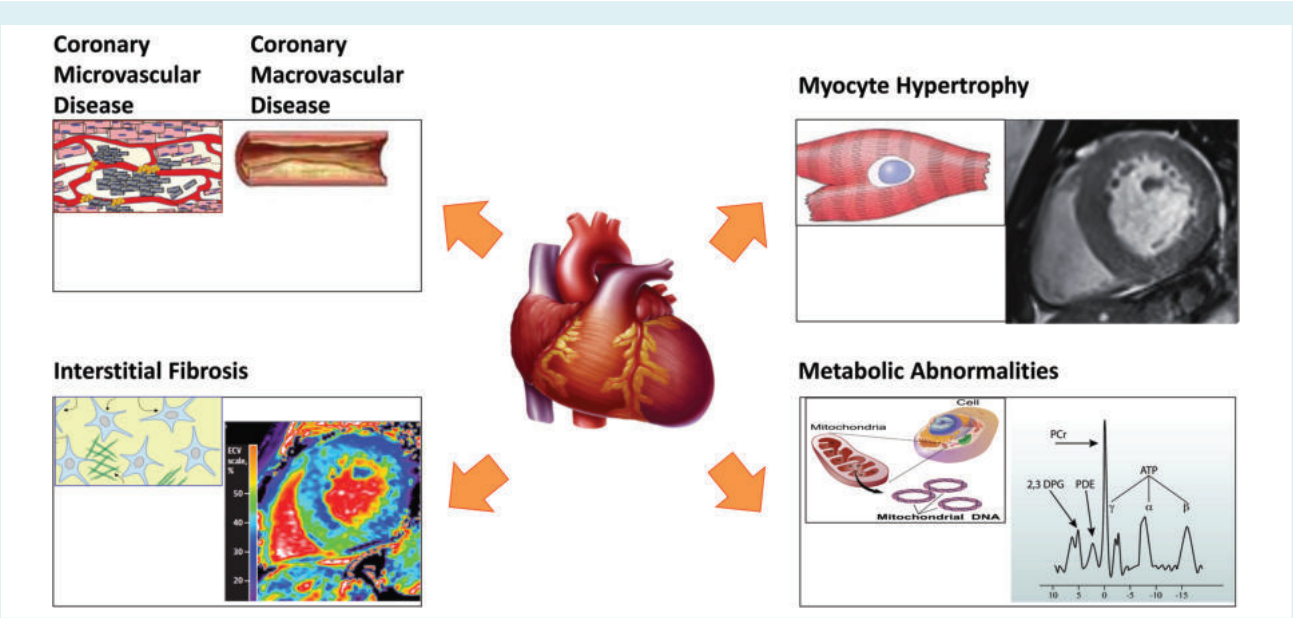

Figure 1 The complex pathophysiology of heart failure with preserved ejection fraction: coronary microvascular and macrovascular disease, interstitial fibrosis, myocyte hypertrophy and metabolic abnormalities. (*Lower left panel*) Extracellular volume (ECV) mapping of a patient with heart failure with preserved ejection fraction showing interstitial expansion from myocardial fibrosis and in the upper right panel the corresponding SSFP diastolic still frame (adapted with permission from Schelbert *et al.*[10]). (*Lower right panel*) ^{31}P-magnetic resonance spectroscopy of the human heart (adapted with permission from Bizino *et al.*[16]). ATP, adenosine triphosphate; DPG, diphosphoglycerate; PCr, phosphocreatine; PDE, phosphodiester.

although less widely available, has the capability for deep tissue characterization that may enable finer dissection of underlying pathophysiologic mechanisms in HFpEF (*Figures 1* and *2*).[10,16,17] This review aims to discuss the potential role of CMR to better define HFpEF phenotypes, specifically as it relates to key emerging target areas in HFpEF; namely the myocardium, interstitium and microvasculature.

Cardiac magnetic resonance: basic principles, advantages, and limitations

Cardiac magnetic resonance is an advanced imaging technique (*Tables 1* and *2*) that uses the intrinsic magnetic properties of tissue to obtain signals to form an image and measure tissue properties from the myocardium. CMR can assess morphology, function (global and regional of the left and right ventricles), flow, and perfusion and is able to depict the great vessels with high accuracy, good blood pool-myocardium contrast, and excellent spatial and temporal resolution. For structure and function, the better reproducibility translates into a smaller detectable difference in clinical care and the need for fewer patients in clinical trials of new therapies.[18]

Cardiac magnetic resonance can provide information on tissue characterization, for example evaluating the presence of oedema, fibrosis or fat infiltration, with and without use of intravenous contrast agents. It is window-independent, so that every imaging plane is available without interference from bones, fat or air, an advantage in patients with obesity or lung disease. CMR minimizes geometric assumptions when estimating volumes and it is less operator-dependent than other imaging techniques. Moreover, it does not use ionizing radiation, making repeated scans, if needed, safer. CMR gadolinium contrast-based agents are not nephrotoxic (although two conditions have been associated with old, linear contrast agents: firstly, a rare condition, called nephrogenic systemic fibrosis, in patients with severely reduced renal function, and secondly brain gadolinium retention of unknown significance with repeat dosing), and very rarely produce allergic reactions.

However, CMR has disadvantages. It is neither widely available nor portable. Additionally, patient cooperation is needed (i.e. breath-holds, lying flat, and not to be claustrophobic). The scanning environment is not ideal for the sickest, most unstable patients. Arrhythmias (irregular atrial fibrillation or frequent premature ectopic beats) can affect image quality. Ferromagnetic foreign bodies or magnetically-activated implants or devices are contraindicated, although technology is rapidly advancing, and nearly all pacemakers and implantable cardioverter-defibrillators can be scanned under appropriate protocols – with most new devices implanted are CMR conditional. Robust free breathing techniques are also emerging rapidly to characterize patients, even those with arrhythmia and inability to hold their breath. CMR requires an expertise in doing and interpreting the images, especially for advanced techniques characterizing the myocyte, interstitium, microvascular, and metabolic abnormalities.

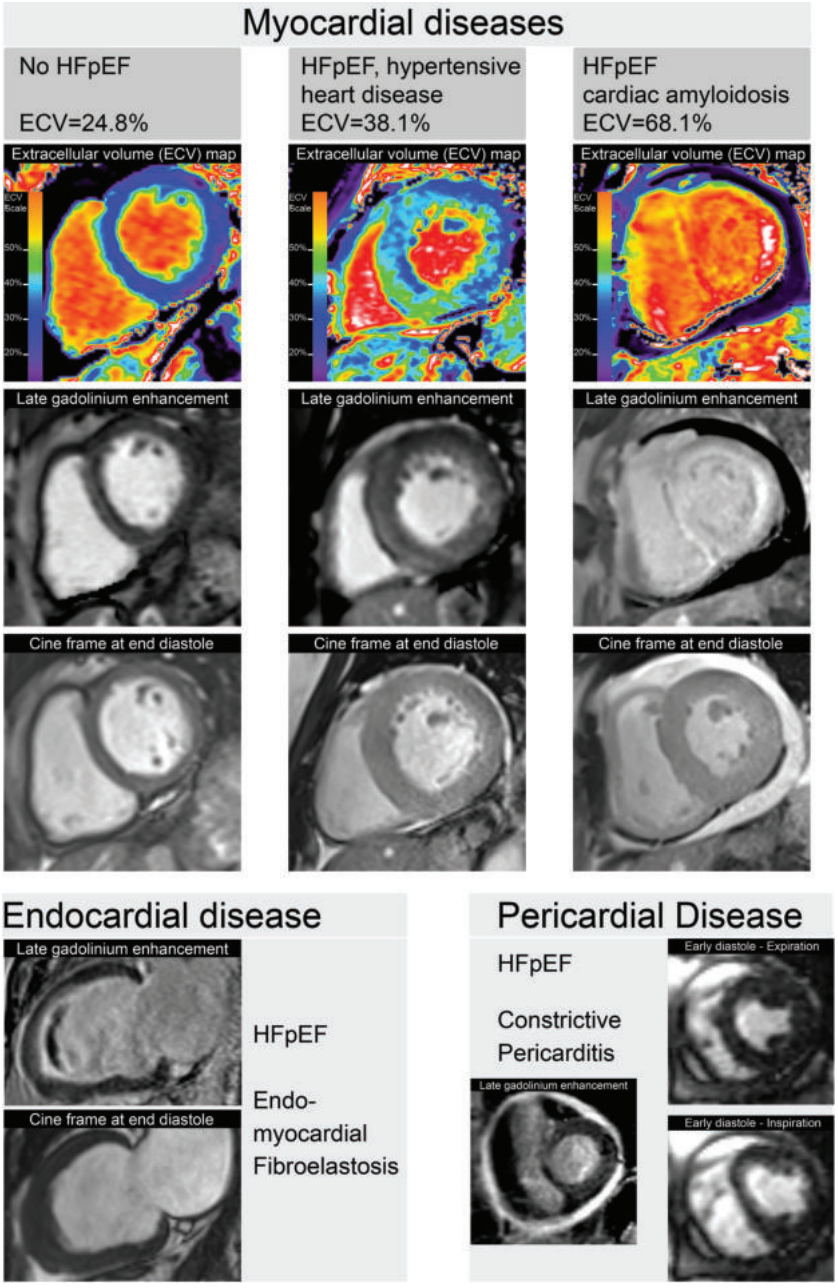

Figure 2 In heart failure with preserved ejection fraction (HFpEF), cardiac magnetic resonance may detect underlying myocardial disease, endocardial disease, or pericardial disease. For example, extracellular volume (ECV) maps quantify the interstitial expansion seen in diffuse myocardial fibrosis, which is usually less than the extreme interstitial expansion observed with cardiac amyloidosis (whether transthyretin-related or light chain). Furthermore, cardiac magnetic resonance with late gadolinium enhancement detects endocardial disease (e.g. endomyocardial fibroelastosis with associated mural thrombus) that may be mistaken for the apical variant of hypertrophic cardiomyopathy. Finally, cardiac magnetic resonance detects pericardial disease (e.g. constrictive pericarditis with marked pericardial thickening), culminating in constrictive physiology manifest by septal flattening with inspiration on real-time cine images.

Myocyte

Given its characteristics, CMR has become the gold standard for global and regional functional assessment.[18] More sophisticated and quantitative analysis of regional dysfunction can be achieved with tagging and strain techniques. While CMR can assess transmitral flow and pulmonary vein flows with phase-contrast imaging, pulsed-wave Doppler echocardiography remains the preferred non-invasive gold standard technique for cardiac haemodynamic assessment. The disadvantages of CMR compared to

Table 1 Advantages and disadvantages of cardiac magnetic resonance in assessing heart failure with preserved ejection fraction patients

	Advantages	Disadvantages
Myocyte		
LV/RV mass, volume, function	No geometric assumptions Less operator-dependent High reproducibility High spatial resolution LVH differential diagnosis	Time-consuming (semi-automated quantification) Low temporal resolution High costs Not portable Quality affected by arrhythmias Specific contraindications (non-MRI compatible device, claustrophobia, etc.)
Diastolic function (mitral-pulmonary flows)	Accurate flow alignment	Low temporal resolution Not performed in real time Time consuming Arrhythmias artefacts Phase-offset errors Systematic underestimation of E and A velocities Limited experience
LA size and function	Accurate LA volume estimation Assess LA function (LA strain and strain rate)	Few prospective studies Limited experience
Interstitium		
T1 mapping/ECV	Unique property of CMR for quantification of replacement and diffuse fibrosis Histologic validation LVH differential diagnosis Prognostic value	Scanner-dependent Non-standardized reference values Components other than fibrosis in the measurement of ECV (oedema, vessels, etc.)
Microvasculature		
Perfusion	High accuracy No radiation exposure	Dark rim artefacts Qualitative assessment Quantitative assessment little standardized and time consuming
Metabolism		
Magnetic resonance spectroscopy	Ability to study different metabolic pathways No radiation exposure Can be integrated with PET scanners	Highly performing scanners and specific software needed Expertise needed Limited experience

CMR, cardiac magnetic resonance; ECV, extracellular volume; LA, left atrial; LV, left ventricular; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; PET, positron emission tomography; RV, right ventricular.

echocardiography in this setting include lower temporal resolution of CMR (around 30–40 ms compared to <10 ms with echocardiography), it is time consuming, it is not performed in real time and can be affected by arrhythmias; in addition, CMR tends to systematically underestimate E and A velocities. Therefore, diastolic assessment by phase-contrast imaging of transmitral flow is currently limited. However, CMR has the potential to assess accurately left atrial (LA) and interstitial characteristics which are related to diastolic function, complementary to echocardiography. CMR was found able to diagnose new pathological conditions (including occlusive coronary artery disease, microvascular dysfunction, probable or definite hypertrophic cardiomyopathy and constrictive pericarditis) in 27% of HFpEF patients (who might have poor echocardiographic windows, given comorbidities such as obesity and chronic obstructive pulmonary disease) with prognostic implications.[19] Regardless, 'structural' metrics of cardiac disease [e.g. extracellular volume (ECV) fraction] appear to agree more with invasive gold standard measures of diastolic dysfunction (time constant of active relaxation, or tau) than non-invasive functional metrics.[11] Finally, myocardial left ventricular hypertrophy (LVH), which is a characteristic finding in HFpEF, can be easily detected by CMR. LVH occurs because of cellular hypertrophy and expansion of extracellular matrix (ECM). CMR using T1 mapping can split LVH into cellular and matrix components by measuring the ECV fraction. Cell and matrix expansion have disease-specific relationships[20]; for example, in athletes, LVH is mainly due to cellular hypertrophy, whereas in cardiac amyloidosis LVH is almost exclusively secondary to matrix expansion; therefore, CMR can add important information to the components of LVH and its pathophysiology. In addition, CMR is a key imaging modality for the differential diagnosis of LVH.[21,22] CMR can measure with high degree of accuracy LA dimensions and function, which are usually abnormal in HFpEF patients. Dimensional measurement is still common by echocardiography, but area, volumes and indexing are better with CMR,

Table 2 Importance of different imaging techniques in heart failure with preserved ejection fraction phenotyping

Aetiologies	Echocardiography findings	CMR findings
Ischaemic	RWMA (at rest or during stress echocardiography)	RWMA Subendocardial/transmural LGE in coronary territory distribution Perfusion defects (stress CMR) Circumferential subendocardial ischaemia (rest/stress CMR, microvascular disease)
Genetic	*HCM*: degree and distribution of hypertrophy (asymmetric septal, lateral, apical), RVH, anterior mitral valve leaflet elongation, SAM, LVOT obstruction (rest/dynamic) *Restrictive cardiomyopathy*: LV wall thickening (+/−), pericardial effusion, sparkling appearance. Restrictive filling pattern, increased E/E′, biatrial enlargement, RVH *Non-compaction cardiomyopathy*: increased ratio of non-compacted to compacted myocardium with reduced thickness of the compacted layer	*HCM*: degree and distribution of hypertrophy (asymmetric septal, lateral, apical), RVH, anterior mitral valve leaflet elongation, papillary muscle hypertrophy, SAM, LVOT obstruction (rest) Typical patchy LGE pattern Perfusion abnormalities *Restrictive cardiomyopathy*: LV wall thickening (+/−), pericardial effusion, biatrial enlargement, RVH, non-ischaemic LGE. Differential diagnosis with constrictive pericarditis. *Anderson–Fabry disease*: reduced T1. Typical LGE pattern (subepicardial basal LV infero-lateral wall), RVH *Non-compaction cardiomyopathy*: increased ratio of non-compacted to compacted myocardium with reduced thickness of the compacted layer, non-ischaemic LGE
Infiltrative	*Amyloidosis*: increased LV/RV wall thickening, pericardial effusion, granular sparkling appearance. Restrictive pattern *Hypereosinophilic syndrome*: increased LV/RV wall thickening. Thrombus detection, restrictive filling pattern, biatrial enlargement, valvular disease *Haemochromatosis*: increased left wall thickening (+/−)	*Amyloidosis*: increased LV/RV wall thickening, pericardial/pleural effusion. Abnormal contrast agent kinetics. Typical LGE pattern, diffuse or subendocardial LGE (LV/RV). Increased T1 and ECV *Hypereosinophilic syndrome*: typical LV/RV subendocardial LGE. Thrombus detection, biatrial enlargement, valvular disease *Haemochromatosis*: increased left wall thickening (+/−) Shortened T2* (correlates with iron cardiac loading), reduced T1
Inflammation	*Myocarditis*: increased wall thickening (+/−), RWMA *Sarcoidosis*: aneurysm formation, regional wall thickening (or wall thinning due to fibrosis), RWMA	*Myocarditis*: Increased wall thickening (+/−), RWMA Typical LGE patterns (mid-wall subepicardial, especially in the basal infero-lateral wall) and myocardial oedema. Myocardial early gadolinium enhancement. It may be associated with pericarditis (pericardial thickening, oedema, LGE, effusion) Increased T1, T2 and ECV *Sarcoidosis*: aneurysm formation, regional wall thickening (or wall thinning due to fibrosis), RWMA. Typical LGE pattern (extensive, patchy, subepicardial), thoracic lymphadenopathy, lung abnormalities

CMR, cardiac magnetic resonance; ECV, extracellular volume; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricular; LVOT, left ventricular outflow tract; RV, right ventricular; RVH, right ventricular hypertrophy; RWMA, regional wall motion abnormalities; SAM, systolic anterior motion.

avoiding issues such as foreshortening on views typically designed and tailored to the ventricle.[23] Using CMR feature tracking technique, LA strain and strain rate can be calculated: these markers of LA dysfunction have been found to be impaired and associated with exercise intolerance in HFpEF patients,[24] although the use of these techniques is not yet widely available in clinical settings.

Cardiac magnetic resonance is the gold standard for evaluating right ventricular (RV) size and function, and RV abnormalities by CMR were found to be independently associated with outcome and clinical status in HFpEF.[2–26] A significant correlation was also demonstrated between the pulmonary artery to aorta ratio assessed by CMR and mean pulmonary artery pressure measured by right heart catheterization and outcome (i.e. hospitalization for heart failure or cardiac mortality) in HFpEF.[27]

Interstitium

Historically, it has been difficult to image and measure cardiac ECM expansion *in vivo* and therefore it has been challenging to translate research in this field into clinical practice. ECM consists of several components. It is made mainly by thick type I collagen fibres, providing strength, by thinner type 3 collagen fibres, which provide elasticity to ECM scaffolding, and by

glycoproteins, proteoglycans and glycosaminoglycans. ECM homeostasis is regulated by fibroblasts that produce collagen and matrix metalloproteinases, inhibitors and cross-linking enzymes, which maintain complex control of collagen. Fibroblast activation may lead to increased collagen formation and ECM, increased cardiac stiffness, diastolic dysfunction, electrical instability and vasomotor dysfunction, all elements in the pathogenesis of HFpEF. Several mediators can promote fibroblast activation, including angiotensin I and II (renin–angiotensin–aldosterone system), interleukins (interleukin-6, etc.), tumour necrosis factor, soluble ST2 (inflammatory state) and reactive oxygen species (oxidative stress). However, a better understanding of their pathogenic role still needs to be ascertained. In particular, it is unclear to what extent ECM expansion promotes myocyte dysfunction or whether the reverse pathway occurs. Myocyte loss (i.e. necrosis, autophagy, apoptosis) can lead to ECM expansion, but positive correlations between left ventricular (LV) mass and fibrosis suggest that simple myocyte loss does not explain much of the observed fibrosis.[28,29] ECM is an active structure, and ECM abnormalities can activate pathways ultimately affecting myocyte function, which can lead to HF.[30]

Cardiac magnetic resonance can now provide a non-invasive method to quantify ECM expansion *in vivo*, opening new frontiers in both research and the clinical setting.[31] While native T1 mapping reflects abnormalities in the entire myocardium, changes in paired pre- and post-contrast injection T1 allow measurement of interstitial gadolinium concentration and ECV, which in absence of oedema or amyloid deposit, reflect mainly ECM expansion by increased type I collagen fibre content. ECV calculated by CMR correlates significantly with collagen volume fraction evaluated by reproducible histologic technology,[32,33] although this relationship is weak where the fibrosis is subendocardial in aortic stenosis (typically ECV is measured at mid myocardium to avoid blood pool contamination).[28] Diffuse myocardial fibrosis evaluated by ECV is correlated with LV stiffness measured invasively by pressure–volume loops[34] and has been associated with disease severity and prognosis in HFpEF.[11,35] In a recent large study, ECV was elevated in patients at risk of HFpEF, given increased brain natriuretic peptide levels, but with no signs or symptoms of HF. The association with future outcomes suggests that ECV abnormalities might precede clinical HFpEF diagnosis.[10] Nevertheless, the technique is still vendor and centre-dependent and partial volume effect may limit its use to LV assessment. Recently, a consensus statement on T1 mapping and ECV quantification has been published, focusing on recommendations for clinical and research studies.[36] It is noteworthy that not only the increased quantity of collagen, but also the composition and chemical organization (e.g. collagen type I to type III ratio and degree of collagen cross-linking) influence myocardial stiffness and diastolic function.[37] CMR cannot assess qualitatively collagen expansion and this is a limitation in the comprehensive assessment of myocardial fibrosis in HFpEF.

An extreme example of a prototype ECM disease is cardiac amyloidosis, which is characterized by deposit of misfolded proteins into amyloid fibrils causing ECM expansion and is associated with high morbidity and mortality.[38] Even if cardiac amyloidosis should be viewed as a mimicker and not a cause of 'common or garden' HFpEF,[8] amyloid myocardial deposition is not as rare as has been traditionally thought. Small deposits of amyloid have been found in the hearts of elderly subjects in up to 25% of autopsies[39,40] and a study, using ^{99m}Tc-DPD scintigraphy to detect transthyretin cardiac amyloidosis (ATTR), reported a prevalence of 13% in HFpEF patients.[41] Noteworthy, new effective therapies for ATTR are becoming available.[42] Thus, it is important to recognize that a significant proportion of elderly patients with a diagnosis of HFpEF might have cardiac amyloidosis and, in this setting, CMR represents an important diagnostic tool. CMR has emerged as key imaging technique able to provide detailed information about the presence, location, and distribution of hypertrophy, as well as visualization of cardiac amyloid infiltration with late gadolinium enhancement imaging and measurement of cardiac amyloid burden with T1 mapping and ECV.[43] A recent study has shown that ECV correlated with amyloid burden and was an independent prognostic factor for survival in a cohort of patients with ATTR[44] and CMR has been used to prove the efficacy of a new drug (CPHPC plus anti-serum amyloid P antibody) in reducing cardiac deposits of amyloid from the heart, liver and spleen.[45]

Additionally, it has been shown that the diffuse fibrosis seen in patients with severe aortic stenosis regresses at 1 year after aortic valve replacement, associated with structural and functional cardiac improvement.[28] Notably, a recent post-hoc analysis of the Aldo-DHF trial demonstrated that a particular biochemical phenotype of high collagen cross-linking might identify a subset of HFpEF patients who are resistant to the beneficial effects of spironolactone. Conversely, the absence of excessive collagen cross-linking enhances the ability of spironolactone to reduce collagen deposition and to improve diastolic function in these patients. These data suggest that diffuse fibrosis is a heterogeneous and possibly dynamic process in humans, measurable by CMR, and thus it might represent a potential therapeutic target.[46,47]

The ability of CMR to detect focal and diffuse fibrosis might have important implications in clinical trials. Depending on the intervention being tested, the detection of fibrosis may be used to select patients expected to respond to agents with anti-fibrotic effects, or for enrichment of clinical events; on the other hand, a high burden of fibrosis may be used to exclude patients who may be expected to be less responsive to treatments that do not have an anti-fibrotic action. Finally, diffuse fibrosis by CMR can be used as a surrogate endpoint for clinical trials involving drugs which can target collagen turnover.

Microvasculature

Coronary microvascular disease is a recognized major contributor to HFpEF pathophysiology.[48] In the largest prospective multinational study of coronary microvascular disease in HFpEF to date,[49] there was a very high (75%) prevalence of coronary microvascular dysfunction in HFpEF (in the absence of unrevascularized macrovascular coronary artery disease). Coronary microvascular dysfunction was associated with HF severity, systemic endothelial dysfunction (reflected by peripheral arterial tonometry and urinary albuminuria), and cardiac dysfunction (reflected by echo strain assessments of the left atrium, left and right ventricles). Coronary

microvascular dysfunction may lead to 'chronic' and 'repetitive' ischaemia, reduced coronary blood reserve, imbalance between myocardial supply and demand, angiogenesis, fibrosis, and disease progression. There is a close relationship between endothelial cells, cardiomyocytes and fibroblasts. Microvascular abnormalities are part of a more systemic endothelial vascular dysfunction. The main mechanism is reduced nitric oxide bioavailability because of the high production of free radicals. Systemic vasomotor response can be assessed by brachial flow-mediated dilatation or forearm blood flow changes in response to acetylcholine, which have been associated with adverse outcome in patients with HF.[50] Fibrosis is associated with capillary rarefaction,[45] decreased perfusion reserve from perivascular fibrosis,[51] and increased diffusion distance for myocardial oxygen. Thus, there may be a role for interstitial fibrosis in the progression of HF.[51–53] Coronary microvascular rarefaction has been shown to be one of the key histologic features in an autopsy study involving HFpEF patients and has been associated with increased myocardial fibrosis.[48] Coronary microvascular rarefaction leads to decreased coronary flow reserve and microvascular ischaemia. Although CMR is not able to directly quantify coronary microvascular density, it can measure its consequences, in terms of reduced coronary flow reserve (perfusion studies) and increased fibrosis (T1 mapping).[48,54]

Coronary endothelial dysfunction has been historically assessed using positron emission tomography (PET), using tracers for flow (e.g. ^{13}N-ammonia) or metabolism (e.g. ^{18}F-fluorodeoxiglucose) at rest and during pharmacological stress. PET is, however, expensive, confined to specialized centres and uses radioactive substances. Perfusion CMR has emerged as an alternative. Recent technological development (*k-t* acceleration/highly constrained back projection) has allowed faster acquisition times resulting in higher spatial resolution and/or wider myocardial coverage. A three-dimensional perfusion CMR is available and allows a more accurate assessment of myocardial ischaemia and microvascular dysfunction. A limitation of perfusion CMR is the presence of dark-rim artefacts at the edge of blood pool/myocardium, which can affect specificity and the qualitative assessment of the test. A quantitative perfusion CMR is available but time consuming, and lacks of standardization. Recently, a new method for perfusion mapping has been developed permitting instant quantification of myocardial blood flow at a pixel level displaying myocardial blood flow on colour maps to represent flow (ml/g/min). This requires no additional scan- or post-processing and has been validated against quantitative PET.[55]

Coronary flow reserve can be calculated using phase-contrast imaging of the coronary sinus. Coronary flow reserve is decreased in HFpEF patients and correlates with brain natriuretic peptide levels.[56] Recently, patients with HFpEF were found to have a prolonged central circulation transit time (from right atrium to ascending aorta), and this was independently correlated to increased pulmonary capillary wedge pressures and reduced pulmonary artery oxygen saturation.[57]

Given its central role in the pathogenesis of myocardial dysfunction and disease progression, microvascular dysfunction is an appealing target for developing drugs for HF. Microvascular dysfunction and myocardial ischaemia are known to be associated with reduced adenosine triphosphate (ATP) fluxes and decreased energy supply, resulting in disturbances in the homeostasis of cardiac myocytes, and in myocardial suffering. An elevation of high-sensitive serum cardiac troponin is frequently observed in HFpEF,[58] even in absence of epicardial coronary disease,[59] probably due to diastolic stress overload and concomitant coronary microvascular dysfunction, which are typical findings in the HFpEF population.[60]

Metabolism

The heart uses free fatty acids (FFA) and glucose as a primary source of chemical energy with a ratio of 3:1. FFA and glucose produce ATP from adenosine diphosphate (ADP) through beta-oxidation and glycolysis, respectively. A creatine kinase system acts as an energy buffer, catalysing the conversion of creatine and ATP to phosphocreatine (PCr). When energy demands outweigh supply, PCr concentration decreases and ADP concentration increases, while ATP concentration remains stable. During myocardial ischaemia, ATP production and PCr formation decrease along with a reduction in the PCr/ATP ratio, indicating a depletion in myocardial energy reserves. Theoretically, myocardial fibrosis can affect metabolism by lowering myocardial perfusion (through perivascular fibrosis, capillary rarefaction, and increased oxygen diffusing distance) while increasing cardiomyocyte preload and afterload through the stiffening effects of collagen.[61–63]

Cardiac magnetic resonance is able to study cardiac metabolism through magnetic resonance spectroscopy (MRS). MRS is technically very demanding and optimization of pulse sequences, gradients, shimming and coils is still needed and often requires highly performing 3.0 T machines. Hydrogen-1 (^{1}H)-MRS is very sensitive and it is used to detect triglycerides, lactate and carnitine. Phosphorus-31 (^{31}P)-MRS is used to calculate the PCr/ATP ratio, which is an important parameter to investigate energy status of the heart. Absolute PCr and ATP concentrations, which are more accurate than their ratio to study the metabolic status (since both PCr and ATP are decreased in HF) while challenging, can also be calculated. The PCr/ATP ratio is directly related to LV ejection fraction in HFrEF and to diastolic dysfunction in HFpEF patients and it is an independent predictor for total and cardiovascular mortality. In addition, improvement in the PCr/ATP ratio and clinical status has been shown with angiotensin-converting enzyme inhibitors and diuretics.[63] Carbon-13 (^{13}C)-MRS has a low sensitivity, although, more recently, a newly developed hyperpolarization technique has increased the sensitivity by 10 000 times, enabling the study of components of pyruvate dehydrogenase and Krebs cycle within the heart.[64] Finally, sodium-23 (^{23}Na)-MRS has been used to detect sodium content, which is altered in ischaemic conditions and in myocardial infarction.

In the failing right ventricle of patients with pulmonary arterial hypertension, a dysregulated cardiac lipid metabolism with reduced FFA oxidation, cardiac steatosis, and lipotoxicity has been demonstrated, both *in vivo* and by MRS.[65] It is not clear whether this is a characteristic of pulmonary vascular disease or whether this may occur also in the right or left ventricles of patients with pulmonary hypertension secondary to HFpEF.

Recently, PET-CMR scanners have been introduced,[66] allowing simultaneous acquisition of PET and CMR information and could represent an important opportunity to deeply investigate cardiac metabolism, structure and function in HFpEF patients in a comprehensive, integrated approach.

Mitochondrial dysfunction and metabolic disarrangement play a key role in the pathogenesis of HFpEF. Mitochondria have been the target for several drug developments, including biogenesis, via AMP-activated protein kinase and endothelial nitric oxide synthase pathways, generation of reactive oxygen species (ROS), via anti-oxidants and ROS scavengers, and mitochondrial iron homeostasis, via specific mitochondrial iron chelating agents. In addition, reversing the deleterious effects of metabolic dysfunction in HF is increasingly becoming central in drug development in HFpEF. In this context, MRS can have a central role in the selection of the target population and in monitoring possible improvements of cardiac metabolism in HFpEF patients.

Emerging role of epicardial adipose tissue in heart failure with preserved ejection fraction

Several studies have underlined the possible role of adipose tissue in the pathophysiology of HFpEF, and obesity is a well-recognized phenotype of HFpEF.[67] Epicardial adipose tissue (EAT) volume is increased in patients with metabolic syndrome and obesity. In addition, similar to other visceral adipose tissues such as intrahepatic and intramuscular fat, EAT may have local metabolic and mechanical effects on the underlying organ.[68] Furthermore, recent studies have shown a direct correlation between EAT and ventricular mass independent of body mass index.[69] Several studies have investigated the role of EAT in HF, but most of them were performed in patients with HF and reduced ejection fraction.[70] The role of EAT in HFpEF patients has been investigated in only few studies that enrolled different phenotypes of HFpEF, using different diagnostic tests to assess EAT. Obokata *et al*.,[71] using echocardiography in obese patients, showed that EAT has a direct mechanical effect caused by increased pericardial restraint and enhanced ventricular interdependence. Vural *et al*.[72] evaluated the relationship between epicardial fat tissue volume and LV diastolic function, using multidetector computed tomography and two-dimensional transthoracic echocardiography, and they showed a significant correlation between diastolic dysfunction and increased EAT. In a population of patients with mid-range and preserved ejection fraction, van Woerden *et al*.[73] recently reported that EAT, assessed by CMR, was associated with the presence of atrial fibrillation, type 2 diabetes mellitus, and with biomarkers related to myocardial injury. Based on these findings and considering also the potential metabolic and inflammatory role of adipose tissue, EAT could have a potential pathophysiologic role in HFpEF which should be investigated in further studies. In addition, CMR, due to its advantages to study anatomic structure and myocardial perfusion, may have a predominant role in investigating the real value of EAT in the pathogenesis of HFpEF.[74] Mahmod *et al*.[75] investigated the role of myocardial steatosis (due to altered substrate metabolism leading to triglyceride accumulation and lipotoxicity) in HFpEF using ^{1}H-MRS (to measure triglyceride accumulation) and ^{31}P-MRS (for myocardial energetics). They found that myocardial steatosis is increased in HFpEF and independently associated with impaired diastolic strain rate, which is related to exercise capacity. Wu *et al*.[76] found that in patients with HF, EAT volume was correlated with ECV, independently of traditional risk factors and LVH or LV volume. Patients with HFpEF had significantly more intramyocardial fat than patients with HF and reduced ejection fraction as shown by CMR. Intramyocardial fat correlated with LV diastolic dysfunction parameters in HFpEF patients, independently of risk factors or gender.[77]

Clinical perspective

The pathological hierarchy of the myriad changes in HFpEF or other diseases remains to be clearly elucidated. Multiple pathways interact, and the order of specific processes in a cascade leading to HF is incompletely resolved. Also when we do understand some pathways, they may be off target, downstream or even protective in HF rather than causal. For example, does mitochondrial dysfunction follow myocardial fibrosis or vice versa? Does cardiomyocyte dysfunction precede or follow myocardial fibrosis? If more than one process co-exists, their prevalence and contribution to HF also require further elucidation. We group diseases together by structure and function based on imaging, but we do not understand how to measure or treat the specific processes that would result in personalized medicine – HFpEF is no exception. CMR provides powerful tools to study these issues helping the development of novel approaches. However, the most promising cutting edge CMR techniques are not in widespread use, and most studies are small. Diagnostic workup of HFpEF remains one of most challenging issues in cardiology and internal medicine. CMR is complementary to echocardiography in the initial phase of diagnostic workup. Importantly, CMR can be useful in more complex cases in which echocardiography does not provide a definitive diagnosis. Thus, the first step should be to identify specific pathologies leading to HFpEF.

Beyond diagnostic assessment *per se*, it is important to keep in mind that identification of the exact cause of HFpEF could identify pathologies with specific treatment options. This is especially relevant for infiltrative diseases. On the other hand, in the setting of coronary heart disease as a cause of HFpEF, a simultaneous assessment of ischaemia extent, viability, and late gadolinium enhancement may be helpful in characterizing patient subsets having a more favourable improvement after revascularization. In addition, pericardial thickness assessment may be another useful feature in identifying patients with congestive HF and preserved ejection fraction.

Aside from this assessment, an accurate CMR assessment may have a potential role in identifying diverse phenotypes within the HFpEF patient population using combined information from CMR. For example, accurate measures of LV mass, RV function, atrial function and enlargement along with LV fibrosis, can be useful for HF phenotyping. Finally, the intriguing possibility of additional prognostic information would be considered. Indeed,

tissue characterization fibrosis along with RV dysfunction may readily suggest a more adverse prognosis among a wide range of clinical HFpEF phenotypes.

Importantly, CMR may paly a crucial role in better recruiting HFpEF patients in the contemporary context of randomized trials. Indeed, in the context of neutral primary findings of large randomized HFpEF trials, albeit several echocardiographic variables have been used, the clinical heterogeneity HFpEF patients may have been confounding in terms of the proved effectiveness of treatment. Hence, we may suggest that HFpEF characterization may benefit from the implementation of CMR findings, which may be crucial to capture clinical categories of HFpEF patients. An ideal goal would be to perform an integration of panel of CMR findings that would fit within a more nuanced knowledge of the cardiac structural and pathophysiological profile.

Cardiac magnetic resonance is becoming a key imaging modality in HF and is likely to become a key part of mechanistic studies for HFpEF drug development. The main cardiac domains studied by CMR may represent fundamental steps towards the crucial translation into a widespread phenotyping of the HFpEF population.

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