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

Giovanni Quarta¹, Mauro Gori¹, Annamaria Iorio¹, Emilia D'Elia¹, James C Moon², Attilio Iacovoni³, Simone Burocchi³, Erik B Schelbert⁴,⁵,⁶, Paolo Brambilla⁷, Sandro Sironi⁷, Sergio Caravita⁸,⁹, Gianfranco Parati⁹,¹⁰, Antonello Gavazzi¹¹, Alan S Maisel¹², Javed Butler¹³, Carolyn SP Lam¹⁴, Michele Senni¹

1) Cardiovascular Department, ASST Papa Giovanni XXIII, Bergamo, IT
2) University College London and Barts Heart Centre, London, UK
3) Cardiovascular Department, Azienda Ospedaliera S Andrea, Rome, IT
4) Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
5) UPMC Cardiovascular Magnetic Resonance Center, Heart and Vascular Institute, Pittsburgh, PA, USA
6) Clinical and Translational Science Institute, University of Pittsburgh, Pittsburgh, PA, USA
7) Diagnostic Radiology, Papa Giovanni XXIII Hospital, University Milano-Bicocca, IT
8) Department of Management, Information and Production Engineering, University of Bergamo, Dalmine (Bergamo), IT
9) Department of Cardiovascular, Neural and Metabolic Sciences, Ospedale San Luca IRCCS Istituto Auxologico Italiano, Milan, It
10) Department of Medicine and Surgery, University of Milano-Bicocca, Milan, IT
11) FROM - Fondazione per la Ricerca dell'Ospedale di Bergamo, ASST Papa Giovanni XXIII, Bergamo, IT
12) Division of Cardiovascular Medicine, University of California San Diego, La Jolla, CA, USA
13) Department of Medicine, University of Mississippi, Jackson, Mississippi, USA
14) National Heart Centre, Singapore, Singapore; Duke-National University of Singapore, Singapore, Singapore; University Medical Centre Groningen, the Netherlands

Corresponding Author

Dr Michele Senni
Cardiovascular Department
ASST Papa Giovanni XXIII,
Pzza OMS 1 24127Bergamo, IT
Tel +39 0352674346
Fax +39 035 2674846

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ejhf.1961
Abstract

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 there is a likely high misdiagnosis rate. True HFpEF is likely to have multiple pathophysiological causes – with these causes themselves clinically ill-defined through 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.
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 there is a likely high misdiagnosis rate (8). True HFpEF is likely to have multiple pathophysiological causes – with these causes themselves clinically ill-defined through 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), although less widely available, has the capability for deep tissue characterization that may enable finer dissection of underlying pathophysiologic mechanisms in HFpEF (Figure 1-2) (16). 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.

CMR: basic principles, advantages, and limitations

CMR is an advanced imaging technique (Tables 1-2) 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 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 to a smaller detectable difference in clinical care and the need for fewer patients in clinical trials of new therapies (17).

CMR can give information on tissue characterization, for example evaluating the presence of edema, fibrosis or fat infiltration, with and without use of intravenous contrast agents. It is window independent so 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 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 not widely available nor portable. There must be some patient cooperation (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 ectopics) 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 (ICDs) 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.

Myocyte

Given its characteristics, CMR has become the gold standard for global and regional functional assessment (17). More sophisticated and quantitative analysis of regional dysfunction can be achieved with tagging and strain techniques. While CMR can assess transmitral flow and pulmonary veins flows with phase-contrast imaging, pulsed-wave Doppler echocardiography remains the preferred non-invasive gold standard technique for cardiac hemodynamic assessment. The disadvantages of CMR compared to echocardiography in this setting include lower the temporal resolution of CMR (around 30-40 msec compared to < 10 msec with echocardiography), it is time-consuming, it is not performed in real-time and can be affected by arrhythmias; in addition, CMR tend 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 and interstitial characteristics which are related to diastolic function, complimentary to echocardiography. CMR was found able to diagnose new pathologic 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 (18). Regardless, “structural” metrics of cardiac disease such as extracellular volume fraction (ECV) appear to agree more with invasive gold standard measures of diastolic dysfunction (time constant of active relaxation, or tau) than noninvasive 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. CMR using T1 mapping can split LVH into cellular and matrix components by measuring the extracellular volume fraction (ECV). Cell and matrix expansion have disease-specific relationships (19); 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 on the components of LVH and its pathophysiology. In addition, CMR is a key imaging modality for the differential diagnosis of LVH (20,21). CMR can measure with high degree of accuracy left atrial (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, avoiding issues such as foreshortening on views typically designed and tailored to the ventricle (22). Using CMR feature tracking technique, LA strain and strain rate can be calculated: these markers of LA dysfunction have been found impaired and associated with exercise intolerance in HFpEF patients (23), although the use of these techniques is not yet widely available in clinical settings.

CMR is the gold standard for evaluating RV size and function, and RV abnormalities by CMR have been independently associated to outcome and clinical status in HFpEF (2-24,25). Another study (26) showed a significant correlation between the pulmonary artery to aorta ratio assessed by CMR and mean
pulmonary artery pressure measured by right catheterization and outcome (i.e. hospitalization for heart failure or cardiac mortality) in HFpEF.

**Interstitium**

Historically, it has been difficult to image and measure cardiac extracellular matrix (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 fibers, providing strength, by thinner type 3 collagen fibers, 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. Fibroblasts 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 fibroblasts activation, including Angiotensin I and II (RAAS system), interleukins (IL-6, etc), tumor 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 LV mass and fibrosis suggest that simple myocyte loss does not explain much of the observed fibrosis (27,28). ECM is an active structure, and ECM abnormalities can activate pathways ultimately affecting myocyte function, which can lead to HF (29).

CMR can now provide a non-invasive method to quantify ECM expansion in vivo, opening new frontiers in both research and the clinical setting (30). 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 extracellular volume (ECV), which in absence of edema or amyloid deposit, reflect mainly ECM expansion by increased type I collagen fibers content. ECV calculated by CMR correlates significantly with collagen volume fraction evaluated by reproducible histologic technology (31,32), 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) (27). Diffuse myocardial fibrosis evaluated by ECV is correlated to LV stiffness measured invasively by pressure-volume loops (33) and has been associated with disease severity and prognosis in HFrEF (11, 34). In a recent large study, ECV was elevated in patients at risk of HFrEF, given increased brain natriuretic peptide (BNP) levels, but with no signs or symptoms of HF. The association with future outcomes suggests that ECV abnormalities might precede clinical HFrEF diagnosis (10). Nevertheless, the technique is still vendor and center dependent and partial volume effect may limit its use to the LV assessment. Recently, a second consensus on T1 mapping and extracellular volume quantification has been published, focusing on recommendations for clinical and research studies (35). It is noteworthy that not only the increased quantity of collagen, but also the composition and chemical organization (e.g. collagen type I:type III ratio and degree of collagen cross-linking) influence myocardial stiffness and diastolic function (36). CMR cannot assess qualitatively collagen expansion and this is a limitation in the comprehensive assessment of myocardial fibrosis in HFrEF.

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 (37). Even if cardiac amyloidosis should be viewed as a mimicker and not a cause of “common or garden” HFrEF (38), 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% (41) in HFrEF patients. 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 HFrEF 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 LGE 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 antiSAP 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 (27). 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 surrogate end-point for clinical trials involving drugs which can target collagen turn-over.

**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 heart failure severity, systemic endothelial dysfunction (reflected by peripheral arterial tonometry and urinary albuminuria), and cardiac dysfunction (reflected by echo strain assessments of the left atrium, LV and RV). Coronary microvascular dysfunction (MD) may lead to “chronic” and “repetitive” ischemia, 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 NO bioavailability because of high production of free radicals. Systemic vasomotor response can be assessed by brachial flow-mediated dilation 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 (54). Coronary microvascular rarefaction leads to decreased coronary flow reserve and microvascular ischemia. 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) (54-55).

Coronary endothelial dysfunction has been historically assessed using PET, using tracers for flow (for example $^{13}$N-Ammonia) or metabolism (for example $^{18}$F-Fluorodeoxiglucose) at rest and during pharmacological stress. PET is, however, expensive, confined to specialized centers 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 3D perfusion CMR is available and allows a more accurate assessment of myocardial ischemia and MD. A limitation of perfusion CMR is the presence of dark-rim artifacts 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, 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 (mls/g/min). This requires no additional scan- or post-processing and has been validated against quantitative PET (56).
Coronary flow reserve can be calculated using phase contrast imaging of the coronary sinus. Coronary flow reserve is decreased in HFrEF patients and correlated to BNP levels (57). Recently patients with HFrEF 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 (58).

Given its central role in the pathogenesis of myocardial dysfunction and disease progression, MD is an appealing target for developing drugs for HF. MD and myocardial ischemia are known to be associated with reduced adenosine triphosphate 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 (HS c-Tn) is frequently observed in HFrEF (59), even in absence of epicardial coronary disease (60), probably due to a diastolic stress overload and concomitant coronary MD, which are typical findings in HFrEF population (61).

Metabolism

The heart uses free fatty acids (FFA) and glucose as primary source of chemical energy with a ratio of 3:1. FFA and glucose produce adenosine triphosphate (ATP) from adenosine diphosphate (ADP) through beta-oxidation and glycolysis respectively. A creatine kinase system acts as an energy buffer, catalyzing 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 ischemia, ATP production and PCr formation decreases and 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 increase oxygen diffusing distance) while increasing cardiomyocyte preload and afterload through the stiffening effects of collagen (62-64).

CMR 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 high performing 3.0T 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. 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 PCr/ATP ratio and clinical status has been shown with ACE-inhibitors and diuretics (64). 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 (65). Finally, sodium-23 ($^{23}$Na)-MRS has been used to detect sodium content, which is altered in ischemic conditions and in myocardial infarction.

In the failing RV 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 (66). It is not clear whether this is a characteristic of pulmonary vascular disease or whether this may occur also in the RV or LV of patients with pulmonary hypertension secondary to HFpEF.

Recently PET-MR scanners have been introduced (67), 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 e-NOS pathways, generation of reactive oxygen species (ROS), via anti-oxidants and ROS scavengers, and mitochondrial iron homeostasis, via specific mitochondrial iron chelants. In addition, reversing the deleterious effects of metabolic dysfunction in HF is increasingly becoming central in drug developing 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 HFpEF

Several studies have underlined the possible role of adipose tissue in the pathophysiology of HFpEF, and obesity is a well-recognized phenotype of HFpEF (68). Epicardial adipose tissue volume (EAT) 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 (69). Furthermore, recent studies have shown a direct correlation between EAT and ventricular mass independently to the BMI (70). Several studies have investigated the role of EAT in HF, but most of them have been performed in patients with heart failure and reduced ejection fraction (71). The role of EAT on HFpEF patients has been investigated in only few studies that have enrolled different phenotypes of HFpEF, using different diagnostic tests to assess EAT. Obokata et al, using echocardiography in obese patients, have shown that EAT has a direct mechanical effect caused by increased pericardial restraint and enhanced ventricular interdependence (72). Vural et al have evaluated the relationship between epicardial fat tissue (EFT) volume and left ventricular diastolic function, using multidetector computed tomography (MDCT) and 2D transthoracic echocardiography, and they showed a significant correlation between diastolic dysfunction and increased EAT (73). In a population of patients with mid-range and preserved ejection fraction van Woerden G et al 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 (74). 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 (75). Mahmod et al. have investigated the role of myocardial steatosis (due to altered substrate metabolism leading to triglyceride accumulation and lipotoxicity) in HFpEF using 1H-MRS (to measure triglyceride accumulation) and 31P-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 (76). Wu et al found that in patient with heart failure EAT volume was...
correlated with ECV, independently of traditional risk factors and LVH or LV volume (77). Patients with HFrEF had significantly more intramyocardial fat than HFrEF patient as shown by CMR. Intramyocardial fat correlated with LV diastolic dysfunction parameters in HFrEF patients, independently from risk factors or gender (78).

Clinical perspective

We do not well understand the pathological hierarchy of the myriad changes in HFrEF or other diseases. Multiple pathways interact, and the order of specific processes in a cascade leading to HF incompletely resolved. Even 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 do not understand how to measure or treat the specific processes that would result in personalized medicine – HFrEF 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 HFrEF remain one of most challenging in cardiology and in internal medicine. CMR is complementary to echocardiography in the initial phase of diagnostic workup. Importantly, CMR can be useful in more challenge cases in which echocardiography does not provide a definitive diagnosis. Thus, the first step should be to identify specific pathologies leading to HFrHF.

Beyond diagnostic assessment per se, it is important to keep in mind that identification of exact cause of HFrEF 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 cause of HFrEF, a simultaneous assessment of extent ischemia, vitality, and LGE may be helpful in characterizing subset patients having a more favorable 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 for identifying diverse phenotypes within the HFP EF patient population by using a combining information of CMR. For example, an 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 right ventricular dysfunction may readily suggest more adverse prognosis among a wide range of clinical HFP EF phenotypes.

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

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

References


Figure legends

Figure 1. The complex patho-physiology of HFP EF: coronary micro and macrovascular disease, interstitial fibrosis, myocyte hypertrophy and metabolic abnormalities. **Lower left panel**, ECV mapping of a patient with HFP EF showing interstitial expansion from myocardial fibrosis and in the **upper right panel** the corresponding SSFP diastolic still frame (adapted with permission from Schelbert EB, Fridman Y, Wong TC, et al. Temporal Relation Between Myocardial Fibrosis and Heart Failure With Preserved Ejection Fraction: Association With Baseline Disease Severity and Subsequent Outcome. JAMA Cardiol. 2017;2:995-1006.). **Lower right panel**, 31P-magnetic resonance spectroscopy of the human heart (adapted with permission from Bizino MB, Hammer S, Lamb HJ. Metabolic imaging of the human heart: clinical application of magnetic resonance spectroscopy. Heart. 2014;100:881-90).
Figure 2. In HFpEF, CMR may detect underlying myocardial disease, endocardial disease, or pericardial disease. For example, 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 ATTR or AL). Furthermore, CMR with LGE detects endocardial disease such as endomyocardial fibroelastosis with associated mural thrombus that may be mistaken for the apical variant of hypertrophic cardiomyopathy. Finally, CMR detects pericardial disease, such as constrictive pericarditis with marked pericardial thickening, culminating in constrictive physiology manifest by septal flattening with inspiration on realtime cines.
### Myocardial diseases

<table>
<thead>
<tr>
<th>Condition</th>
<th>ECV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HfPEF</td>
<td>24.8%</td>
</tr>
<tr>
<td>HfPEF, hypertensive heart disease</td>
<td>38.1%</td>
</tr>
<tr>
<td>HfPEF cardiac amyloidosis</td>
<td>68.1%</td>
</tr>
</tbody>
</table>

**Late gadolinium enhancement**

**Cine frame at end diastole**

---

### Endocardial disease

- HfPEF
- Endomyocardial Fibroelastosis

**Late gadolinium enhancement**

**Cine frame at end diastole**

---

### Pericardial Disease

- HfPEF
- Constrictive Pericarditis

**Early diastole -Expiration**

**Late gadolinium enhancement**

**Early diastole -Inspiration**

---

*This article is protected by copyright. All rights reserved.*
Table 1. Advantages and disadvantages of CMR in assessing HFpEF patients.

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

**Abbr:** CMR = cardiac magnetic resonance; ECV = extracellular volume; LA = left atrium/atrial; LV= left ventricle/ventricular; LVH = left ventricular hypertrophy; MRI = magnetic resonance imaging; RV = right ventricle/ventricular.
Table 2. Importance of different imaging techniques in HFrEF phenotyping.

<table>
<thead>
<tr>
<th>Etiologies</th>
<th>Echocardiography findings</th>
<th>CMR findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischaemic</strong></td>
<td>RWMA (at rest or during stress echocardiogram)</td>
<td>RWMA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subendocardial/transmural LGE in coronary territory distribution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perfusion defects (stress CMR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Circumferential subendocardial ischaemia (rest/stress CMR, microvascular disease)</td>
</tr>
<tr>
<td><strong>Genetic</strong></td>
<td>HCM: Degree and distribution of hypertrophy (asymmetric septal, lateral, apical), RVH, anterior mitral valve leaflet elongation, SAM. LVOT obstruction (rest/dynamic).</td>
<td>HCM: Degree and distribution of hypertrophy (asymmetric septal, lateral, apical), RVH, anterior mitral valve leaflet elongation, papillary muscles hypertrophy, SAM, LVOT obstruction (rest)</td>
</tr>
<tr>
<td></td>
<td>Restrictive cardiomyopathy:</td>
<td>Restrictive cardiomyopathy:</td>
</tr>
<tr>
<td></td>
<td>LV Wall thickening (+/-), pericardial effusion, sparkling appearance. Restrictive filling pattern, increased E/E', biatrial enlargement, RVH</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>Non-compaction cardiomyopathy:</td>
<td>Non-compaction cardiomyopathy:</td>
</tr>
<tr>
<td></td>
<td>Increased ratio of non-compacted to compacted myocardium with reduced thickness of the compacted layer</td>
<td>Increased ratio of non-compacted to compacted myocardium with reduced thickness of the compacted layer, non-ischaemic LGE</td>
</tr>
<tr>
<td><strong>Infiltrative</strong></td>
<td>Amyloidosis: increased LV/RV Wall thickening, pericardial effusion, granular sparking appearance. Restrictive pattern</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>Hypereosinophilic syndrome:</td>
<td>Hypereosinophilic syndrome:</td>
</tr>
<tr>
<td></td>
<td>Increased LV/RV wall thickening.</td>
<td>Typical LV/RV subendocardial LGE. Thrombus detection, bi-atrial enlargement, valvular disease</td>
</tr>
<tr>
<td></td>
<td>Thrombus detection, restrictive filling pattern, bi-atrial enlargement, valvular disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haemochromatosis:</td>
<td>Haemochromatosis:</td>
</tr>
<tr>
<td></td>
<td>Increased left wall thickening (+/-)</td>
<td>Increase left wall thickening (+/-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shortened T2* (correlates with iron cardiac loading), reduced T1</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>Myocarditis:</td>
<td>Myocarditis:</td>
</tr>
<tr>
<td></td>
<td>increased wall thickening (+/-), RWMA</td>
<td>Increased wall thickening (+/-), RWMA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>Sarcoidosis:</td>
<td>Sarcoidosis:</td>
</tr>
<tr>
<td></td>
<td>aneurysm formation, regional wall thickening (or wall thinning due fibrosis), RWMA.</td>
<td>Aneurysm formation, regional wall thickening (or wall thinning due fibrosis), RWMA.</td>
</tr>
</tbody>
</table>

Abbr. CMR = Cardiovascular Magnetic Resonance; ECV = extracellular volume; HCM = hypertrophic cardiomyopathy; LGE = late gadolinium enhancement; LV = left ventricle/ventricular; LVOT = left ventricular outflow tract; RV = right ventricle/ventricular; RVH = right ventricular hypertrophy; RWMA = regional wall motion abnormalities; SAM = systolic anterior motion.

This article is protected by copyright. All rights reserved.