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

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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 HFpEF (11, 34). In a recent large study, ECV was elevated in patients at risk of HFpEF, 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 HFpEF 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 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 (37). Even if cardiac amyloidosis should be viewed as a mimicker and not a cause of "common or garden" HFpEF (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 HFpEF 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 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 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 HFpEF patients and correlated to BNP levels (57). 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 (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 HFpEF (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 HFpEF 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 HFpEF had significantly more intramyocardial fat than HFrEF patient as shown by CMR. Intramyocardial fat correlated with LV diastolic dysfunction parameters in HFpEF patients, independently from risk factors or gender (78).

Clinical perspective

We do not well understand the pathological hierarchy of the myriad changes in HFpEF 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 – 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 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 HFpHF.

Beyond diagnostic assessment per se, it is important to keep in mind that identification of 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 cause of HFpEF, 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 HFpEF 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 HFpEF phenotypes.

Importantly, CMR may be a crucial role for better recruiting HFpEF in the contemporary context of randomized trials, wherein a high heterogeneity of HFpEF patients. Indeed, in the contest of a neutral primary findings of large randomized HFpEF trials, albeit several echocardiographic variables have been used, the clinical heterogeneity HFpEF patients may been confound the proved effectiveness of treatment. Hence, we may suggest that a characterization of HFpEF may benefit from the implementation of CMR findings that may result 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 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 HFpEF drug development. The main cardiac domains studied by CMR may represent fundamental steps towards the crucial translation to a widespread phenotyping of the HFpEF population.

References

1) Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 2017; 14: 591-602.

2) Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail. 2020;22:391-412.

3) Cleland JG, Tendera M, Adamus J, Freemantle N, Gray CS, Lye M, O'Mahony D, Polonski L, Taylor J. PEP-CHF. Perindopril for elderly people with chronic heart failure: the PEP-CHF study. The PEP investigators. Eur J Heart Fail 1999; 1: 211-217.

4) Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;362:777-81.

5) Carson P, Massie BM, McKelvie R, McMurray J, Komajda M, Zile M, Ptaszynska A, Frangin G; I-PRESERVE Investigators. The irbesartan in heart failure with preserved systolic function (I-PRESERVE) trial: rationale and design. J Card Fail. 2005;11:576-85.

6) Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014; 370: 1383-392.

7) Desai AS, Jhund PS. After TOPCAT: What to do now in Heart Failure with Preserved Ejection Fraction. Eur Heart J 2016; 37: 3135-140.

8) Zakeri S, Cowie MR. Heart failure with preserved ejection fraction: controversies, challenges and future directions. Heart 2018; 104: 377-384.

9) Senni M, Paulus WJ, Gavazzi A, Fraser AG, Díez J, Solomon SD, Smiseth OA, Guazzi M, Lam CS, Maggioni AP, Tschöpe C, Metra M, Hummel SL, Edelmann F, Ambrosio G, Stewart Coats AJ, Filippatos GS, Gheorghiade M, Anker SD, Levy D, Pfeffer MA, Stough WG, Pieske BM. New strategies for heart failure with preserved ejection fraction: the importance of targeted therapies for heart failure phenotypes. Eur Heart 2014; 35: 2797-815.

10) Schelbert EB, Fridman Y, Wong TC, Abu Daya H, Piehler KM, Kadakkal A, Miller CA, Ugander M, Maanja M, Kellman P, Shah DJ, Abebe KZ, Simon MA, Quarta G, Senni M, Butler J, Diez J, Redfield MM, Gheorghiade M. 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.

11) Rommel KP, von Roeder M, Latuscynski K, Oberueck C, Blazek S, Fengler K, Besler C, Sandri M, Lücke C, Gutberlet M, Linke A, Schuler G, Lurz P. Extracellular Volume Fraction for Characterization of Patients With Heart Failure and Preserved Ejection Fraction. J Am Coll Cardiol 2016; 67: 1815-82.

12) Paulus WT, Tschope G. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation J Am Coll Cardiol 2013; 3;62:263-271.

13) Hunter WG, Kelly JP, McGarrah RW 3rd, Khouri MG, Craig D, Haynes C, Ilkayeva O, Stevens RD, Bain JR, Muehlbauer MJ, Newgard CB, Felker GM, Hernandez AF, Velazquez EJ, Kraus WE, Shah SH. Metabolomic Profiling Identifies Novel Circulating Biomarkers of Mitochondrial Dysfunction Differentially Elevated in Heart Failure With Preserved Versus Reduced Ejection Fraction: Evidence for Shared Metabolic Impairments in Clinical Heart Failure. J Am Heart Assoc 2016; 29:5.

14) Senni M, Gavazzi A, Gheorghiade M, Butler J. Heart failure at the crossroads: moving beyond blaming stakeholders to targeting the heart. Eur J Heart Fail 2015; 17:760-763.

15) Shah A, Pfeffer M. Heart failure: The many faces of heart failure with preserved ejection fraction. Nat Rev Cardiol 2012; 9: 555-556.

16) Čelutkienė J, Plymen CM, Flachskampf FA, de Boer RA, Grapsa J, Manka R, Anderson L, Garbi M, Barberis V, Filardi PP, Gargiulo P, Zamorano JL, Lainscak M, Seferovic P, Ruschitzka F, Rosano GMC, Nihoyannopoulos P. Innovative imaging methods in heart failure: a shifting paradigm in cardiac assessment. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20:1615-1633.

17) Liu S, Han J, Nacif MS, Jones J, Kawel N, Kellman P, Sibley CT, Bluemke DA. Diffuse myocardial fibrosis evaluation using cardiac magnetic resonance T1 mapping: sample size considerations for clinical trials. J Cardiovasc Magn Reson 2012; 14:90.

18) KanagalaP, Cheng ASH, Singh A, McAdam J, Marsh AM, Arnold JR, Squire IB, Ng LL, McCann GP. Diagnostic and prognostic utility of cardiovascular magnetic resonance imaging in heart failure with preserved ejection fraction - implications for clinical trials. J Cardiovasc Magn Reson 2018: 20:4.

19) Treibel TA, Kozor R, Menacho K, Castelletti S, Bulluck H, Rosmini S, Nordin S, Maestrini V, Fontana M, Moon JC. Left Ventricular Hypertrophy Revisited: Cell and Matrix Expansion Have Disease-Specific Relationships. Circulation. 2017;136:2519-2521.

20) Quarta G, Aquaro GD, Pedrotti P, Pontone G, Dellegrottaglie S, Iacovoni A, Brambilla P, Pradella S, Todiere G, Rigo F, Bucciarelli-Ducci C, Limongelli G, Roghi A, Olivotto I. Cardiovascular magnetic resonance imaging in hypertrophic cardiomyopathy: the importance of clinical context. Eur Heart J Cardiovasc Imaging. 2018;19:601-610.

21) Quarta G, Papadakis M, Donna PD, Maurizi N, Iacovoni A, Gavazzi A, Senni M, Olivotto I. Grey zones in cardiomyopathies: defining boundaries between genetic and iatrogenic disease. Nat Rev Cardiol. 2017;14:102-112.

22) Vassiliou VS, Patel HC, Rosen SD, Auger D, Hayward C, Alpendurada F, Lyon AR, Pennell DJ, Di Mario C, Prasad SK. Left atrial dilation in patients with heart failure and preserved ejection fraction: Insights from cardiovascular magnetic resonance. Int J Cardiol 2016; 210: 158-160.

23) von Roeder M, Rommel KP, Kowallick JT, Blazek S, Besler C, Fengler K, Lotz J, Hasenfuß G, Lücke C, Gutberlet M, Schuler G, Schuster A, Lurz P. Influence of Left Atrial Function on Exercise Capacity and Left Ventricular Function in Patients With Heart Failure and Preserved Ejection Fraction. Circ Cardiovasc Imaging 2017; 10.

24) Aschauer S, Kammerlander AA, Zotter-Tufaro C, Ristl R, Pfaffenberger S, Bachmann A, Duca F, Marzluf BA, Bonderman D, Mascherbauer J. The right heart in heart failure with preserved ejection fraction: insights from cardiac magnetic resonance imaging and invasive haemodynamics. Eur J Heart Fail 2016; 18: 71-80.

25) Gorter TM, van Veldhuisen DJ, Bauersachs J, Borlaug BA, Celutkiene J, Coats AJS, Crespo-Leiro MG, Guazzi M, Harjola VP, Heymans S, Hill L, Lainscak M, Lam CSP, Lund LH, Lyon AR, Mebazaa A, Mueller C, Paulus WJ, Pieske B, Piepoli MF, Ruschitzka F, Rutten FH, Seferovic PM, Solomon SD, Shah SJ, Triposkiadis F, Wachter R, Tschöpe C, de Boer RA. Right heart dysfunction and failure in heart failure with preserved ejection fraction: mechanisms and management. Position statement on behalf of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20:16-37.

26) Karakus G, Kammerlander AA, Aschauer S, Marzluf BA, Zotter-Tufaro C, Bachmann A, Degirmencioglu A, Duca F, Babayev J, Pfaffenberger S, Bonderman D, Mascherbauer J. Pulmonary artery to aorta ratio for the detection of pulmonary hypertension: cardiovascular magnetic resonance and invasive hemodynamics in heart failure with preserved ejection fraction. J Cardiovasc Magn Reson. 2015;17:79.

27) Treibel TA, Kozor R, Schofield R, Benedetti G, Fontana M, Bhuva AN, Sheikh A, López B, González A, Manisty C, Lloyd G, Kellman P, Díez J, Moon JC. Reverse Myocardial Remodeling Following Valve Replacement in Patients With Aortic Stenosis. J Am Coll Cardiol 2018; 71:860-871.

28) Schelbert EB, Fonarow GC, Bonow RO, Butler J, Gheorghiade M. Therapeutic targets in heart failure: refocusing on the myocardial interstitium. J Am Coll Cardiol 2014; 63: 2188-198.

29) Eckhouse SR, Spinale FG. Changes in the myocardial interstitium and contribution to the progression of heart failure. Heart Fail Clin 2012; 8: 7-20.

30) de Boer RA, De Keulenaer G, Bauersachs J, Brutsaert D, Cleland JG, Diez J, Du XJ, Ford P, Heinzel FR, Lipson KE, McDonagh T, Lopez-Andres N, Lunde IG, Lyon AR, Pollesello P, Prasad SK, Tocchetti CG, Mayr M, Sluijter JPG, Thum T, Tschöpe C, Zannad F, Zimmermann WH, Ruschitzka F, Filippatos G, Lindsey ML, Maack C, Heymans S. Towards better definition, quantification and treatment of fibrosis in heart failure. A scientific roadmap by the Committee of Translational Research of the Heart Failure Association (HFA) of the European Society of Cardiology. Eur J Heart Fail. 2019;21:272-285.

31) Flett AS, Hayward MP, Ashworth MT, Hansen MS, Taylor AM, Elliott PM, McGregor C, Moon JC. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: preliminary validation in humans. Circulation. 2010;122:138-44.

32) Diao KY, Yang ZG, Xu HY, Liu X, Zhang Q, Shi K, Jiang L, Xie LJ, Wen LY, Guo YK. Histologic validation of myocardial fibrosis measured by T1 mapping: a systematic review and meta-analysis. J Cardiovasc Magn Reson. 2016;18:92.

33) Ellims AH, Shaw JA, Stub D, Iles LM, Hare JL, Slavin GS, Kaye DM, Taylor AJ. Diffuse myocardial fibrosis evaluated by post-contrast t1 mapping correlates with left ventricular stiffness. J Am Coll Cardiol. 2014;63:1112-8.

34) Duca F, Kammerlander AA, Zotter-Tufaro C, Aschauer S, Schwaiger ML, Marzluf BA, Bonderman D, Mascherbauer Interstitial Fibrosis, Functional Status, and Outcomes in Heart Failure With Preserved Ejection Fraction: Insights From a Prospective Cardiac Magnetic Resonance Imaging Study. J. Circ Cardiovasc Imaging 2016; 9 (12).

35) Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, Mascherbauer J, Nezafat R, Salerno M, Schelbert EB, Taylor AJ, Thompson R, Ugander M, van Heeswijk RB, Friedrich MG. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular MagneticResonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson 2017;19:75.

36) Franssen C, González Miqueo A. The role of titin and extracellular matrix remodeling in heart failure with preserved ejection fraction. Neth Heart J. 2016;24:259-67.

37) Maurer MS, Elliott P, Comenzo R, Semigran M, Rapezzi C. Addressing Common Questions Encountered in the Diagnosis and Management of Cardiac Amyloidosis. Circulation 2017; 135: 1357-377.

38) Zakeri R, Cowie MR. Heart failure with preserved ejection fraction: controversies, challenges and future directions. Heart. 2018 Mar;104:377-384.

39) Tanskanen M, Peuralinna T, Polvikoski T, Notkola IL, Sulkava R, Hardy J, Singleton A, Kiuru-Enari S, Paetau A, Tienari PJ, Myllykangas L. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population-based autopsy study. Ann Med 2008;40:232–239.

40) Mohammed SF, Mirzoyev SA, Edwards WD, Dogan A, Grogan DR, Dunlay SM, Roger VL, Gertz MA, Dispenzieri A, Zeldenrust SR, Redfield MM. Left ventricular amyloid deposition in patients with heart failure and preserved ejection fraction. JACC Heart Fail 2014;2:113–122.

41) González-López E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, Bornstein B, Salas C, Lara-Pezzi E, Alonso-Pulpon L, Garcia-Pavia P. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J 2015;36:2585-94.

42) Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C; ATTR-ACT Study Investigators. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379:1007-1016.

43) Fontana M, Banypersad SM, Treibel TA, Maestrini V, Sado DM, White SK, Pica S, Castelletti S, Piechnik SK, Robson MD, Gilbertson JA, Rowczenio D, Hutt DF, Lachmann HJ, Wechalekar AD, Whelan CJ, Gillmore JD, Hawkins PN, Moon JC. Native T1 mapping in transthyretin amyloidosis. J Am Coll Cardiol Img 2014;7:157–65.

44) Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS, Kotecha T, Francis R, Hutt DF, Rezk T, Rosmini S, Quarta CC, Whelan CJ, Kellman P, Gillmore JD, Moon JC, Hawkins PN, Fontana M. Magnetic Resonance in Transthyretin Cardiac Amyloidosis. J Am Coll Cardiol. 2017;70:466-477.

45) Richards DB, Cookson LM, Berges AC, Barton SV, Lane T, Ritter JM, Fontana M, Moon JC, Pinzani M, Gillmore JD, Hawkins PN, Pepys MB. Therapeutic Clearance of Amyloid by Antibodies to Serum Amyloid P Component. N Engl J Med. 2015;373:1106-14.

46) Schelbert EB, Sabbah HN, Butler J, Gheorghiade M. Employing Extracellular Volume Cardiovascular Magnetic Resonance Measures of Myocardial Fibrosis to Foster Novel Therapeutics. Circ Cardiovasc Imaging 2017;10(6).

47) Ravassa S, Trippel T, Bach D, Bachran D, González A, López B, Wachter R, Hasenfuss G, Delles C, Dominiczak AF, Pieske B, Díez J, Edelmann F. Biomarker-based phenotyping of myocardial fibrosis identifies patients with heart failure with preserved ejection fraction resistant to the beneficial effects of spironolactone: results from the Aldo-DHF trial. Eur J Heart Fail. 2018;20:1290-299.

48) Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. Circulation 2015; 131: 550-559.

49) Shah SJ, Lam CSP, Svedlund S, Saraste A, Hage C, Tan RS, Beussink-Nelson L, Fermer ML, Broberg MA, Gan LM, Lund LH. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. Eur Heart J. 2018;39:3439-3450.

50) Fischer D, Rossa S, Landmesser U, Spiekermann S, Engberding N, Hornig B, Drexler H. Endothelial dysfunction in patients with chronic heart failure is independently associated with increased incidence of hospitalization, cardiac transplantation, or death. Eur Heart J. 2005:65-9.

51) Schwartzkopff B, Brehm M, Mundhenke M, Strauer BE. Repair of coronary arterioles after treatment with perindopril in hypertensive heart disease. Hypertension 2000; 36: 220-225.

52) Sabbah HN, Sharov VG, Lesch M, Goldstein S. Progression of heart failure: a role for interstitial fibrosis. Mol Cell Biochem. 1995;147:29-34.

53) Sabbah HN. Apoptotic cell death in heart failure. Cardiovasc Res 2000; 45:704-712.

54) Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. Circulation. 2015;131:550-9.

55) Zeng H, Chen JX. Microvascular Rarefaction and Heart Failure With Preserved Ejection Fraction. Front Cardiovasc Med. 2019;6:15.

56) Engblom H, Xue H, Akil S, Carlsson M, Hindorf C, Oddstig J, Hedeer F, Hansen MS, Aletras AH, Kellman P, Arheden H. Fully quantitative cardiovascular magnetic resonance myocardial perfusion ready for clinical use: a comparison between cardiovascular magnetic resonance imaging and positron emission tomography. J Cardiovasc Magn Reson. 2017;19:78.

57) Kato S, Saito N, Kirigaya H, Gyotoku D, Iinuma N, Kusakawa Y, Iguchi K, Nakachi T, Fukui K, Futaki M, Iwasawa T, Kimura K, Umemura S. Impairment of Coronary Flow Reserve Evaluated by Phase Contrast Cine-Magnetic Resonance Imaging in Patients With Heart Failure With Preserved Ejection Fraction. J Am Heart Assoc 2016; 5 (2).

58) Cao JJ, Li L, McLaughlin J, Passick M. Prolonged central circulation transit time in patients with HFpEF and HFrEF by magnetic resonance imaging. Eur Heart J Cardiovasc Imaging 2018; 19: 339-346.

59) Jhund PS, Claggett BL, Voors AA, Zile MR, Packer M, Pieske BM, Kraigher-Krainer E, Shah AM, Prescott MF, Shi V, Lefkowitz M, McMurray JJ, Solomon SD; PARAMOUNT Investigators. Elevation in high-sensitivity troponin T in heart failure and preserved ejection fraction and influence of treatment with the angiotensin receptor neprilysin inhibitor LCZ696. Circ Heart Fail 2014: 6: 953-959.

60) Takashio S, Yamamuro M, Izumiya Y, Sugiyama S, Kojima S, Yamamoto E, Tsujita K, Tanaka T, Tayama S, Kaikita K, Hokimoto S, Ogawa H. Coronary microvascular dysfunction and diastolic load correlate with cardiac troponin T release measured by a highly sensitive assay in patients with nonischemic heart failure. J Am Coll Cardiol 2013; 62: 632-640.

61) D'Elia E, Fiocca L, Ferrero P, Iacovoni A, Baio P, Medolago G, Duino V, Gori M, Gavazzi A, Senni M. Ranolazine in heart failure with preserved left ventricular ejection fraction and microvascular dysfunction: case report and literature review. J Clinic Pharmacol 2013; 53: 665-669.

62) Brilla CG, Funck RC, Rupp H. Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease. Circulation 2000; 102: 1388-393.

63) Izawa H, Murohara T, Nagata K, Isobe S, Asano H, Amano T, Ichihara S, Kato T, Ohshima S, Murase Y, Iino S, Obata K, Noda A, Okumura K, Yokota M. Mineralocorticoid receptor antagonism ameliorates left ventricular diastolic dysfunction and myocardial fibrosis in mildly symptomatic patients with idiopathic dilated cardiomyopathy: a pilot study. Circulation 2005; 112: 2940- 945.

64) Díez J, Querejeta R, López B, González A, Larman M, Martínez Ubago JL. Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients. Circulation 2002;105:2512-517.

65) Apps A, Lau J, Peterzan M, Neubauer S, Tyler D, Rider O. Hyperpolarised magnetic resonance for in vivo real-time metabolic imaging. Heart 2018;104:1484-491.

66) Brittain EL, Talati M, Fessel JP, Zhu H, Penner N, Calcutt MW, West JD, Funke M, Lewis GD, Gerszten RE, Hamid R, Pugh ME, Austin ED, Newman JH, Hemnes AR. Fatty Acid Metabolic Defects and Right Ventricular Lipotoxicity in Human Pulmonary Arterial Hypertension. Circulation 2016; 133: 1936-944.

67) Bergquist PJ, Chung MS, Jones A, Ahlman MA, White CS, Jeudy J. Cardiac application of PET-MR. Curr Cardiol Rev 2017; 19: 42.

68) Packer M. Leptin-Aldosterone-Neprilysin Axis: Identification of Its Distinctive Role in the Pathogenesis of the Three Phenotypes of Heart Failure in People With Obesity. Circulation. 2018;137:1614-1631.

69) Iacobellis G, Bianco AC. Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features. Trends Endocrinol Metab 2011;22:450–457.

70) Ansaldo AM, Montecucco F, Sahebkar A, Dallegri F, Carbone F. Epicardial adipose tissue and cardiovascular diseases. Int J Cardiol. 2019;278:254-260.

71) Doesch C, Haghi D, Flüchter S, Suselbeck T, Schoenberg SO, Michaely H, Borggrefe M, Papavassiliu T. Epicardial adipose tissue in patients with heart failure. J Cardiovasc Magn Reson. 2010;12:40.

72) Obokata M, Reddy YN, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. Circulation 2017;136:6–19.

73) Vural M, Talu A, Sahin D, Elalmis OU, Durmaz HA, Uyanık S, Dolek BA.Evaluation of the relationship between epicardial fat volume and left ventricular diastolic dysfunction. Jpn J Radiol. 2014;32:331-9.

74) van Woerden G, Gorter TM, Westenbrink BD, Willems TP, van Veldhuisen DJ,Rienstra M. Epicardial fat in heart failure patients with mid-range and preserved ejection fraction. Eur J Heart Fail. 2018;20:1559-1566.

75) Mahajan R, Kuklik P, Grover S, Brooks AG, Wong CX, Sanders P, Selvanayagam JB. Cardiovascular magnetic resonance of total and atrial pericardial adipose tissue: a validation study and development of a 3 dimensional pericardial adipose tissue model. J Cardiovasc Magn Reson. 2013;15:73.

76) Mahmod M, Pal N, Rayner J, Holloway C, Raman B, Dass S, Levelt E, Ariga R, Ferreira V, Banerjee R, Schneider JE, Rodgers C, Francis JM, Karamitsos TD, Frenneaux M, Ashrafian H, Neubauer S, Rider O. The interplay between metabolic alterations, diastolic strain rate and exercise capacity in mild heart failure with preserved ejection fraction: a cardiovascular magnetic resonance study. J Cardiovasc Magn Reson. 2018;20:88.

77) Wu CK, Tsai HY, Su MM, Wu YF, Hwang JJ, Lin JL, Lin LY, Chen JJ. Evolutional change in epicardial fat and its correlation with myocardial diffuse fibrosis in heart failure patients. J Clin Lipidol. 2017;11:1421-1431.

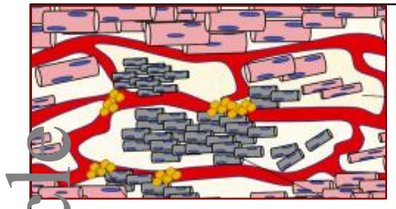
78) Wu CK, Lee JK, Hsu JC, Su MM, Wu YF, Lin TT, Lan CW, Hwang JJ, Lin LY. Myocardial adipose deposition and the development of heart failure with preserved ejection fraction. Eur J Heart Fail. 2020; 22:445-454.

Figure legends

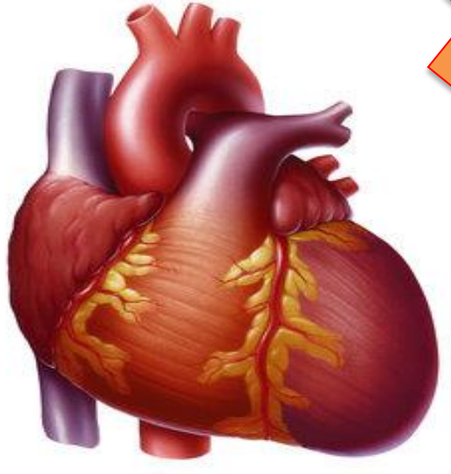
Figure 1. The complex patho-physiology of HFpEF: coronary micro and macrovascular disease, interstitial fibrosis, myocyte hypertrophy and metabolic abnormalities. **Lower left panel**, ECV mapping of a patient with HFpEF showing interstitial expansion from myocardial fibrosis and in the **upper right 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**, ^{31}P-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.

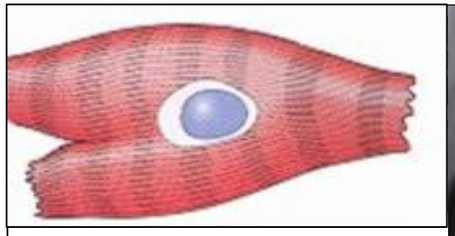
Coronary Microvascular Disease

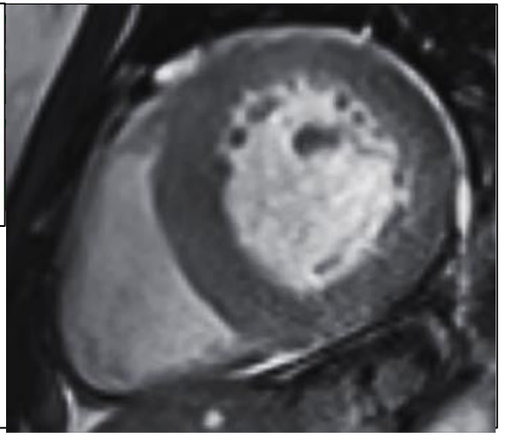


Coronary Macrovascular Disease



Myocyte Hypertophy





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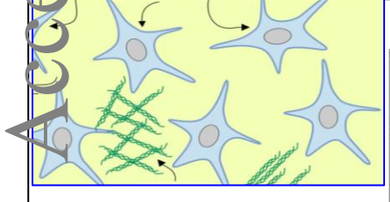
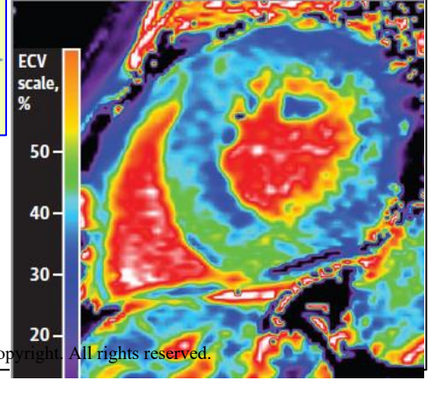
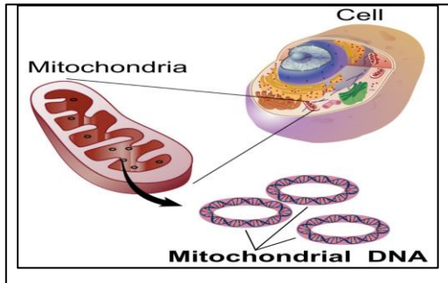
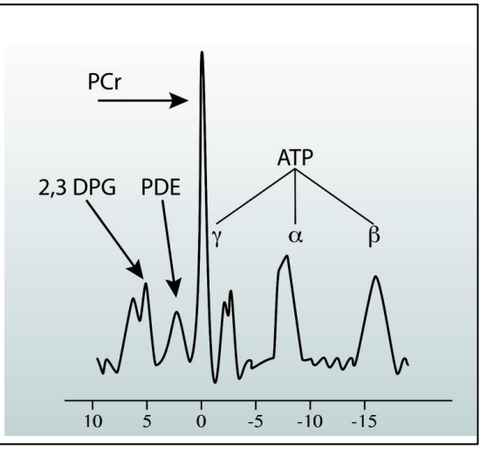


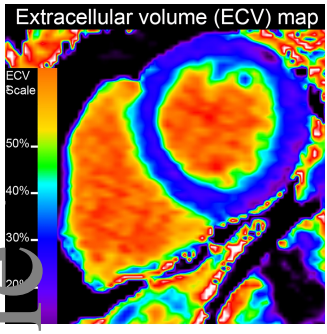
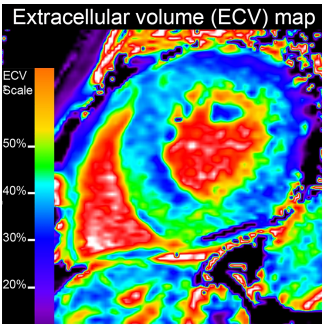
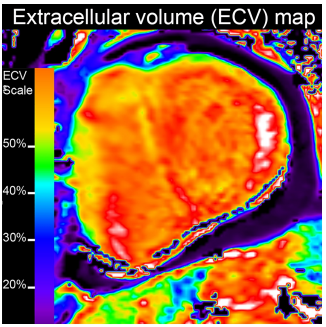
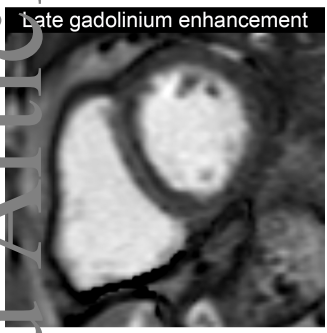
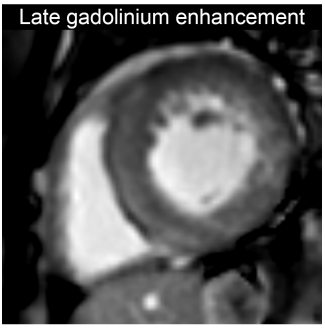
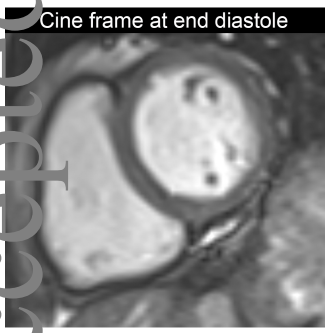
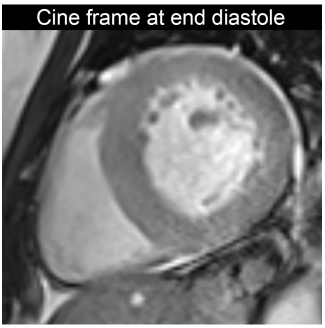
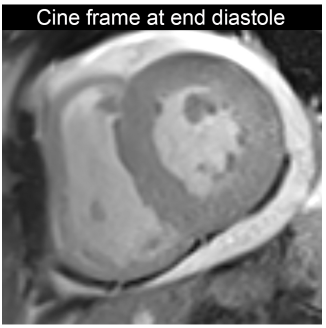


Metabolic Abnormalities

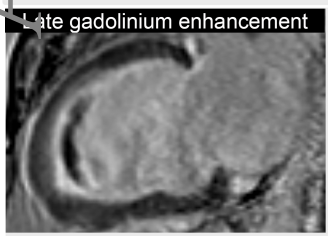




Myocardial diseases

No HFpEF ECV=24.8%	HFpEF, hypertensive heart disease ECV=38.1%	HFpEF cardiac amyloidosis ECV=68.1%
		
		
		

Endocardial disease



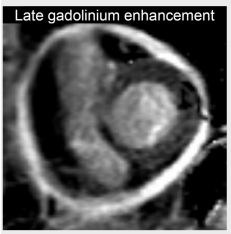
HFpEF

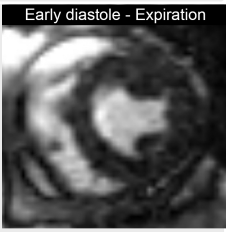
Endo-myocardial Fibroelastosis

Pericardial Disease

HFpEF

Constrictive Pericarditis





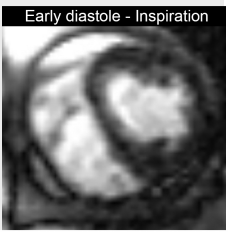


Table 1. Advantages and disadvantages of CMR in assessing HFpEF patients.

	Advantages	Disadvantages
Myocyte		
LV/RV mass, volume, function	No geometric assumptions Less operator dependant 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 contra-indications (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	High performing scanners and specific software needed Expertise needed Limited experience

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 HFpEF phenotyping.

Etiologies	Echocardiography findings	CMR findings
Ischaemic	RWMA (at rest or during stress echocardiogram)	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).	*HCM:* Degree and distribution of hypertrophy (asymmetric septal, lateral, apical), RVH, anterior mitral valve leaflet elongation, papillary muscles hypertrophy, SAM, LVOT obstruction (rest) Typical patchy LGE pattern Perfusion abnormalities
	Restrictive cardiomyopathy: LV Wall thickening (+/-), pericardial effusion, sparkling appearance. Restrictive filling pattern, increased E/E', biatrial enlargement, RVH	*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-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	*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: increased LV/RV wall thickening. Thrombus detection, restrictive filling pattern, bi-atrial enlargement, valvular disease	*Hypereosinophilic syndrome* : typical LV/RV subendocardial LGE. Thrombus detection bi-atrial enlargement, valvular disease
	Haemochromatosis: increased left wall thickening (+/-)	*Haemochromatosis*: Increase left wall thickening (+/-) Shortened T2* (correlates with iron cardiac loading), reduced T1
Inflammation	*Myocarditis:* increased wall thickening (+/-), 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 fibrosis), RWMA.	*Sarcoidosis:* aneurysm formation, regional wall thickening (or wall thinning due fibrosis), RWMA. Typical LGE pattern, (extensive, patchy, subepicardial) thoracic lymphadenopathy , lung abnormalities

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.