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► **To cite this version:**

Theo Pezel, Magalie Viallon, Pierre Croisille, Laurent Sebbag, Thomas Bochaton, et al.. Imaging Interstitial Fibrosis, Left Ventricular Remodeling, and Function in Stage A and B Heart Failure. JACC: Cardiovascular Imaging, 2020, 10.1016/j.jcmg.2020.05.036 . hal-03129209

HAL Id: hal-03129209

<https://hal.science/hal-03129209v1>

Submitted on 9 May 2023

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Imaging Interstitial Fibrosis, Left Ventricular Remodeling and Function in Stage A and B Heart Failure

Running Title: Cardiovascular Imaging in Stage A and B Heart Failure

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ABSTRACT

Myocardial interstitial fibrosis is part of the advanced disease stage of most cardiovascular pathologies. It has been characterized histologically in various disease settings from hypertensive heart disease and diabetic cardiomyopathy to severe aortic stenosis. It is also involved in the process of ageing. In cardiovascular medicine, myocardial interstitial fibrosis is associated with several adverse outcomes, especially heart failure (HF) and sudden cardiac death. Until recently, clinical measures of interstitial fibrosis could only be made by invasive myocardial biopsy. The availability of cardiac magnetic resonance (CMR) T1 mapping techniques allows for the indirect measurement of interstitial space characteristics and extracellular volume size, which is closely correlated to collagen content and interstitial infiltration by amyloid and other molecules. There has been significant improvement in the accuracy and reproducibility of T1 acquisition sequences in the last decade, however the correct use of this technique requires a solid CMR expertise in daily imaging practice. CMR has become the gold standard to assess left ventricular remodeling and functional features associated with interstitial fibrosis. These features can be detected in the early stages of HF. This paper main objective is to review the relevant results of pre-clinical as well as clinical observational studies that demonstrate the prognostic impact of interstitial fibrosis assessed by T1 mapping and adverse left ventricular remodeling, as determinants of heart failure. Therefore, this review focuses on the pathologic mechanisms underlying left ventricular (LV) remodeling and interstitial fibrosis, the technical considerations involved in the assessment of interstitial LV fibrosis by CMR, providing therefore a thorough review of the clinical evidence demonstrating the association of interstitial fibrosis and other CMR derived LV phenotypes with stages A and B HF.

Key words: Interstitial Fibrosis; Left Ventricular Remodeling; Heart Failure; T1 mapping; Cardiovascular risk factors.

Abbreviations:

BMI: body mass index
CMR: cardiac magnetic resonance
ECV: extracellular volume
EDV: end-diastolic volume
ESV: end-systolic volume
HF: heart failure
HFpEF: heart failure with preserved ejection fraction
LGE: late gadolinium enhancement
LV: left ventricular
LVEF: left ventricular ejection fraction
MESA: multi-ethnic study of atherosclerosis
MOLLI: modified look-locker inversion recovery

Highlights:

- The myocardium undergoes important tissue composition (hypertrophy, interstitial and replacement fibrosis...) as well as remodeling changes in stage A and B heart failure.
- Cardiac magnetic resonance offers a comprehensive and reproducible assessment of LV tissue and anatomy modifications with the potential to monitor different phenotypes in stage A and B heart failure.

- T1 mapping and extra cellular volume assessment by CMR require careful acquisition protocol and solid expertise for routine practice.
- Clinical use of these CMR measurements for therapeutic management still requires randomized controlled clinical trials.

PATHOPHYSIOLOGY OF INTERSTITIAL FIBROSIS

Interstitial fibrosis and left ventricular (LV) adverse remodeling have been associated with different comorbidities including diabetes and hypertension. They are ultimately associated with congestive heart failure (HF) and arrhythmic events(1). LV remodeling and interstitial fibrosis also occur with ageing and in that setting may not necessarily translate into heart disease. The complex combination of ageing with modifiable risk factors such as hypertension, diabetes mellitus, obesity, smoking and lack of physical exercise may initiate systemic inflammation together with significant increase in myocardial mechanical stress. Studies performed in HF with preserved ejection fraction (HFpEF) patients show a clear pro-inflammatory profile(2,3). In addition to these pathways, the involvement of extracardiac processes such as renal insufficiency and arterial vessel stiffening, together with renin angiotensin system hyperactivation, further increase chronic myocardial stress and interstitial collagen deposition(4–8).

Recently, obstructive and non-obstructive coronary artery disease have also been identified as potential aetiologies for interstitial fibrosis and LV remodeling. They share similar contributing factors (coronary microvascular dysfunction, increased conduit vessel stiffness, subclinical atherosclerosis, platelet dysfunction and abnormal adrenergic nerve function) to those that lead to the HFpEF syndrome(9). All these mechanisms may trigger acute clinical and sub-clinical events including arrhythmias (atrial fibrillation, sinus dysfunction) and ischemic events (myocardial infarction). These events cause abrupt increases in myocardial stress and result in myocardial cell death by necrosis which induces myocardial replacement fibrosis (scar). This in turn, further increases LV mechanical stress and adverse remodeling creating a vicious cycle that fuels the progression from stage A to B, C and D HF. The principal cellular pathways and mediators underlying such vicious cycle are summarized in

Figure 1.

In this review, we will focus only on heart failure etiologies related to the principal cardiovascular risk factors (hyperlipidemia, diabetes, hypertension, smoking, aging, obesity). Our review will not cover all other HF etiologies related to a structural/functional anomaly within the cardiomyocytes (primary dilated cardiomyopathy) or any other toxic, infiltrative or infectious cause (myocarditis, amyloid, chemotherapy...). In these settings, the pathophysiology is distinct from that of exposure to traditional cardiovascular risk factors.

The American College of Cardiology/American Heart Association (ACC/AHA) have proposed a heart failure classification system in four stages with increasing severity(10,11) as follows:

Stage A: High risk of heart failure, but no structural heart disease or symptoms of heart failure;

Stage B: Structural heart disease, but no symptoms of heart failure;

Stage C: Structural heart disease and symptoms of heart failure;

Stage D: Refractory heart failure requiring specialized interventions.

Typically, myocardial tissue is approximately composed of 75% myocardial intracellular tissue, which consists of myocardial cells, other cells, and blood cells, while 25% constitutes the ECV with the space between all cells including plasma in the vasculature. Myocardial interstitial space accounts for approximately 90% of the ECV and is composed of fibrillary proteins (collagen I & III, elastin), non-fibrillary proteins (aminoglycans, fibronectin, laminin), bioactive proteins (transforming growth factor beta, matrix metalloproteinases) and cells (fibroblasts, resident monocytes)(12). Interstitial fibrosis induced by the increase in TGF-beta secretion, results in the increase of collagen synthesis by activated resident fibroblasts. These fibroblasts are activated by the monocyte/macrophage myocardial

infiltration(13) in response to a wide array of stimuli leading to myocardial inflammation. Each step of the collagen metabolism is altered in this pathological process, with increased collagen synthesis, anarchic collagen deposition and dysfunctional collagen degradation. However, conversely to replacement fibrosis, interstitial fibrosis appears to be reversible and improved by pharmacological agents such as spironolactone and the combination of sacubitril with the angiotensin receptor blocker (ARB) valsartan(14–16). The interaction among all of these different pathophysiology tracks induce modifications in myocardial tissue composition as well as LV volumes, mass and shape. These early stage alterations can be reversibly modified by risk factor control.

Three pathophysiological phenotypes can be described in this setting and are depicted in the **Central Illustration** and **Figure 2**, depending on the principal risk factors.

The first phenotype corresponds to **healthy ageing** heart. In the normal process of ageing, systolic function is preserved as the LV cavities shrinks at a relatively fast pace. The LV end systolic and end diastolic volume decrease proportionally. LV mass also decreases with age, but at a much slower pace, which results in concentric remodeling and increased LV mass to volume ratio. At the tissue level, low rate diffuse cell death due to senescence and apoptosis occurs, associated with slightly increased interstitial fibrosis, which results in a relative extracellular volume increase.

The second phenotype corresponds to **stage A HF**(11). The heart is exposed to various risk factors that influence LV tissue composition as well as LV structure. The factors that have the greatest impact are obesity, diabetes and hypertension. The interaction among these factors is complex. They are also potentially combined with ageing, smoking, lack of exercise and chronic ischemia due to microvascular disease alone, or in combination with

epicardial coronary artery atherosclerosis. It is therefore difficult to specifically isolate the individual effect of each factor on LV architecture and myocardial tissue structure.

Conversely, in stage A HF, LV volumes may be moderately enlarged, and accompanied by significant increase in LV mass with concentric remodeling. At the tissue level, cardiomyocytes are significantly hypertrophied, and there may also be a significant increase in interstitial fibrosis first surrounding blood vessels and then more diffuse, in association with a reduction in capillary density. At this stage however, global LV systolic function may still be preserved, thanks to the hypertrophic process, augmented by greater LV torque(17).

The third phenotype is **stage B HF**(11,18). The pathophysiological processes activated in stage A continue and the microstructural and macrostructural LV remodeling become more severe.

At this stage, two phenotypes can be individualized: the preserved ejection fraction phenotype and the reduced ejection phenotype:

- In the HFpEF phenotype, the interstitial fibrosis becomes irreversible and diffuse and causes the stiffening of the left ventricle along with the intracellular modifications that occur at the same time in hypertrophied cardiomyocytes (loss of titin phosphorylation), further increasing the concentric remodeling.
- In the reduced ejection phenotype, cardiomyocyte death is significantly more prominent (infarction, micro-infarcts during acute events) associated with abnormal cellular function (apoptosis, metabolic abnormalities, calcium handling derangement...). Therefore, a macroscopic scar tissue appears which causes a shift towards eccentric remodeling.

In the pathophysiology of stage A and B HF, monitoring of LV shape and functional status (LV remodeling and functional assessment) as well as tissue composition could be of significant therapeutic interest. Developing non-invasive robust and reproducible imaging

techniques to define specific myocardial “imaging biomarkers” would potentially allow for: 1) definition of image endpoints in interventional randomized trials for stage A and B HF patients; 2) routine monitoring of patients at risk under effective therapy; 3) stratification of patients to facilitate decision making for therapeutic management. For these purposes, cardiac magnetic resonance (CMR) may appear to be a well-suited imaging technique. CMR is the gold standard for LV anatomy and functional assessment(19). Late gadolinium enhancement (LGE) CMR imaging is also a major clinical feature to characterize macroscopic replacement fibrosis(20). Finally, in the last ten years, the assessment of interstitial fibrosis has become accessible with T1 mapping sequences(21).

CMR IMAGING TECHNIQUES FOR INTERSTITIAL FIBROSIS

All technical and practical elements to achieve a quality native T1 mapping and ECV have been summarized by Robinson et al. in a recent review(22). Up-front, it is important to remember that T1 mapping and ECV assessment are not specific of fibrosis and can also be significantly modified in case of edema (myocarditis/ acute infarction), and myocardial infiltration (amyloid). These specific clinical settings should be ruled out before further analysis of T1 mapping for fibrosis quantification.

Also, a high-quality acquisition is mandatory in order to obtain a clinically relevant imaging study. We propose a brief summary of the main issues affecting T1 mapping accuracy as well as solutions to improve imaging acquisition, post-processing and analysis in **Table 1**.

Normal native T1 mapping time of the healthy myocardium is 976 ± 7 ms at 1.5-T and $1,159 \pm 16$ ms at 3.0-T(23). Nevertheless, the normal range of T1 values differs between different T1 sequences, field strengths and different heart rates(24).

INTERSTITIAL FIBROSIS AND REMODELING IN STAGE A HF

In the literature, many reports present T1 mapping results in different populations, with different sample sizes, various CMR acquisitions and post-processing protocols. In this study, we review the literature on interstitial fibrosis assessment by CMR, with particular details on data published as part of the Multi-Ethnic Study of Atherosclerosis (MESA) CMR literature. The MESA study is a prospective study designed to evaluate mechanisms that underlie development and progression of subclinical cardiovascular disease among asymptomatic individuals in the general population. Details of the MESA study design have been previously described(25). In this multi-ethnic cohort followed-up through more than 15 years, serial CMR assessments were performed with extensive CMR phenotyping in various risk factor settings. There are therefore extensive data, assessing the pathophysiology of stage A and B HF with CMR assessment in this cohort. In MESA, data were acquired and post-processed according to a standardized protocol. The following paragraphs review the results from those studies. Stage A HF is defined by patients at risk for HF who have not yet developed irreversible structural heart changes(10).

EFFECTS OF HEALTHY AGING ON LV INTERSTITIAL FIBROSIS, LV REMODELING AND LV FUNCTION

Table 2 summarizes the data obtained from the literature about the effects of healthy aging on all parameters of LV interstitial fibrosis, remodeling and function.

In the MESA cohort, LV remodeling during healthy aging is well described. First, LV mass significantly increased with age in men, and remained stable in women(26–29). At the same time, a significant decrease in LV EDV(17,26,27,30,31) and in LV stroke volume occurs (17,31). This leads to an increased LV mass/volume ratio(17,26–28,30). This causes a LV

concentric remodeling with an increase of LV mass/volume ratio of 0.03 g/mL every decade(17).

Healthy aging is associated with a significant relative increase in LV tissue composition including interstitial fibrosis as measured by native T1 mapping (mean 988 ± 39 ms with 15 ms of increase/decade) and ECV (mean 28.7 ± 2.7 % with 2.2 % of increase/decade)(32,33) without any scar(17,26–34). Donekal et al. showed that a greater ECV (i.e. lower post-contrast T1 value) is associated with reduced body surface area indexed LV EDV and LV mass. In addition, greater ECV is associated with reduced circumferential shortening, lower early diastolic strain rate, and a preserved left ventricular ejection fraction (LVEF) in women. In men, greater ECV is associated with LV systolic function abnormalities as reduced circumferential shortening, reduced LV torsion, and reduced LVEF(35).

In terms of LV systolic function, healthy aging subjects have a preserved LVEF associated with a reduction of LV strain(17,26–34). A lower circumferential shortening with a decrease of 0.14 points every decade was reported, as well as an increased torsion with progressive concentric remodeling(28).

EFFECTS OF CARDIOVASCULAR RISK FACTORS ON LV REMODELING AND FIBROSIS

Each cardiovascular risk factor has detrimental effects on LV function, remodeling and interstitial fibrosis. **Table 2** reports the effects of diabetes, hypertension, obesity, smoking and dyslipidemia on LV interstitial fibrosis, remodeling and function.

In MESA, there was no significant effect of any cardiovascular risk factors on LVEF.

However, as shown in **Table 2**, many studies showed significant changes in contractility measured by strain with MR myocardial tagging and cine-CMR.

Effect of diabetes mellitus

Patients with type 2 diabetes had an increased LV mass, a decreased LV EDV and LV stroke volume with a concentric LV remodeling and an increased LV mass/volume ratio.

Most data concerning the impact of diabetes on LV remodeling refers to type 2 diabetes patients. In this patient population, it is challenging to discriminate the impact of diabetes alone from hypertension and obesity. These conditions are often combined in the same patient. In MESA, type 2 diabetic patients had an increased LV mass(31,36) (except patients from the Asian ethnic group(37)). In addition, diabetic patients presented a decreased LV EDV and a decreased LV stroke volume(37). Diabetes is associated with concentric LV remodeling independently of body mass index (BMI), with an increase in LV mass/volume ratio(36,38). Turkbey et al. reported the same trends of LV remodeling abnormalities in patients with type 1 diabetes as described in patients with type 2 diabetes(39).

In terms of tissue composition including interstitial fibrosis, patients with type 1(40) or type 2(41) diabetes had a significant increase in native T1 native value (+54ms) and ECV (+0.8%) (using MOLLI sequence) compared to non-diabetic patients.

Diabetes mellitus was associated with reduced longitudinal and circumferential LV shortening together with reduced LV torsion as compared to healthy participants(36).

Effect of hypertension

Overall, hypertensive patients had an increased LV mass, a decreased LV EDV with a concentric LV remodeling and an increase in LV mass/volume ratio.

Studies on hypertensive patients without history of previous cardiovascular events showed an increase in LV mass(17,28). In addition, LV mass was directly related to systolic and diastolic blood pressure (BP)(42) with a 9.6 g increase of LV mass for every 21 mmHg

increase of systolic BP(43). Hypertension lead to a concentric remodeling with an increased LV mass/volume ratio. This was associated with a significant decrease in LV volumes(17,28) and an increase in left atrium volume indexed to the body surface as a marker of LV end-diastolic filling pressure increase. Finally, an effective anti-hypertensive therapy was associated with significant LV mass reduction(28).

In terms of tissue composition including interstitial fibrosis, patients with hypertension had an increase in native T1 native value (+16 ms) and ECV (+2.3%) compared to healthy non-hypertensive controls (using MOLLI sequence)(32,33).

Hypertensive patients had a significant reduction in circumferential shortening(17,28,44). Also, in hypertensive patients LV torsion was increased(17,28). One hypothesis to explain the increased torsion is the compensatory mechanism to maintain an adequate stroke volume to balance the progressive reduction in LV volumes and myocardial shortening associated with hypertension(17). Conversely, in patients with efficient antihypertensive therapy there was a significant improvement in circumferential shortening and LV torsion was not significantly different from non-hypertensive participants(17,28).

Effect of obesity

Obesity, defined as a BMI > 30 kg/m² was also associated with increased LV mass with a concentric LV remodeling and an increased LV mass/volume ratio. In MESA, Turkbey *et al.* described a 6 ± 2 g increase in LV mass for every 10 kg increase in patient weight(45); in a second study Heckbert *et al.* showed a 12 g increase in LV mass every 10 kg increase in body surface area (43). Conversely, every 5% weight loss was associated with a 1.3% decrease in height-indexed LV mass independently of age, race, gender or BMI(46).

The increase in LV end-diastolic volume per each 10-kg/m² increased in BMI for obese was 10 ml. For men with an average LV volume (140 ml), a 10-unit changed in BMI

corresponded to a 19% increase in LV volume. Similar relationships were also observed for women(45).

LV concentric remodeling is related to the severity of obesity with 0.04 g/mL increase in mass/volume ratio every 10 kg increase, due to a greater increase in LV mass relative to LV EDV(45). This relation was confirmed by another study which showed that every 5% weight loss was associated with a 1.3% decrease in LV mass/volume ratio independently of age, race, gender or BMI(46). This LV concentric remodeling was also associated with an increase in left atrium volume indexed to the body surface(47), a marker of increased LV filling pressures.

In terms of tissue composition including interstitial fibrosis, obese patients had an increase in native T1 native value (+ 45 ms) (using MOLLI sequence)(31).

Effect of smoking and dyslipidemia

Heckbert *et al.* showed that smoking was not associated with significant change in LV mass, no effect on LV volume and a slight increase in mass/volume ratio(43). In the same study, they described the effect of dyslipidemia with no significant change in LV mass, LV EDV and LV stroke volume (43).

In terms of tissue composition including interstitial fibrosis, there was no effect of smoking and dyslipidemia on native T1 value and ECV values in patients without prior history of cardiovascular events(31). In MESA, these factors were not significantly associated with the presence of scar defined by LGE.

For 10 years smoking patients, smoking causes a lower regional LV circumferential shortening(28) compared to non-smokers. Furthermore, it was reported a dose-response relationship between cigarette consumption, measured in pack-years, and regional LV dysfunction by circumferential strain(44).

INTERSTITIAL FIBROSIS AND REMODELING IN STAGE B HF

Stage B HF is defined by pathologic alterations of LV structure and function without symptoms of HF. Most of the structural and functional modifications assessed by CMR at this stage are predictive of HF adverse events. The following paragraphs review the link between these alterations and their predictive value on subsequent HF events (stage C HF). However, to our knowledge, there is no data to show that any therapeutic intervention at this stage based on a CMR imaging finding prevents subsequent HF events.

Table 3 summarizes the data obtained from the literature about the effects of LV remodeling, interstitial fibrosis and systolic function on the occurrence of stage C HF.

RELATIONSHIP BETWEEN LV REMODELING PARAMETERS AND SYMPTOMATIC HF

LV mass was associated with incident HF events after a median follow-up of 4 years with a hazard ratio of 1.4 per 10 g/m² increment. Higher LV mass at baseline (LV mass >95th percentile) is strongly associated with incident HF with a hazard ratio of 8.6 (95% confidence interval: 3.7 to 19.9) (48,49). This risk of HF occurrence was present in patients with(50) or without(48,51) myocardial replacement scar. This link between LV hypertrophy and HF has been confirmed in the Framingham study and other cohorts(52,53).

In MESA, LVED volume was significantly associated with incident HF events with a hazard ratio of 1.3 per 10% increment(48). LVED dilation (end-diastolic diameter >52 mm or >95th percentile) was associated with HF after a median follow-up of 9.4 years with a hazard ratio of 2.2 and 7.4 in patients with preserved LVEF and reduced LVEF, respectively. Overall, LV dilation predicts incident HF independently of LVEF(30). LV eccentric remodeling (defined

by high LV mass index, normal mass/volume ratio) and concentric remodeling (defined by normal LV mass index, an increased mass/volume ratio) patterns are also significantly associated with increased risk of HF as well, as compared with participants with normal-shape LV (54). Eccentric remodeling with increased sphericity is also significantly associated with higher NT-proBNP levels and lower LVEF(55).

In MESA, concentric remodeling with higher LV mass/volume ratio was associated with incident HF events with a hazard ratio of 2.3 per 10% increment(48). This pattern of ventricular remodeling appears to confer significant HF risk, especially when present earlier in life(34). This concentric remodeling has also been associated with replacement fibrosis in MESA(56).

THE EFFECT OF LV FIBROSIS ON THE OCCURRENCE OF STAGE C HF

Interstitial fibrosis and replacement fibrosis are both predictors of HF events. Replacement (scarring) fibrosis is present in the more advanced stages of disease. It is always synonymous of cardiomyocyte death and impaired myocardial performance. It is detectable by CMR with LGE imaging with a high degree of accuracy and reproducibility(57,58). The simple presence of LGE has been reported in various cardiomyopathies and pathology settings(21). Its presence is also systematically and independently associated with adverse cardiovascular outcomes(21).

In MESA, of the total 1840 participants who underwent contrast-enhanced CMR, with a mean age of 68 years, 7.9% had subendocardial or transmural LGE of myocardial infarction, and 78% of these latest were undetected by ECG or by clinical adjudication(56). In a recent study, Ambale-Venkatesh *et al.* showed that the proportion of participants with myocardial scar was significantly higher in patients with incident HF (37.5%) compared to patients without HF(59).

In the MESA study, asymptomatic individuals with positive LGE had a concentric hypertrophy in women and LV dilatation in men, with altered LVEF. Conversely, individuals without myocardial scar maintained LV function(32). Therefore, the presence of replacement fibrosis was associated with changing LV volumes and reduced function over time even in individuals from lower-risk populations.

In MESA, interstitial fibrosis determined by T1 mapping, was significantly associated with LV function. Male subjects had a linear decline in LV systolic function with interstitial fibrosis, whereas women had a progressive decline in LV diastolic function with fibrosis(35,57). Hence, restrictive filling with eventual diastolic dysfunction could progress to a stiffer left ventricle. In addition, men had progressively increased interstitial fibrosis with burden of CVD risk factors, while women were likely to have more interstitial fibrosis independently of cardiovascular risk factors(33,60).

More recently, T1 mapping values were significantly associated with invasively measured LV stiffness in HFpEF patients. Additionally, ECV measurements were correlated with exercise response with impaired active relaxation(61). Schelbert *et al.* showed in 1174 patients with normal systolic function, that myocardial interstitial fibrosis, defined by ECV, was similarly prevalent in HFpEF patients or at risk for HFpEF, suggesting that myocardial fibrosis might precede clinical HFpEF diagnosis (62). In this report, myocardial fibrosis was associated with disease severity (peptide natriuretic levels) and adverse outcomes.

Also, ECV and T1 mapping values in MESA have been shown to be significantly correlated with NT-proBNP levels. Liu *et al.* showed that each 1-SD increment (0.44 pg/mL) of log NT-pro BNP was associated with a 0.62% increment in ECV fraction, and 4.7 ms increment in native T1(63). This further confirms the link between HF events and CMR measures of interstitial fibrosis as NT-pro BNP showed an association with incident HF events after a

median follow-up of 4.7 years with a hazard ratio of 2.5 per unit log increment(51). The same finding was reported by Schelbert *et al.* (62) in a HFpEF patient population.

With all these precise functional, remodeling and tissue characterization features, CMR allows an in-vivo assessment of different pathophysiology processes. The ability to scan large groups of patients or to repeat acquisitions in time in a single patient exposed to several cardiovascular risk factors offers the potential to understand the progression of disease within the myocardium. It also offers the potential to assess the effect of therapeutic interventions.

INTEGRATING CMR IN THE ROUTINE CLINICAL WORKUP OF STAGE A & B HEART FAILURE PATIENTS

Today, in routine clinical practice, the first imaging technique that is widely available for therapeutic management is echocardiography. However, this imaging technique does not provide precise tissue characterization; therefore its ability to discriminate between several mechanisms of systolic myocardial dysfunction is poor. This was illustrated by Lupon *et al.* who assessed the evolution of LVEF over an 11-year period in HFpEF patients (64). In that study, LVEF declined significantly in 27.8% of patients with, versus 6.6% of patients without ischemic history. Thus, at one point in time, a complete assessment of myocardial functional, anatomic and underlying tissue characterization to accurately phenotype a patient with HFpEF is crucial for therapeutic management, as demonstrated above. However, several frontiers remain to be crossed beyond observational studies, before CMR becomes the first widely accepted imaging technique for the therapeutic management of HFpEF specifically, and heart failure in general. Three principal areas need to be addressed before such stage is reached.

1) Phase 2 Randomized Clinical Studies: the use of CMR imaging endpoints in interventional randomized studies for stage A and B HF patients is necessary to demonstrate, improve understanding, and set CMR at the core of patient clinical management. The assessment of LV function and remodeling, as well as LGE by CMR, have already been well established as imaging endpoints by numerous prior phase 2 randomized clinical studies, especially in the field of acute MI(21,65–67). For stage A and B HF patients, CMR parameters such as LV mass and ECV should be used as primary endpoints in interventional studies assessing the efficacy of drugs or other interventions. Such trials in selected group of patients will consolidate the efficacy of new drugs, will put CMR assessment at the center of patient management, and at the same time create hypotheses for phase 3 studies. These types of trial were performed in the past using endomyocardial biopsy where myocardial fibrosis regression after antihypertensive treatment was first demonstrated(68,69). Serial assessment with CMR offers the opportunity to assess non-invasively the impact of novel interventions designed to reduce LV fibrosis, improve myocardial function and induce reverse remodeling. In this regard, ongoing Phase 2 clinical trials such as the PIROUETTE trial (NCT02932566) are designed to examine the potentially beneficial effects of pirfenidone, a new antifibrotic agent, in HFpEF patients with ECV $\geq 27\%$.

2) Phase 3 Randomized Clinical Studies: However, the routine utilization of CMR in the assessment and management of patients with heart failure or suspected myocardial dysfunction will require the demonstration of its effectiveness in randomized clinical trials in terms of improved outcomes and/or cost-effectiveness when compared to routine clinical care. Currently, there are a few clinical trials using CMR as a screening or risk stratifying tool in patient management to improve clinical outcomes. In the CMR GUIDE trial (Cardiovascular Magnetic Resonance-GUIDEd management of light to moderate ventricular systolic

dysfunction; NCT01918215) for example, HF patients with moderate systolic dysfunction and increased risk of sudden cardiac death are randomized to primary prevention implantation of a cardioverter-defibrillator or not according to their LGE status(70). Similar studies could be performed in type A and type B HF patients, where CMR could help select specific patient phenotypes (increased LV mass index, increased ECV, presence of LGE) that are associated with a higher risk of future adverse cardiac events. These patients could then be randomized in interventional trials designed to assess the efficacy of drugs, devices or specific cardiovascular procedures.

3) Improving diagnostic accuracy/ reliability and accessibility for patients with Heart Failure.

In order to place CMR at the center of HF patient management, CMR accessibility in routine clinical practice should improve significantly. In an ideal system, CMR assessment should be as simple as a NTproBNP measurement. This will only be possible through standardization of CMR acquisition protocols among different institutions as well as among different scanner manufacturers. CMR scanning time for patients has to be significantly reduced, and education/ training of medical and paramedical staff involved in CMR utilization needs to be improved. Imaging post processing time should also be reduced in the future. As a guideline for this paradigm shift, imaging protocols that used in multicenter phase 3 positive studies should be simple to allow the results of to be widely disseminated beyond centers of concentrated expertise. Finally, education to the practicing cardiologist should be directed at how to best use CMR to expedite care, improve clinical outcomes and the overall effectiveness of the health care system.

Conclusion

CMR could become the most useful non-invasive imaging technique to provide reliable and reproducible “imaging biomarkers” in the management of stage A & B HF patients. In this regard, CMR can provide:

- 1) precise definition of imaging endpoints in interventional randomized trials for stage A and B HF patients,
- 2) reproducible landmarks for routine monitoring of patients at risk for clinical complications, drug side effects, and clinical improvement or deterioration.
- 3) stratification of patients to decide upon appropriate therapy and management demonstrated in randomized clinical trials.

In summary, personalized approaches based on clinically important pathophysiological mechanisms, and technical developments to further improve the robustness of imaging results are required to improve the performance of phase 3 trials to deliver “the right intervention to the right patient at the right time.”(71).

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Figure Legends:

Figure 1. Underlying Pathology Pathways associated With Interstitial Fibrosis and LV remodeling. Comorbidities and aging together with extracardiac organ involvement and acute myocardial events induce systemic inflammation with increased levels of inflammatory biomarkers (soluble interleukin 1 receptor-like 1 (IL1RL1) or ST2, C-reactive protein, growth differentiation factor 15 (GDF 15) and galectin 3). This concurs with increased myocardial wall stress induced by hypertension or obesity, together with acute events (ischemic events) that cause myocardial cell death. Myocardial remodeling and interstitial fibrosis begin with endothelial dysfunction that attracts infiltrating leukocytes and produces reactive oxygen species with reduced nitric oxide (NO) bioavailability. Activated interstitial leukocytes secrete transforming growth factor beta which enhances interstitial collagen deposition. This endothelial dysfunction combined with the increased myocardial mechanical stress reduces soluble guanylate cyclase (sGC) activity, cyclic guanosine monophosphate (cGMP) content and the beneficial phosphorylation of protein kinase G (PKG) inducing cardiomyocyte stiffness and hypertrophy.

Figure 2. Representative cases of co-registered left ventricular native T1 maps, ECV and end-diastolic cine frame in short axis in healthy ageing, stage A and stage B heart failure. *Native T1 and ECV measurements performed by integrating the MI area into the measurement. Measurements of the myocardium excluding the scar zone were native T1 = 1205ms and ECV = 33.9%.

Native T1 mapping (left column) and ECV mapping (middle column) quantify the wide spectrum of myocardial interstitial fibrosis ranging from healthy subjects to stage B HF through stage A HF. Cine images (right column) describe the evolution of LV remodeling at different stages.

Images from a young and normal patient (A); a healthy ageing patient with a concentric remodeling pattern and a slight significant increase in relative interstitial fibrosis extent (B); a patient in stage A HF with diabetes, hypertension and obesity leading to a significant LV hypertrophy and a greater increase in interstitial fibrosis (C), a patient in stage B HF with HFpEF and interstitial fibrosis becomes irreversible and diffuse, further increasing the concentric remodeling (D), and a patient in stage B HF with HFrfEF and a macroscopic scar of lateral MI which causes a shift towards eccentric remodeling (E) demonstrate the spectrum of disease severity.

ECV: Extracellular Volume; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrfEF: heart failure with reduced ejection fraction; MI: myocardial infarction

CENTRAL ILLUSTRATION. Left ventricular macrostructural and microstructural remodeling in healthy ageing, stage A and stage B heart failure. The normal left ventricle undergoes normal remodeling during the process of healthy ageing (upper panel). In stage A heart failure, the left ventricle is exposed to increased blood pressure, diabetes, obesity, lack of exercise (central panel), which leads to an increase in LV mass to volume ratio (concentric remodeling). In stage B heart failure, the pathophysiological processes activated in stage A continue and the microstructural and macrostructural LV remodeling become more severe (bottom panel). At this stage, two phenotypes can be individualized: the preserved ejection fraction phenotype and the reduced ejection phenotype. The latter may be linked to an MI as a consequence of the risk factors mentioned above, although there is also the case of reduced ejection phenotype with non-ischemic dilated cardiomyopathy not mentioned here

Comorbidities

Ageing

Loss of cell repair
Cell senescence
Cell death

Modifiable Risk Factors

Obesity
Diabetes
Hypertension
Lack of exercise
Smoking

RAS Hyperactivation

Renal Insufficiency

Arterial Wall Stiffness

Acute Events

Ischemic events: micro-macro
infarcts
Rhythmic disorders (AF, flutter,
sinus incompetence)

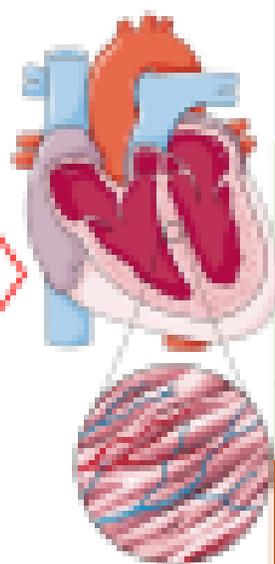
Systemic Inflammation

IL1β
GM-CSF
IFN
Selectin E

Rest Myocardial
Workload Increase

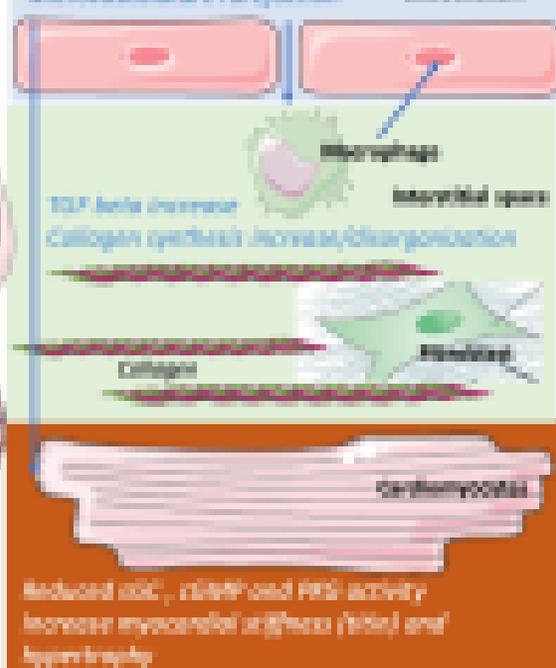
Myocardial Cell
Death

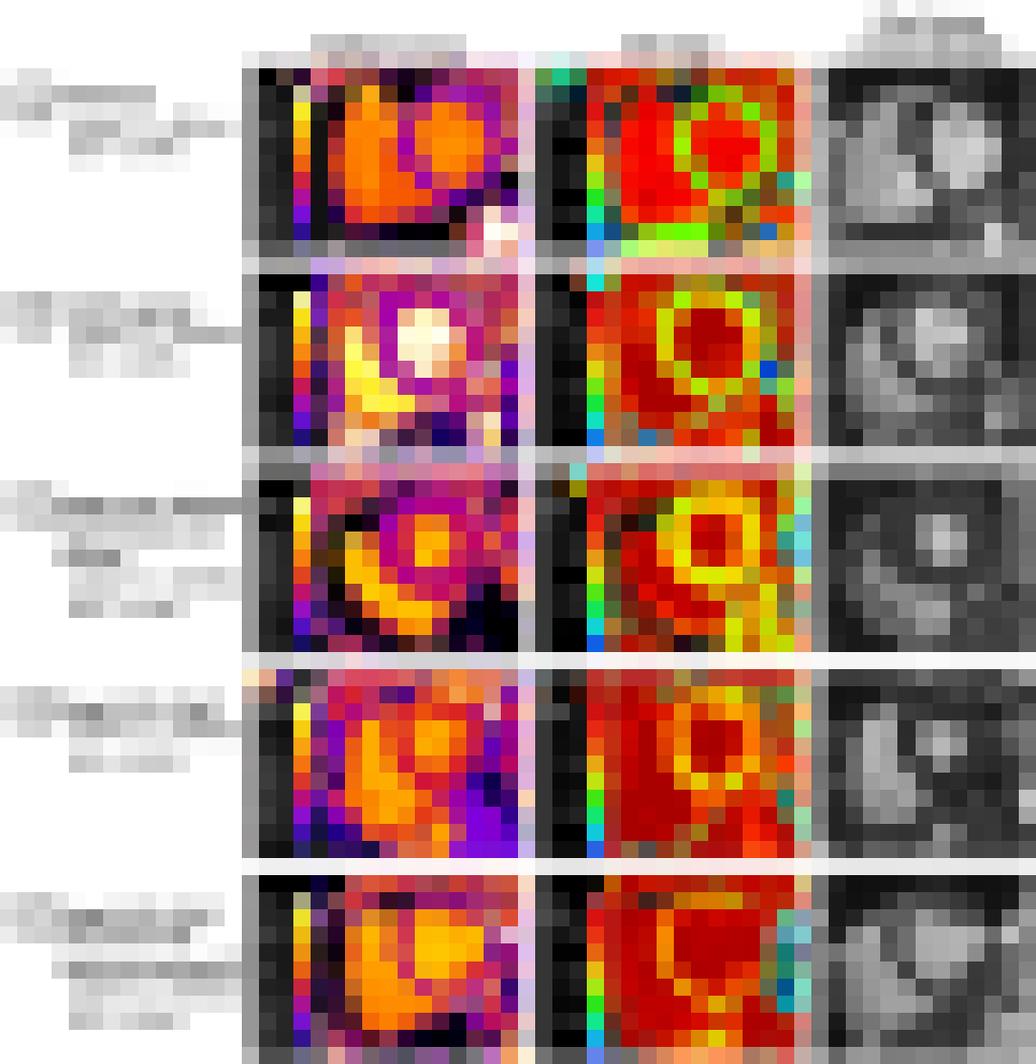
Myocardial involvement



Endothelium-Interstitial tissue-cardiomyocyte signaling

Increase in VCAM and E-selectin expression
Reduced NO
Microvascular rarefaction





TABLES

Table 1. Important Parameters to Control in order to Improve T1 mapping Reproducibility and Accuracy

Level	Source	Error	Quality control	Solution
Patient				
	Respiratory motion	Motion in-plane	Always check native images	Breath-hold and motion-correction algorithm (MOCO) ⁽⁷²⁾
		Motion through-plane	Always check native images	None (repeat acquisition)
	Heart rate	Arrhythmia	RR length	inSil reconstructions ⁽⁷³⁾ use recovery periods in seconds to ensure HR independent measures
		Tachycardia	HR > 90 bpm	
Sequence / setup				
	Native and post-Gd T1 differences	T1 sequence cannot measure long and short T1 with the same setup	different inversion time needed to optimize T1 estimation	Use optimized recommended scheme: 5(3)3 for native T1 and 4(1)3(1)1 post-Gd ⁽⁷⁴⁾
	Unproper choice of scanning window in RR interval	Intra-scan motion	Motion blurring at edges	HR capture and mid-diastole positioning
	Hematocrit value for ECV calculation	Unproper hematocrit sampling leads to underestimated ECV	Blood sampling timing	Blood sampling during MR scanning or after 20-30' supine rest position
Post-processing				
	Image registration	-acquisition geometry mismatch (matrix, orientation ≠ etc..) -slice level mismatch	Always check native images	none (repeat acquisition)
Image analysis				
	ROI positioning	Positioning bias, partial volume effect	-Exclude contaminated pixels at endocardium and epicardium - Selection of remote and lesion in the same slice	Use of automatic rejection strategies after myocardial segmentation

Table 2. Effects of Healthy aging and Cardiovascular risk factors on LV interstitial fibrosis, LV remodeling and LV function

	Normal ^p	Healthy aging ^{pp}	Diabetes	Hypertension	Obesity ^{ppp}	Smoking	Dyslipidemia ^{pppp}
LV Remodeling							
LV mass	<u>Men</u> = 74 ± 8.5 g/m ² <u>Women</u> = 62 ± 7.5 g/m ²	<u>Men</u> increased ^(26-28,75-78) (mean 80 ± 8.5 g/m ² with 6 g/m ² of increase) <u>Women</u> no difference ^(30,75,76,78,79) (mean 67 ± 7.5 g/m ² with 5 g/m ² of increase)	<u>Men</u> increased ^(31,36) (mean 88 ± 10.5 g/m ² with 14 g/m ² of increase) <u>Women</u> increased ^(31,36) (mean 67 ± 11.5 g/m ² with 5 g/m ² of increase)	<u>Men</u> increased ^(17,28) (mean 82 ± 3.5 g/m ² with 8 g/m ² of increase) <u>Women</u> increased ^(17,28) (mean 69 ± 3.5 g/m ² with 6 g/m ² of increase)	<u>Men</u> Increased ^(45,46) (mean 89 ± 10.5 g/m ² with 15 g/m ² of increase) <u>Women</u> Increased ^(45,46) (mean 69 ± 10.5 g/m ² with 7 g/m ² of increase)	No difference ⁽⁴³⁾ (mean 71 ± 10.5 g/m ²)	Decreased ⁽⁴³⁾
LV volume	EDV = 147 ± 21 mL Stroke volume = 97 ± 14 mL	Decreased EDV ^(17,26,27,30,31,75-78) (mean 125 ± 21 mL with 22 mL of decrease) Decreased Stroke volume ^(17,31,75-78) (mean 72 ± 14 mL with 25 mL of decrease)	Decreased LV EDV ⁽³⁷⁾ (mean 125 mL ± 28 mL with 22 mL of decrease) Decreased Stroke volume ⁽³⁷⁾ (mean 85 mL ± 21 mL with 12 mL of decrease)	Decreased LV EDV ^(17,28) (mean 122 mL ± 21 mL with 25 mL of decrease) Decreased Stroke volume ^(17,28) (mean 84 mL ± 14 mL with 13 mL of decrease)	Increased EDV ⁽⁴⁵⁾ (mean 157 ± 21 mL with 10 mL of increase)	No difference ⁽⁴³⁾ (Stroke volume mean 95.1 ± 14 mL)	Decreased LV EDV and stroke volume ⁽⁴³⁾
LV Masse/Volume Ratio	MVR = 0.86 ± 0.21	Increased ^(17,26-28,30,34) (mean 0.89 ± 0.15 with 0.03 of increase)	Increased ^(36,38) (mean 0.91 ± 0.17 with 0.05 of increase)	Increased ^(17,28) (mean 0.93 ± 0.20 with 0.07 of increase)	Increased ^(43,45,46) (mean 0.89 ± 0.15 with 0.03 of increase)	No difference ⁽⁴³⁾ (mean 0.89 ± 0.15 with 0.03 of increase)	No difference ⁽⁴³⁾
LAVI	LAVI = 32 ± 6.7 mL/m ²	Increased ^(47,75,80,81) (mean 39 ± 6.7mL/m ² with 7mL/m ² of increase)	No difference ⁽⁴⁷⁾	Increased ⁽⁴⁷⁾ (mean 38 ± 12.2 mL/m ² with 6mL/m ² of increase)	No difference ⁽⁴⁷⁾ (mean 34 ± 6.7mL/m ²)	No difference ⁽⁴⁷⁾	Decreased ⁽⁴⁷⁾ (mean 31 ± 6.7mL/m ² with 1mL/m ² of decrease)
Interstitial fibrosis							
Native T1 value (MOLLI sequence)	976 ± 7 ms ⁽²³⁾	Increased ^(32,33,82) (mean 988 ± 39 ms with 12 ms of increase)	Increased ^(31,41) (mean 1027 ± 41 ms with 51 ms of increase)	Increased ^(32,33,83) (mean 989 ± 45 ms with 13 ms of increase)	Increased ^(30,31) (native T1 mean 1015 ± 45 ms with 39 ms of increase)	No difference ^(30,31) (native T1 mean 980 ± 42 ms)	No difference ^(30,31) (native T1 mean 971 ± 38 ms)
LV interstitial fibrosis ECV (%)	ECV = 25.9 ± 0.4% ^(30,32)	Increased ^(32,33) (mean 28.7 ± 2.7 % with 2.8 % of increase)	Increased ^(31,41) (mean 26.7 ± 2.4 % with 0.8 % of increase)	Increased ^(32,33,83) (mean 28.2 ± 2.5 % with 2.3 % of increase)			

LGE macroscopic Scar		No scar	No scar ^(17,26-34)	No scar ^(31,36-38,41)	No scar ^(17,28,32,33)	No scar ^(43,45,46)	No scar ⁽⁴³⁾	No scar ⁽⁴³⁾
LV Function								
LVEF		LVEF = 66 ± 4.5 %	Preserved ^(17,26-34,78) (mean 69 ± 4.6%)	Preserved ^(31,36-38,41) (mean 68 ± 8.0%)	Preserved ^(17,28,32,33)	Preserved ^(43,45,46)	Preserved ⁽⁴³⁾ (mean 65 ± 4.5 %)	Preserved ⁽⁴³⁾
CMR strain	Longitudinal global	No abnormality	NA	Decreased ⁽³⁶⁾	No effect ^(17,28,84)			
	Radial		NA	No difference ^(17,28,84)				
	Circumferential*		Decreased ^(17,28)	Decreased ⁽³⁶⁾	Decreased ^(17,28,85)	Decreased ^(30,40,84)	Decreased ⁽⁸⁵⁾ in a dose-dependent manner	No difference ^(30,40,84)
	Torsion**		Increased ⁽²⁸⁾	Increased ⁽³⁶⁾	Increased ^(17,28)	-	Decreased ⁽²⁸⁾	-

Values are Mean ± SDp.

Meanp = pooled weighted mean; SDp = pooled standard deviation

All comparisons of this table were obtained against a subgroup of healthy individuals.

Measures reported from studies mixing steady-state free precession (SSFP) and fast gradient echo (GRE) sequences.

All strain data comes from MESA using tagging.

^P normal values for healthy adults ages 20 to 60 with pooled weighted mean values from references^(33,75-78,80,81).

^{PP} defined by healthy elderly patients over 65 years of age without cardiovascular factors

^{PPP} defined by BMI ≥ 30 kg/m²

^{PPPP} defined by the elevation of LDL-c above the recommended thresholds

*peak systolic circumferential strain

**torsion: defined as the difference between apical and basal rotation divided by slice distance

Abbreviations: BMI: body mass index; CMR: cardiac magnetic resonance; DM: diabetes mellitus; ECV: extracellular volume; EDSR: end-diastolic strain rate; EDV: end-diastolic volume; LAVI: left atrium volume indexed to the body surface; LGE: late gadolinium enhancement; LV: left ventricle; LVEF: left ventricular ejection fraction; SRI: strain relaxation index.

Table 3. Effects of LV remodeling, interstitial fibrosis and systolic function on the occurrence of stage C HF

	Risk of stage C HF
LV Remodeling	
LV mass	Increased LV mass (mean HR 8.6 and HR of 1.4 per 10 g/m ²) ^(48,49)
LV volume	Increased LV end-diastolic volume (mean HR 2.2 with preserved LVEF or HR 7.4 with reduced LVEF; and mean HR of 1.3 per 10% increment) ⁽⁴⁸⁾ Reduced LV sphericity (mean HR 1.5) ⁽⁵⁵⁾
LV mass/volume Ratio	Higher LV mass/LV volume (mean HR of 2.3 per 10% increment) ⁽⁴⁸⁾
Size and Function of LA	Higher LAVI (mean HR 1.5 for > 32 mm ³ /m ²) ⁽⁸⁶⁾ Lower LA strain ^(87,88)
Interstitial fibrosis	
LGE macroscopic Scar	Increased (mean HR 1.5) ⁽⁸⁹⁾
Native T1 value	No difference ⁽⁵⁹⁾
LV interstitial fibrosis ECV (%)	Increased (mean HR 1.4 for ECV > 26%) ⁽⁹⁰⁾
LV Systolic Function	
CMR strain	Impaired LV circumferential shortening (mean HR 1.2) ⁽⁹¹⁾

Abbreviations: CMR: cardiac magnetic resonance; ECV: extracellular volume; EDV: end-diastolic volume; HF: heart failure; HR: hazard ratio; LA: left atrium; LAVI: left atrium volume corrected for the body surface area; LGE: late gadolinium enhancement; LV: left ventricle.

