Published in final edited form as:

Curr Cardiovasc Imaging Rep. 2014 April ; 7: 9269–. doi:10.1007/s12410-014-9269-x.

Subclinical Myocardial Disease in Heart Failure Detected by CMR

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Abstract

Noninvasive cardiac imaging plays a central role in the assessment of patients with heart failure at all stages of disease. Moreover, this role can be even more important for individuals with asymptomatic cardiac functional or structural abnormalities—subclinical myocardial disease—because they could have benefits from early interventions before the onset of clinical heart failure. In this sense, cardiac magnetic resonance offers not only precise global cardiac function and cardiac structure, but also more detailed regional function and tissue characterization by recent developing methods. In this section, some of the main methods available for subclinical myocardial disease detection are reviewed in terms of what they can provide and how they can improve heart failure assessment.

Keywords

Cardiac Magnetic Resonance; Heart Failure; Myocardial Tagging; Late Gadolinium Enhancement; T1 mapping

Introduction

Heart Failure (HF) is the result of advanced myocardial dysfunction and continues to be a major cause of morbidity and mortality in developed nations. In the United States alone, over 5 million adults carry the diagnosis of HF and the disease prevalence continues to escalate with aging of the population [1]. In addition to conferring a significant burden of illness to affected individuals, management of HF imposes enormous expense to the health care system [2].

Noninvasive cardiac imaging plays an essential role in the diagnosis of HF, assessment of patients, and monitoring of therapy, however, cardiac imaging may have the most to offer

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Conflict of Interest

Yoshiaki Ohyama, Gustavo J. Volpe, and Joao A.C. Lima declare that they have no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

individuals with stage B disease — the presence of asymptomatic cardiac structure or functional abnormalities [3]—because these patients stand to substantially benefit from early interventions before the onset of overt HF. As such, cardiac magnetic resonance (CMR) imaging can serve as a particularly important imaging modality for providing both diagnostic and prognostic information because of detecting the presence and extent of subclinical myocardial disease.

In general, it remains widely recognized that CMR provides the most precise and reproducible noninvasive assessment of cardiac systolic function [4]. Compared with echocardiography, CMR offers the advantage of excellent visualization of the endocardial border in addition to high spatial resolution, without the limitation of poor echo windows. Furthermore, compared with radiograph-based imaging modalities, CMR does not use ionizing radiation which is favorable in younger patients or patients in need of repeat imaging. CMR also has several powerful tools to detect myocardial changes which can cause overt HF. Myocardial tagging is a technique that can be used to quantify variations in regional and global myocardial performance as deformation—even in the presence of a normal ejection fraction (EF). In addition, CMR is currently the only noninvasive imaging modality that can be used for myocardial tissue characterization in order to aid clinicians in identifying the cause of a given cardiomyopathy. The late gadolinium enhancement (LGE) method can detect replacement fibrosis, in other words, myocardial scar, whereas T1 mapping can determine diffuse myocardial fibrosis.

It is well established that conventional measurements of cardiac function and structure, such as LVEF and LV mass are strong predictors of future HF and of poor prognosis [5–7]. In this review, we focus on the three current methodologies that allow the assessment of subclinical myocardial disease in HF stage B by CMR: myocardial tagging, LGE imaging, and T1 mapping.

Myocardial tagging imaging

Assessments of global ventricular function—and its reduced indices, such as LVEF—are clearly strong predictors of future HF and of poor prognosis [7]; however, global measures are insensitive to reductions in regional performance, where even a normal LVEF can obscure significant underlying regional dysfunction. Thus, measures of regional function, such as quantification of myocardial strain and torsion, have emerged as more accurate tools for defining degrees of myocardial disease. Myocardial strain—defined as the change in length of a segment of myocardium relative to its resting length—is expressed as a percentage; strain rate is the rate of this deformation with respect to time. In 3D space, myocardial strain can be divided into 3 directions: longitudinal, circumferential, and radial strain. Longitudinal and circumferential shortening results in negative strain values, whereas radial thickening results in a positive value. Torsion is the wringing motion of the ventricle around its long axis induced by contracting myofibers in the LV wall. Abnormalities in these measures can serve as a more specific marker of subclinical myocardial dysfunction.

Although tissue Doppler imaging [8] and speckle tracking [9] are two novel echocardiographic techniques that have been introduced for strain quantification, CMR

tagging remains the reference standard for assessment of regional function [10]. Initially designed to analyze myocardial contraction during systole, tags are typically created upon detection of the QRS complex of electrocardiogram (ECG). The resulting tags then follow myocardial motion during the cardiac cycle, thus reflecting the underlying myocardial deformation (Figure 1). Specifically, CMR tagging allows for precise measurements of regional strain, ventricular torsion, and segmental synchrony.

Harmonic phase (HARP) analysis is currently the most widely used method for strain quantification from tagging image since it is highly automated and, thus, limits both analysis time and subjective interference. The HARP method analyzes the motion in the tagging data by filtering the harmonic peaks in the frequency domain of the image. It computes a displacement map of the tag lines by tracking their phase changes through time. HARP can, thus, track the motion of a single point or of a whole myocardial segment (by taking the average of multiple adjacent points) through time to generate a dense regional dynamic color strain map throughout the cardiac cycle [11, 12]. Figure 2 shows the representative image of analysis with circumferential strain (Ecc) by this method. HARP analysis of myocardial tagged images proved highly reproducible for detecting silent myocardial dysfunction in asymptomatic populations in Multi-Ethnic Study of Atherosclerosis (MESA) [13]; MESA was initiated in 2000 to investigate the prevalence, correlates, and progression of subclinical cardiovascular disease in a community-based population of about 6500 men and women of different racial/ethnic backgrounds, free of cardiovascular disease at the baseline [14].

Several studies have identified the association between deformation and cardiovascular risk factors in MESA. Increased diastolic blood pressure and smoking were associated with lower Ecc in the left anterior descending and right coronary territories, with dose dependent effect seen between LV function and smoking [15]. With respects to the structural changes associated with long-standing hypertension, in particular, asymptomatic MESA individuals with LV hypertrophy had reduced early diastolic regional function, quantified using diastolic strain rate. This finding remains significant even in the setting of preserved regional systolic function [16], supporting the concept of hypertensive heart disease and diastolic dysfunction as potential precursors to clinical HF. Furthermore, changes in regional myocardial function also correlated with more specific markers of subclinical atherosclerosis in MESA. Coronary artery calcification burden, quantified by computed tomography, was related to reduced regional Ecc and to its strain rate in the corresponding coronary territory, suggesting a link between coronary atherosclerosis and incipient regional dysfunction [17]. Increased carotid wall stiffness and intima-media thickness (IMT) were also strongly related to reduced systolic and diastolic regional function among individuals free of known cardiovascular disease [18, 19]. Moreover, Choi et al. recently reported that Ecc provides robust, independent, and incremental predictive value for incident HF in asymptomatic subjects without any history of previous clinical cardiovascular disease[20] using MESA cohort. With respect to cardiomyopathy, alternations in regional and global systolic and diastolic strain also have also been detected by CMR in the setting of myocardial ischemia or infarction, non-ischemic dilated cardiomyopathy (DCM), and hypertrophic cardiomyopathy (HCM) [21, 22].

The extent to which the LV normally undergoes a global twisting motion in systole and untwisting motion (recoil) in diastole, quantified by CMR as measures of torsion, can be impaired in the setting of hypertension and diabetes even when global LV function seems otherwise preserved [23, 24]. Furthermore, Yoneyama et al. reported that torsion may represent a compensatory mechanism to maintain an adequate stroke volume and cardiac output in the face of the progressively reduced LV volumes and myocardial shortening associated with hypertension and aging among individuals without cardiovascular disease in the MESA study [25]. Likewise, the degree to which myocardial segments contract with decreased synchrony can be quantified using CMR tissue tagging and has also been associated with cardiovascular risk factor burden in the absence of frank LV dysfunction of HF symptoms [26].

Therefore, CMR tissue tagging is a robust non-invasive tool for quantifying regional systolic and diastolic myocardial function among patients with stage B HF, regardless of EF.

Late Gadolinium Enhancement Imaging

One of the most common histological features of a failing heart is myocardial fibrosis. Replacement fibrosis (myocardial scar), often reported in the terminal stages of heart failure, has been reported in histological autopsy studies [27, 28]. The pathophysiological mechanisms that lead to this fibrosis are various, with some being acute, as in myocardial infarction [29], and others being progressive and potentially reversible, as in hypertensive cardiomyopathy [30]. Myocardial fibrosis in animal and human studies is associated with worsening ventricular systolic function, abnormal cardiac remodeling, increased ventricular stiffness [31–33], and provides a substrate for ventricular reentrant arrhythmias [34–36].

Gadolinium-based MRI contrast agents can be effectively used for LGE imaging of the heart. These agents rapidly diffuse across the capillary membranes after injection and distribute in the interstitial space without penetrating intact cell membranes, which causes a shortening in T1 relaxation times proportional to the contrast concentration. It has been shown that approximately 10 minutes after injection the equilibrium volume of distribution of gadolinium is higher in necrotic or fibrotic myocardium than in viable myocardium [37]. In other words, the relative concentration of gadolinium per gram of tissue is higher in those areas, causing greater T1 shortening in scarred tissue than in viable tissue. In order to further increase the contrast between normal and fibrotic myocardium, an inversion-recovery magnetization preparation pulse is set to null viable tissue signal (inversion time), so in the final image viable tissue is black and nonviable myocardial tissue is bright white. Specific patterns of enhancement have been associated with some causes of LV HF [38, 39]. Myocardial scar imaging with LGE can identify an ischemic etiology in patients with HF. Based on the pathophysiology of myocardial infarction (MI), patients with CAD are expected to have subendocardial or transmural myocardial scar tissue, with a distribution area corresponding to the vascular bed of an epicardial coronary artery and usually covering more than 5% of the total LV mass. Conversely, patients with non-ischemic cardiomyopathy usually have small focal fibrotic areas or more extensive involvement without segmental localization characteristic for CAD, with different mural presentation (i.e., midwall or subepicardial location; patchy distribution [39]). Some typical patterns of LGE in

ischemic and non-ischemic cardiomyopathy are shown in Figure 3. Therefore, the presence, extent and localization of LGE may distinguish LV dysfunction related to ischemic versus non-ischemic cardiomyopathy..

With respect to cardiomyopathy, it has recently been reported that LGE-CMR provides prognostic information that could be used to define more appropriate therapeutic strategies. In patients with ischemic cardiomyopathy, the presence of LGE and size of the peri-infarct zone (“grey zones”) represent noninvasive CMR parameters that can be used to estimate the risk of adverse outcomes [34, 35, 40]. It is reported that LGE extent predicts regional functional recovery in patients undergoing surgical revascularization, with segments in which more than 50% of its mass is fibrotic related to poor functional improvement after treatment [41]. Current guidelines recommend the use of LGE-CMR in the assessment of myocardial viability [42]. On the other hand, the role of CMR in risk stratification of patients with non-ischemic cardiomyopathy depends on the underlying cause. In patients with DCM, midwall fibrosis determined by CMR is a predictor of the combined end point of all-cause mortality and cardiovascular hospitalization, which is independent of ventricular remodeling or systolic function, and also predicts sudden cardiac death and ventricular tachycardia [43, 44]. In patients with HCM, LGE often reflects regions with decreased myocardial contractility [45] and has been associated with a risk of nonsustained ventricular tachycardia on Holter monitoring [46]. Also, a meta-analysis correlates the presence of LGE with cardiovascular mortality, heart failure death, and all-cause mortality in HCM [47]. In the same way, LGE is significantly and independently associated with adverse cardiac events in patients with cardiac amyloidosis [48, 49].

Additional prognostic value of LGE was recently demonstrated in patients free of any cardiac symptoms. Krittayaphon et al. reported that LGE is the most important and independent predictor for cardiac events in hypertensive patients with known or suspected CAD [50]. Yoon et al. showed that LGE can detect unrecognized MI and may improve the risk stratification of diabetic patients with no coronary artery disease history, normal ECG, and normal LV systolic function [51]. The clinical significance of LGE also offers potential targets for new therapeutic strategies designed for the purpose of personalizing medical management, although such paradigm requires further development and testing. In this regard, there is a crucial need for LGE-CMR assessment standardization in clinical practice [42].

T1 mapping

The ability of CMR to identify diffuse myocardial collagen content may provide a novel approach to the detection of subclinical disease in at-risk populations. Addressing an inherent limitation of conventional LGE image analysis, which can detect local replacement fibrosis (where signal intensities must be evaluated relative to a reference region of normal myocardium) but not the diffuse interstitial fibrosis, a new cardiovascular magnetic resonance technique called T1 mapping can now noninvasively quantify the myocardial extracellular volume (ECV), reflecting that type of fibrosis [52]. CMR T1 mapping was validated by studies correlating myocardial fibrosis by histological assessment with raw T1 times and ECV [53, 32, 54]. This technique may allow the serial evaluation of diffuse

cellular changes—such as those recognized to occur with aging, hypertension, diabetes, and infiltrative myocardial diseases—as well as the assessment of therapeutic strategies aimed at reducing diffuse myocardial fibrosis.

A T1 map of the myocardium is a parametric reconstructed image, where each pixel's intensity directly corresponds to the T1 relaxation time of the corresponding myocardial voxel. Signal recovery from each myocardial voxel is sampled with multiple measurements after a specific preparation pulse sequence; the associated T1 relaxation time is calculated from these measurements by the combination of all acquisitions.[55]. The most widely used T1 mapping sequence is the Modified Look-Locker Inversion-recovery (MOLLI) sequence described by Messroghi et al. [56, 55, 57, 58]. MOLLI provides high-resolution T1 maps of human myocardium in native and post-contrast situations within a single breath-hold. An example of the MOLLI acquisition and the parametric map calculation can be seen in Figure 4. T1 maps can be obtained at different slice levels, with an average acquisition time of 15 to 20 s (1 breath hold) for 1 T1 map. Figure 5 demonstrate T1 maps at the mid-ventricle level.

It is important to remark that factors other than fibrosis can interfere with the T1 mapping evaluation. Pre-contrast T1 inherently embodies composite signal from both cells and interstitium and varies with water content and may increase in cases of diffuse myocardial fibrosis. After gadolinium-based contrast administration T1 is dominated by and is inversely proportional to the concentration of gadolinium, so its value is more related to the interstitium volume in a given voxel While pre-contrast T1 varies with field strength and water content, post-contrast T1 times also varies due to gadolinium dose, clearance rate, time post bolus, body composition, and hematocrit [59]. If the change in T1 pre-contrast and post-contrast is measured in both blood and myocardium after the contrast reaches a dynamic steady state, the partition coefficient can be calculated. ECV is derived from the adjustment of the partition coefficient by the blood volume of distribution (1-hematocrit). Flett et al. validated a robust and fully quantitative CMR measure of the ECV that correlates highly with the collagen volume fraction in human myocardium ($R^2 = 0.8$) [53]. ECV is less sensitive to confounding factors such as heart rate, body composition, renal clearance variability, and field strength and seems to be more suitable to clinical use [59].

The utility of T1 mapping is increasingly reported across the spectrum of cardiology. Messroghli et al. reported that pre-contrast and post-contrast T1 values enable the detection of acute and chronic myocardial infarction [56, 58]. Iles et al. showed that T1 mapping identifies changes in myocardial T1 times in heart failure [32]. It has recently been reported that ECV and the partition coefficient quantification have a low variability across scans and could be a viable measurement for evaluating clinical outcome [60]. The utility of ECV measurement is increasingly being reported across the spectrum of cardiology [61], and new data show that ECV, in unselected patients, predicts outcomes at least as strongly as left ventricular ejection fraction [62]. Wong et al. reported that diabetes is associated with increased ECV [63]. ECV detects amelioration of extracellular matrix associated with blocking of the renin-angiotensin-aldosterone system, and is associated with mortality and/or incident hospitalization for heart failure in diabetic patients [63].

The emergence of T1 mapping further improves our knowledge and clinical assessment of myocardial diffuse fibrosis and further refines the information provided by LGE-CMR. It might help us to better stratify much larger and lower cardiovascular risk patient populations, by detecting subclinical myocardial changes before onset of diastolic and systolic function.

Conclusions

CMR is a powerful and unique diagnostic tool that can be used to determine the subclinical myocardial changes that causes developing HF. While LGE imaging is an more common technique in clinical practice, there is increasing evidence that measurements such as myocardial tagging and T1 mapping can be used for prognostic value and assessment of therapy, but more information are still needed from epidemiologic studies and randomized trials to establish these methods as tools in everyday clinical practice to improve identification of individuals with subclinical dysfunction. Especially the combination of these methods can provide a comprehensive and complete assessment of heart. Ongoing developments in technology, imaging techniques, and analytical tools used to implement CMR will likely further advance current capabilities for performing sophisticated analyses for detecting myocardial disease. As such, CMR is likely to continue playing an important role in improving the diagnosis and management of patients at risk for HF.

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Figure 1.

Short axis tagging at the mild ventricular level covering the cardiac cycle (A–F). Tagging is applied upon detection of QRS complex at end diastole (A). Tag lines follow the myocardial deformation during systole (B, C, and D) and relax in diastole (E,F). Fading of tag lines occurs near end diastole (F) due to T1 tissue relaxation.

Figure 2. Tagged cardiovascular magnetic resonance imaging study with a sample circumferential strain curve using Harmonic phase (HARP) software.

Figure 3.

Examples of some hyperenhancement patterns in late gadolinium enhancement imaging.

The arrows point the main areas of scar. Ischemic: A - subendocardial; B - transmural.

Nonischemic: C, D, and E - midwall, F - diffuse. Note that enhancement of ischemic cardiomyopathy always involves the subendocardium; it is consistent with the perfusion area of an epicardial coronary artery, in these examples the left anterior descending. The midwall patterns are unspecific and can be found in idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy, myocarditis, sarcoidosis, Chagas disease and Anderson-Fabry disease. The diffuse pattern is consistent with infiltrative disease like cardiac amyloidosis.

Figure 4.

T1 maps construction and T1 recovery graph after contrast administration.

T1 map after 15 min of gadolinium administration in an inferior infarct case. This is the Modified Look-Locker Inversion Recovery Sequence that uses 17 heart-beats to reconstruct 11 images with different inversion times during mid-diastole. It is necessary to combine all images to generate the final T1 map. For that, it is necessary to apply algorithms to define the best fitting curve over the 11 acquired initial voxels linking for the same location. Those fitting algorithm are very sensitive to motion and image quality/artifacts. The result is a T1 map imaging where the T1 time for the global or segmented left ventricle can be assessed. Reprinted with permission from Mewton et al.[64].

Figure 5.

T1 maps of the myocardium at the mid-ventricular short-axis level in a healthy volunteer.

(A) Pre-contrast, (B) post-gadolinium contrast at 12min with MOLLI sequence. Left panels are conventional T1 maps and right panel are corresponding color maps.