Cardiac Magnetic Resonance Visualization of the Myocardial Microstructure in Non-Ischemic Cardiomyopathies

Yun Tang1, Xuan Ma1, Zhixiang Dong1, Xingrui Chen1, Shujuan Yang1, Xiuyu Chen1, Kai Yang1 and Shihua Zhao1

1Department of Magnetic Resonance Imaging, Fuwai Hospital, National Center for Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Received: 30 March 2024; Revised: 7 June 2024; Accepted: 29 June 2024

Abstract
Cardiac magnetic resonance (CMR), a non-radiation based type of examination, can achieve the simultaneous comprehensive multi-parameter, multi-plane, and multi-sequence evaluation of the anatomical structure of the heart; and at the same time, determine systolic and diastolic function, and blood perfusion and tissue characteristics. Traditional late gadolinium enhancement imaging based on CMR reflects focal replacement fibrosis, in contrast to normal myocardial signal intensity, but cannot effectively identify diffuse myocardial fibrosis. T1 mapping and its derived extracellular volume fraction can be used to quantitatively analyze the extracellular space in myocardial tissue and evaluate diffuse myocardial interstitial fibrosis that is invisible to the naked eye. Diffusion tensor imaging reveals the direction of cardiomyocyte aggregates by quantifying the anisotropy of water molecule diffusion, and can be applied to evaluate the integrity of myocardial tissue and arrangement structure of myocardial microstructural characteristics. On the basis of the micro-motion of myocardial tissue, feature tracking analysis decomposes myocardial deformation into three dimensions of micro-mechanical changes, and can identify early systolic and diastolic dysfunction before heart enlargement or ejection fraction reduction. This Commentary discusses current research advances in these new techniques, as well as their clinical application prospects and limitations for non-ischemic cardiomyopathies.

Introduction
Cardiomyocytes, fibroblasts, vessels, nerves, and the surrounding supporting collagen matrix constitute the heart. Myocardial fibrosis—excessive deposition of activated fibroblasts and myofibroblasts—as well as remodeling of the myocardial microstructure, which is fundamental to maintaining myocardial structure and function, are common responses of the body to a series of pathological and physiological states [1]. A variety of non-invasive imaging modalities can detect the extent and pattern of myocardial scarring. Cardiac magnetic resonance (CMR) provides innovative sequences and excellent soft-tissue contrast, and is completely non-invasive. Consequently, CMR enables comprehensive assessment of the type and severity
of myocardial fibrosis and disease prognosis. In recent years, rapid advances in tissue characterization have played essential roles in disease diagnosis, risk stratification, and treatment guidance, and have led to the concept of imaging mimicking pathology [2].

However, conventional CMR imaging assesses myocardial replacement fibrosis and cardiac morpho-functional changes primarily from a macroscopic perspective, without identifying micropathological and mechanical changes in myocardial tissue. These problems may be addressed by emerging multimodal CMR imaging technologies, such as T1 mapping, extracellular volume (ECV), diffusion tensor imaging (DTI), and feature tracking (FT), which can be used to evaluate the micro-remodeling of cardiovascular diseases in vivo. This Commentary considers state-of-the-art advances in microscopic detection of fibrosis and other myocardial characteristics by using new CMR technologies, including their clinical applications in cardiovascular diseases, particularly in non-ischemic cardiomyopathies (Table 1 and Figure 1).

**Pathology**

The myocardial microstructure, a continuous network-like complex composed of multiple cardiomyocytes and their surrounding collagenous matrix, is essential to myocardial maintenance of structure and function [3]. Myocardial microscopic remodeling, including diffuse interstitial fibrosis, perturbed cardiomyocyte arrangement, and diminished atrial micromechanics, is a key pathophysiological underpinning of these microstructural and functional alterations, which have important roles in the development of clinical phenotypes and changes in disease risk. The onset of microscopic remodeling precedes macroscopic remodeling of the heart. Histopathological examination is an important tool for assessing myocardial fibrosis and other micro-remodeling, and usually requires right ventricular endomyocardial biopsy or autopsy. However, these techniques are invasive, yield limited samples, and have high false-negative rates, thus severely limiting their clinical applications.

---

**Table 1** Detection of Myocardial Microstructure Through Novel Magnetic Resonance Technologies.

<table>
<thead>
<tr>
<th>Target</th>
<th>Diagnosis</th>
<th>Risk stratification</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGE</td>
<td>Replacement fibrosis</td>
<td>Positive or negative</td>
<td>Existence, extent, and pattern; guiding revascularization and the use of implantable cardioverter-defibrillators</td>
</tr>
<tr>
<td>T1 mapping/ECV</td>
<td>Interstitial fibrosis</td>
<td>Early identification of diffuse interstitial fibrosis</td>
<td>Positive or negative; location, extent, and pattern; monitoring of myocardial disease processes and the efficacy of cardiac therapies</td>
</tr>
<tr>
<td>DTI</td>
<td>Microstructural organization characteristics</td>
<td>Preclinical dynamic characterization of myocardial microstructural changes</td>
<td>Positive or negative; location, extent, and pattern; monitoring of myocardial disease processes and the efficacy of cardiac therapies</td>
</tr>
<tr>
<td>FT</td>
<td>Microstructural remodeling</td>
<td>Assessment of diastolic function of the myocardium in the longitudinal, circumferential, and radial directions</td>
<td>Positive or negative; location, extent, and pattern; monitoring of myocardial disease processes and the efficacy of cardiac therapies</td>
</tr>
</tbody>
</table>

Table 1 Detection of Myocardial Microstructure Through Novel Magnetic Resonance Technologies.

<table>
<thead>
<tr>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to identify subtle and diffuse interstitial fibrosis</td>
</tr>
<tr>
<td>Particular in early-stage patients with negative LGE, no obstruction, mild hypertrophy, and/or preserved EF</td>
</tr>
<tr>
<td>Poorer stability and repeatability than LGE; inconclusive normal reference values</td>
</tr>
<tr>
<td>Long scanning times; susceptibility to cardiac motion artifacts</td>
</tr>
<tr>
<td>Inconclusive normal reference values</td>
</tr>
</tbody>
</table>
Myocardial fibrosis can be induced by a series of pathological conditions [1]. The resting fibroblasts are activated by the pathological conditions and transformed into myofibroblasts, which synthesize extracellular matrix (ECM). Excessive expansion and deposition of ECM, a condition known as myocardial fibrosis, leads to structural disorders and diastolic dysfunction [1]. Myocardial fibrosis is usually divided into two types: replacement fibrosis and interstitial fibrosis.

Replacement fibrosis, a secondary change arising from the apoptosis or necrosis of cardiomyocytes due to a variety of causes, is observed to be localized and densely distributed within pathological specimens. Replacement fibrosis is currently considered an important substrate for the development of heart failure (HF) and malignant arrhythmias, and is irreversible. Interstitial fibrosis, in contrast, is considered a hallmark of the early stages of the disease, and is associated with widespread and chronic myocardial injury. Interstitial fibrosis shows a diffuse distribution in the myocardium; although it can also progress to irreversible replacement fibrosis, it can potentially be reversed after elimination of the causative agent, thus leading to subsequent recovery of myocardial function.

Currently, late gadolinium enhancement (LGE) derived from CMR imaging serves as the gold standard for evaluating myocardial viability and represents the most effective non-invasive, in vivo method for assessing replacement fibrosis: the pattern and extent of enhancement are important in disease prognosis and risk stratification [4–7].

In non-ischemic cardiomyopathies, LGE imaging can also be used to identify areas of scar tissue, which may indicate underlying critical diagnostic and prognostic information [4, 6, 7]. Additionally, LGE sequences can monitor the efficacy of cardiac therapies, such as detecting microvascular obstruction after myocardial reperfusion therapy and assessing recurrence risk after surgical valve replacement [8, 9].

The extent and specific pattern of LGE are associated with adverse outcomes, and can be used to further stratify the risk of SCD in patients with non-ischemic cardiomyopathy [4, 5].

As LGE has become more widely used, its limitations have gradually emerged: first, the use of gadolinium-based contrast agents has limited its use in some populations; second, LGE cannot identify subtle, diffuse interstitial fibrosis; and third, approximately half of all patients with HCM have no LGE on CMR, and a negative LGE cannot exclude the risk of interstitial fibrosis [10]. The newly developed T1 mapping technique overcomes these difficulties and can directly measure the T1 value of myocardial tissue, displayed as unit pixels. More importantly, it can quantitatively assess the biological properties of the myocardium locally or as a whole. This method is much more sensitive and objective than traditional qualitative methods. In addition, on the basis of T1 mapping imaging before and after contrast injection, the ECV, i.e., extracellular interstitial volume as a percentage of the whole myocardial tissue volume, can be calculated. Because interstitial fibrosis is a major factor in increased extracellular volume, ECV is considered a more direct parameter reflecting interstitial fibrosis and is highly correlated with the results of pathological biopsies [11].

In recent years, T1 mapping and ECV have been progressively studied to confirm the ability to assess interstitial fibrosis, and have been found to be independent predictors of SCD. Changes in native T1 are independently associated with mortality, and serial native T1 measurements can be used to track the cardiac treatment response [12]. The T1
mapping technique may potentially be an essential tool for early identification of myocardial fibrosis, particularly in early-stage patients with negative LGE, no obstruction, mild hypertrophy, and/or preserved ejection fraction (EF). Although such patients are classified as having low risk according to traditional methods, the development of myocardial microscopic remodeling cannot be identified, corrected, and reversed in a timely manner because of a lack of early and sensitive predictive indicators. Consequently, the risk of major adverse cardiovascular events (MACE) persists and cannot be ignored.

**DTI: Targeting Microstructural Organization Characteristics of the Myocardium**

The DTI technique quantitatively evaluates the anisotropy of water molecule dispersion (i.e., tissue inhomogeneity dispersion characteristics) within each voxel through the dispersion tensor, which indirectly reflects the integrity of cardiomyocyte aggregates and their alignment changes. The reliability of this method has been confirmed through both in vitro tissue and in vivo imaging experiments; this method therefore provides a new imaging tool for non-invasive, in vivo, dynamic characterization of myocardial microstructural changes (Supplementary material online) [3]. Under normal circumstances, the DTI shows a change in the helix angle from positive to negative from the subendocardial layer to the subepicardial layer. In particular, the normal arrangement of myocardial fibers drives the myocardial rotation and torsion during ventricular contraction, thereby maintaining normal ventricular function [13].

DTI-based CMR imaging has tremendous promise in the field of HCM, by providing a non-invasive, in vivo method for early detection, characterization, and risk stratification of myocardial microstructural changes. This modality not only can identify myocardial microstructural changes in HCM but also is expected to have important value in early HCM diagnosis and prognostic assessment, particularly by detecting cardiomyocyte hypertrophy and disordered arrangement in the subclinical stage before myocardial hypertrophy. These findings have unique implications for the early identification and further risk stratification of HF and fatal arrhythmias due to HCM. By detecting myocardial microstructural changes in the preclinical stage, DTI allows for early HCM intervention and management, and may potentially improve patient outcomes. However, DTI-based CMR is currently not routinely used in clinical practice because of limitations in scanning time and susceptibility to cardiac motion artifacts. Moreover, the sample size of available studies is limited, and more active exploration remains necessary.

**CMR-FT: Targeting Microstructural Remodeling of Myocardial Mechanics**

The FT technique of CMR based on cine sequences overcomes prior limitations in assessing the diastolic function of the myocardium from a macroscopic or indirect perspective. This method can assess the diastolic function of the myocardium in the longitudinal, circumferential, and radial directions. The main parameters measured by this technique are the degree and rate of end-systolic relative to end-diastolic deformation, i.e., the strain and strain rate, as well as the torsional and asynchronous myocardial motion.

Diastolic dysfunction stands as a pivotal characteristic of HCM, serving as a crucial foundation for the progression of HF. HF with preserved EF is the main manifestation of HF in patients with HCM, and some of these patients may develop systolic dysfunction secondary to HF with reduced EF, or even irreversible end-stage HF. However, current assessment of diastolic function is based primarily on the comprehensive diagnosis of multiple indirect ultrasound indexes, and its insufficient sensitivity and high operator variation limit its clinical application. Moreover, this method fails to achieve early, direct, and accurate identification of diastolic motion abnormalities in HCM.

With the widespread use of CMR-FT, the extent of micro-functional alterations in myocardial disease and their relationship to traditional imaging, serological, and pathological markers are being recognized. Myocardial strain has independent relationships with clinical outcomes in various
non-ischemic cardiomyopathy, and plays an important role in prognosis evaluation and risk stratification. Ventricular and atrial strain parameters can be used to detect diastolic dysfunction before changes in volume and clinical parameters are observed, and are independent predictors of MACE [14, 15].

Other State-of-the-Art Imaging Methods

Many other state-of-the-art imaging methods can detect myocardial microstructure, particularly coronary microvascular dysfunction. The integration of various methods and multimodal analysis also warrant further investigation. A recent study has indicated that myocardial contrast echocardiography, a non-invasive, bedside and inexpensive technique, can be used for early evaluation of coronary microvascular dysfunction, thereby providing useful information for subsequent treatment methods and prognostication [16]. Given CMR’s high cost and complicated procedures requiring special training, Zhao et al. have used machine learning based on electrocardiogram and vectorcardiogram data to explore and identify myocardial ischemia, as well as one of its important causes, coronary microvascular dysfunction [17, 18]. To overcome the limitations of invasive measurement, index of microcirculatory resistance-based computational fluid dynamics simulation has shown promise in estimating the hemodynamics of coronary artery disease and coronary microcirculatory dysfunction [19, 20].

Conclusion

CMR provides a multimodal, large-scale magnetic resonance assessment system based on LGE and new technologies such as T1 mapping, ECV, DTI, and FT, to assess the four aspects of myocardial replacement fibrosis, interstitial fibrosis, cardiomyocyte aggregate microstructural characteristics, and myocardial mechanical remodeling, respectively. This method enables not only early identification of myocardial tissue and functional alterations, but also dynamic tracking of the developmental process of cardiac and myocardial diseases. Therefore, the method may become a key technology for improving and constructing prognostic models, and guiding clinical interventions.

In the future, we expect that further explorations will characterize myocardial micro-remodeling through multimodal CMR imaging, while performing feature extraction and model construction with the help of artificial intelligence to screen for early warning indicators correlating with MACE; further optimize risk prediction models for myocardial diseases; and provide new targets for early screening and effective intervention in high-risk patients.

Acknowledgments

This study received funding from the National Key R&D Program of China (Nos. 2021YFF0501400, 2021YFF0501401, and 2021YFF0501404) and the Key Project of the National Natural Science Foundation of China (No. 81930044).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Material

Supplementary material for this paper can be found at the following link: https://cvia-journal.org/wp-content/uploads/2024/07/Supplementary_material-002.pdf.

REFERENCES

3. Nielles-Vallespin S, Khalique Z, Ferreira PF, de Silva R, Scott AD,


