

## Imaging Diastolic Dysfunction with Cardiovascular Magnetic Resonance

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### ABSTRACT

Heart failure with preserved ejection fraction (HFpEF) has high prevalence involving up to 55% of all patients with congestive heart failure. Cardiac imaging modalities play a central role in the evaluation of systolic and diastolic function, which is crucial in the diagnosis and management of HFpEF. Cardiovascular magnetic resonance (CMR) imaging has emerged over the last years and currently represents the gold standard in the quantification of systolic function. Its role in the characterization of diastolic function has not equally been established. Historically available techniques for diastolic function quantification such as myocardial tagging remain relatively time consuming, thereby limiting their clinical applicability. Recent advances in deformation quantification based on myocardial feature tracking from routine clinical standard sequences allow for easy and quick quantification of ventricular and atrial physiology. This report aims to review available CMR modalities for the evaluation of diastolic dysfunction including the latest advancements in the field with an emphasis on their potential future role and clinical implications.

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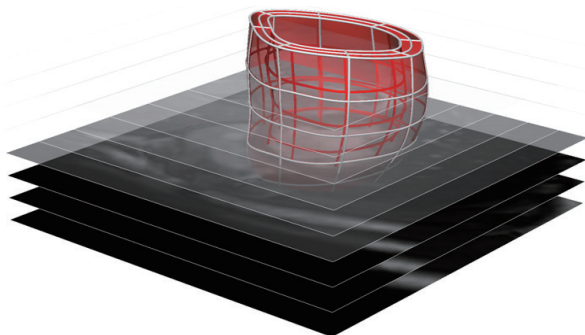
**Key words:** Cardiovascular magnetic resonance imaging; Diastolic dysfunction; Heart failure with preserved ejection fraction; Myocardial feature tracking; Fractional area change; Left atrial contractile function

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### INTRODUCTION

With the ageing population and the concomitant change of the compound of risk factors heart failure with preserved ejection fraction (HFpEF) has increased in prevalence and has developed into a major health problem in the western world<sup>[1,2]</sup>. Today, HFpEF accounts for up to 55% of all patients with congestive heart failure<sup>[3,4]</sup>. Studies investigating patients hospitalized for heart failure reasons documented that the prognosis associated with HFpEF is similar to that associated with heart failure with reduced ejection fraction with only a minimal mortality difference between both groups<sup>[2-5]</sup>. According to current consensus statements<sup>[6]</sup>, the diagnosis of HFpEF requires the presence of three obligatory conditions: (1) presence of signs or symptoms of congestive heart failure; (2) presence of normal or mildly abnormal left ventricular (LV) systolic function; and (3) evidence of diastolic LV dysfunction. Cardiac imaging modalities therefore have a central role in the diagnosis of HFpEF with a clear need for easy and comprehensive non-invasive imaging techniques.

An impaired diastolic ventricular filling can be caused by three mechanical factors: a decreased relaxation capability of myocytes, an increased stiffness of the ventricular wall, or an impaired atria-ventricular conduction of blood flow. Current diagnostic guidelines are based on surrogates of these mechanisms, captured by invasive catheterized blood pressure sensors, blood tests or echocardiography<sup>[6]</sup>. A direct assessment of tissue stiffness is feasible with a proper analysis of the relationship between pressure and imaging data<sup>[7]</sup>, and recent advances in computational techniques have enabled to decouple the combined effects of stiffness and decaying active tension from CMR<sup>[8]</sup>, see figure 1. Nevertheless,



**Figure 1** Computational analysis of CMR for the assessment of diastolic biomarkers, where mathematical models of geometry and mechanical function are used to interpret the data of deformation and pressure. This figure illustrates the personalization of a mechanical computational mesh of the left ventricle to a stack of short axis slices using a previously described automatic method<sup>[9]</sup>.

these more accurate methodologies rely on invasive pressure recordings.

Currently, echocardiography represents the imaging modality of choice to evaluate and to grade diastolic function including a wide range of corresponding technical approaches<sup>[6,9]</sup>, but has some limitations regarding systolic function assessment<sup>[10,11]</sup>. On the other hand, cardiovascular magnetic resonance (CMR) imaging has developed into the gold standard for volumetric quantification of systolic function<sup>[10,12]</sup>. In contrast, the role of CMR in the evaluation of diastolic dysfunction is less-well established in clinical routine. Several innovative CMR imaging techniques including tissue phase-contrast<sup>[13]</sup>, elastography<sup>[14]</sup>, MR spectroscopy<sup>[15]</sup>, displacement encoding with stimulated echoes (DENSE)<sup>[16]</sup> and strain encoded imaging (SENC)<sup>[17]</sup> have been introduced with a potential use in the diagnosis of diastolic dysfunction. However, practical obstacles, e.g. the need for additional sequence acquisition, time-consuming post-processing and image analysis limit their clinical applicability at the present time. Recently, novel techniques have been introduced that may allow for a reliable and less time-consuming evaluation of diastolic function based on clinically available standard cine sequences. This report aims to review the potential of diastolic function assessment with CMR with an emphasis on novel CMR techniques that enable an easy and quick evaluation of diastolic function from routinely available standard steady-state free-precession (SSFP) cine CMR images.

## CONVENTIONAL CMR IMAGING TECHNIQUES

### Mitral inflow and pulmonary venous flow

Phase-contrast MR or velocity-encoded flow quantification can be employed at any arbitrary location within the chest and therefore has the ability to evaluate mitral inflow and pulmonary venous flow patterns. The technique is based on moving spins that acquire a shift in their phase of rotation while moving along a magnetic field gradient. Assuming that linear magnetic field gradients are applied, this phase shift is proportional to the velocity of moving spins<sup>[18,19]</sup>. Typically, retrospective ECG-gating is used to cover the entire heart cycle. Data acquisition can be performed with either breath-hold or free-breathing techniques.

For the evaluation of mitral inflow, the acquisition plane is typically placed perpendicular (through-plane acquisition) to the flow direction at the position of the mitral valve at end-systole. A circular region of interest is placed at the center of the mitral valve orifice

to quantify transmitral flow profiles. Similarly to echocardiographic pulsed-wave Doppler examination, the analysis results in the quantification of early (E) and atrial (A) peak filling velocities. The E/A ratio and the deceleration time of the E peak filling velocity can be used to classify different grades (I-III) of diastolic dysfunction<sup>[6,9]</sup>. Increased E/A ratio and decreased deceleration time is associated with worsening of diastolic dysfunction and presents a strong prognostic marker for major cardiac events and mortality<sup>[20]</sup>. Although acceptable correlation was found between Doppler and phase-contrast MR studies, the cutoff values cannot be used interchangeably for both techniques. Due to the lower temporal resolution of phase-contrast MR, velocities tend to be underestimated when compared to Doppler echocardiography<sup>[21]</sup>. Recently, real-time flow MRI methods with higher temporal resolution have been developed but need to be validated with regard to mitral inflow<sup>[22]</sup>.

The pulmonary venous inflow pattern also affects LV diastolic function. Through-plane flow, typically with an imaging plane positioned 0.5 cm or further into the upper pulmonary vein<sup>[9]</sup>, can be utilized to evaluate the pulmonary venous flow by looking at characteristic wave forms: S, D and A; where S (systole) depends on LA relaxation and LV systolic function, D (early diastole) depends on LV relaxation and myocardial stiffness and A (end-diastole) on LA contractile function and myocardial stiffness.

### Left atrial size

LV diastolic dysfunction directly influences the left atrium (LA) and causes LA enlargement. LA enlargement can be used as diagnostic parameter both in diastolic dysfunction and overt HFpEF. It further represents a risk factor for major cardiac events and leads to a poorer prognosis in patients with diastolic dysfunction and HFpEF<sup>[23]</sup>. A reliable assessment of LA volume is therefore crucial in clinical routine. CMR constitutes not only a valid alternative to echocardiography but has become the gold standard in the evaluation of atrial volumes<sup>[6]</sup>. Especially, if small changes in LA volumes are expected (e.g. when evaluating progression of disease or follow-up of therapeutic interventions is required) CMR represents the method of choice. LA volume can be assessed by Simpson's volumetric method based on disc summation and therefore requires the acquisition and analysis of short-axis slices covering the entire LA. In clinical routine, the biplane area length method offers a compromise between accuracy and analytical speed. The LA area (A) and anterior-posterior length (L) are measured in 2- and 4- chamber views. LA volume is calculated with the following equation: LA volume (mL) =  $0.85 * A_{2c} * A_{4c} / L$ , where  $A_{2c}$  and  $A_{4c}$  are the LA areas on 2-chamber and 4-chamber views and L is the shorter length of the LA from either the 2-chamber or the 4-chamber views.

### Left ventricular filling curve

The LV filling curve enables accurate assessment of the time varying LV volume change during the cardiac cycle and provides evaluation of peak filling rates, time to peak filling rates and atrial contribution to LV filling<sup>[24,25]</sup>. Diastolic dysfunction is associated with decreased peak filling rates and increased time to peak filling rates. Typically a short-axis stack of cine SSFP images covering the LV is acquired. The technique requires subsequent tracing of the endocardium of typically 250-350 images. Compared with conventional gradient-echo sequences, the image quality of LV short axis views significantly improved with the development of SSFP techniques resulting in a better definition of endocardial borders<sup>[26]</sup>. However, since manual correction remains necessary in the large majority of cases the method remains time-consuming and cumbersome from

a clinical perspective. Clearly, the performance of fully automated segmentation algorithms needs optimization.

### Myocardial tagging

With CMR tagging a radiofrequency pulse is applied to label the myocardium by grid lines. These lines can be tracked throughout the cardiac cycle allowing the calculation of myocardial strain in radial, longitudinal, and circumferential direction. However, this technique has not yet found widespread use in clinical practice, as several challenges regarding technical acquisition and analysis still need to be overcome. A major limitation of myocardial tagging for the assessment of diastolic function is the fading of grid lines over the cardiac cycle which leads to difficulties in the assessment of late diastolic deformation. In a large study population with left ventricular hypertrophy, early diastolic strain rate could be measured in 80% of segments while late diastolic strain rate induced by atrial contraction could be assessed in only 32% of patients<sup>[27]</sup>. Further limitations of myocardial tagging are the requirement to acquire additional sequences and complex analysis both leading to increased examination and post processing time. Furthermore, long breath-hold times limit the clinical application particularly in patients with heart failure.

## NOVEL CMR IMAGING TECHNIQUES

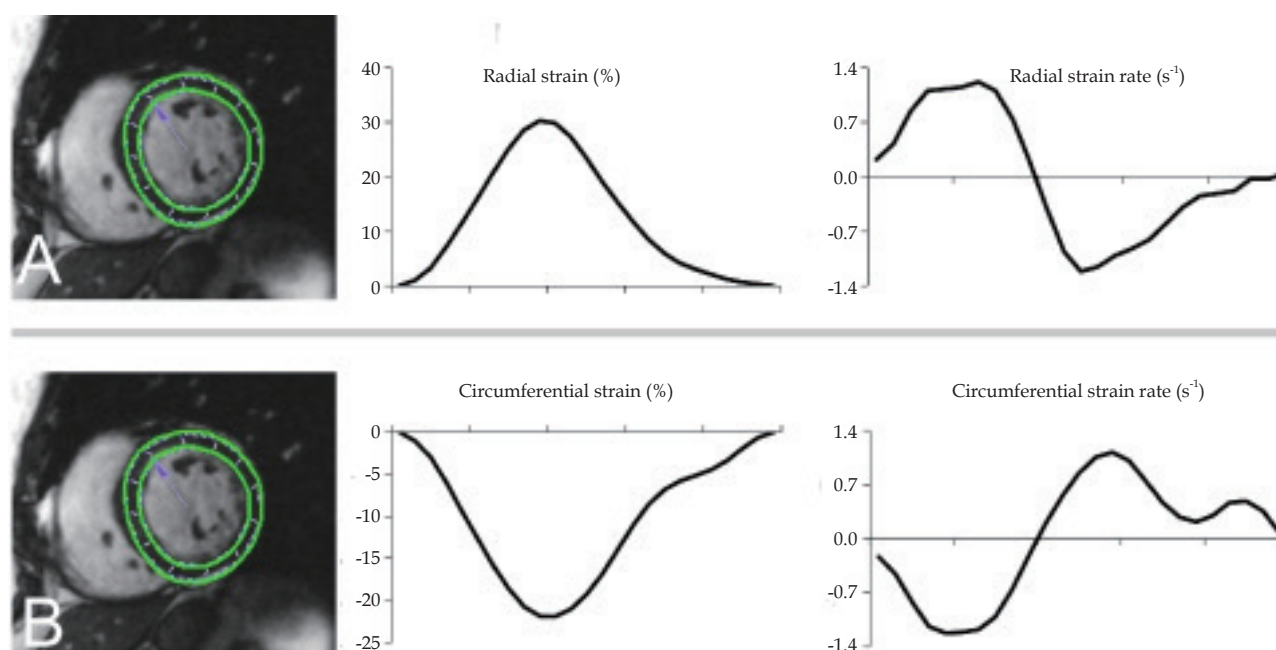
### Myocardial feature tracking

CMR feature tracking (CMR-FT)-a technique analogous to echocardiographic speckle tracking-allows the quantification of myocardial deformation directly from clinical, standard SSFP cine CMR images, without the need to acquire additional tagged images<sup>[28,29]</sup>. A moderate to good agreement of CMR-FT with myocardial tagging and echocardiographic speckle tracking has been demonstrated<sup>[30,31]</sup>. CMR-FT is based on offline software analysis and applicable to both 1.5 T and 3 T magnetic field strengths<sup>[32]</sup>. Whilst its values in patients with systolic dysfunction has been recently described<sup>[33]</sup> there is still a need to investigate its potential role in diastolic function assessment. The software tracks features,

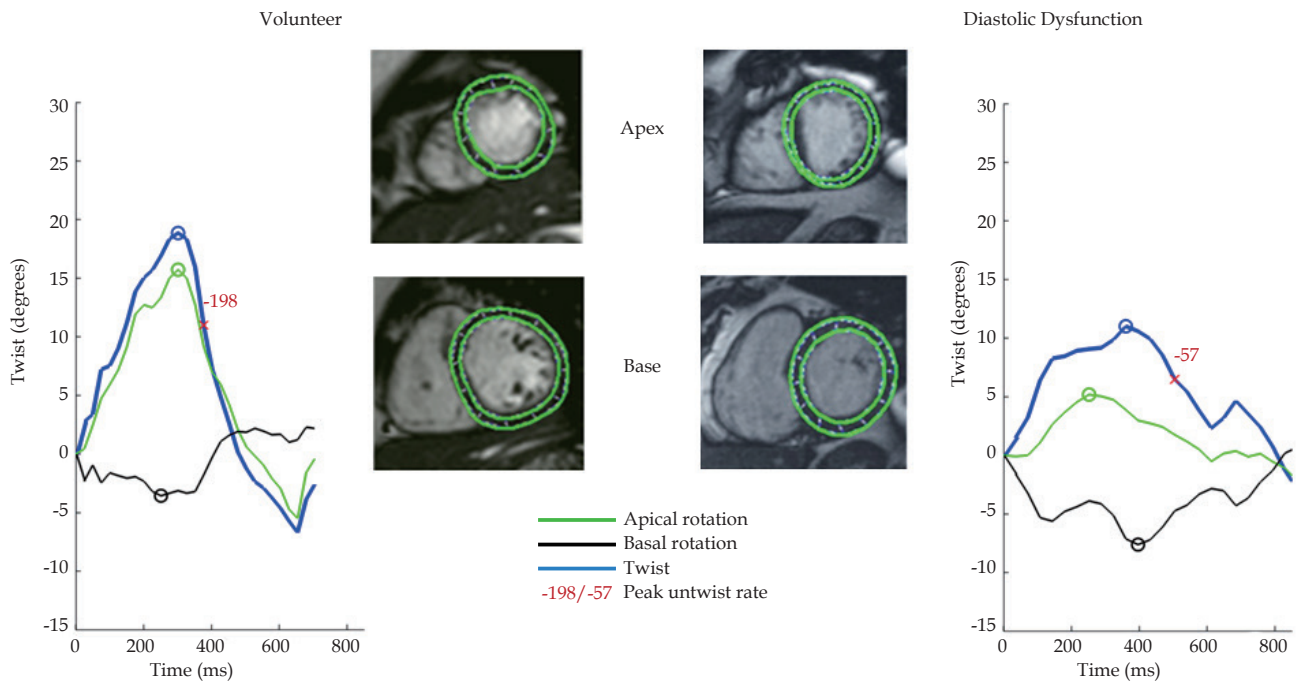
such as the apparent cavity boundary or tissue patterns, related to a predefined contour. The movement of features from frame-to-frame is used to quantify myocardial deformation in the longitudinal, circumferential and radial directions, as well as strain rates (Figure 2), velocity, displacement, twist and untwist (Figure 3)<sup>[34,35]</sup>. Untwisting contributes to LV diastolic relaxation and early diastolic filling<sup>[36,37]</sup>. In contrast to flow velocity and time-volume relations, LV strain rate and untwist rate represent a direct correlate of myocardial diastolic function as measured with speckle tracking echocardiography<sup>[38]</sup> and myocardial tagging<sup>[27]</sup>. Future studies need to elucidate whether or not CMR-FT may deliver similar information in patients with diastolic dysfunction.

Since LA function represents an important parameter in LV diastolic dysfunction pathophysiology, recent studies especially focused on LA dysfunction in HFpEF. An increase in LA afterload caused by elevated LV filling pressures secondary to severe LV diastolic dysfunction has long been considered the main underlying mechanism of LA dysfunction<sup>[39,40]</sup>. However, studies proposed that the degree of elevated LV filling pressures may not fully explain LA failure and that - similar to the LV - LA myocardial fibrosis may contribute to LA dysfunction<sup>[41,42]</sup>. In contrast to myocardial tagging, speckle-tracking echocardiography is able to evaluate LA longitudinal strain and strain rates during late ventricular diastole<sup>[43]</sup>. LA profiles from CMR-FT may deliver similar information and could be used to calculate longitudinal positive strain (corresponding to LA conduit function) and three strain rate (SR) parameters (peak positive SR, early negative SR and late negative SR), corresponding respectively to commencement of ventricular systole, commencement of ventricular diastole and atrial contraction. Echocardiographic speckle tracking demonstrated LA longitudinal peak strain and late negative strain rates to be reduced in HFpEF compared to patients with asymptomatic diastolic dysfunction<sup>[44]</sup>.

The role of CMR-FT in the evaluation of LV longitudinal strain, radial strain, circumferential deformation, twist and untwist and LA strain and strain rates in patients with HFpEF and asymptomatic diastolic dysfunction remains to be investigated.



**Figure 2** CMR myocardial feature tracking. Averaged left ventricular radial strain and strain rate (A) and circumferential strain and strain rate (B) in mid-ventricular short-axis view.



**Figure 3** Twist assessed by CMR myocardial feature tracking in a healthy volunteer (left) and a patient with diastolic dysfunction (right). Global left ventricular twist corresponds to the difference between apical counterclockwise rotation and clockwise basal rotation. Please note the decreased peak untwist rate in the patient with diastolic dysfunction.

### CMR Fractional area change

LV fractional area change (FAC) analysis represents a method to determine LV relaxation indices based on the degree of endocardial area expansion during the first 30% of diastole with minimal efforts from a single mid-ventricular short-axis cine SSFP slice<sup>[45]</sup>. Initial quantitative LV fractional area change results demonstrated good correlation with echocardiographic parameters for the evaluation of LV diastolic dysfunction. However, studies using myocardial tagging showed that the analysis of different slices may yield different results in basal, mid-ventricular and apical orientations<sup>[46]</sup>. The proposed method is therefore limited since it only assesses regional relaxation indices. Therefore FAC should next be explored in multiple cardiac views, including short- and long-axis views to assess global diastolic relaxation parameters. Furthermore, these relaxation indices should be related to clinical parameters and serum markers of diastolic dysfunction such as cardiopulmonary exercise testing or natriuretic peptide levels to better understand their clinical relevance.

### Left atrial contractile function

The increasing relevance of the left atrial function in the pathophysiology of diastolic dysfunction led to CMR studies focusing on the role of LA contractile function. In healthy subjects without diastolic dysfunction passive emptying of the LA during LV diastole contributes up to 75-80% of LV filling, whilst LA contraction normally contributes to about 25%. On the one hand, LA contraction contribution to LV filling increases in mildly impaired relaxation up to 38%<sup>[47,48]</sup>, whereas on the other hand, markedly increased LV filling pressure might cause pseudo-normalization or even decrease of LA contraction with decreased contribution to LV filling to less than 20%<sup>[23,39]</sup>. The evaluation of LA function typically comprises measurements of LA maximum volumes, LA volumes prior to atrial contraction and LA minimum volumes. Volumes can be evaluated using Simpson's disc summation method or, more easily, with the biplane area length method from standard 2-chamber view and 4-chamber view SSFP cine CMR images. Corresponding

volumes allow the estimation of left atrial contractile function due to the calculation of total, passive and contractile LA emptying functions<sup>[24,49]</sup>. Recent studies highlight the relevance of increased LA minimum volumes rather than LA maximum volumes as a correlate of increased left ventricular end-diastolic pressures in patients with diastolic dysfunction<sup>[50,51]</sup>. Decreased LA contractile emptying function quantified by CMR has been shown to be a better predictor of adverse cardiac events and death compared to LA maximum and minimum volumes in patients with suspected diastolic dysfunction with a history of chronic hypertension<sup>[49]</sup>. The relation of quantitative LA contractile function with clinical markers and serum markers of diastolic dysfunction remains to be investigated.

### 4D velocity mapping

Acquisition of blood flow velocity from 4D velocity mapping enables the computation of pressure gradients<sup>[52,53]</sup>, and even the analysis of the relative contribution of the different components of pressure to blood flow dynamics<sup>[54]</sup>. Recent studies demonstrated that intraventricular pressure gradients at late ejection predict an impaired relaxation<sup>[55]</sup>. Even more, imaging methods for the assessment of blood pressure could overcome the need for invasive catheter pressure recordings for the estimation of myocardial stiffness and relaxation<sup>[56]</sup>.

## CONCLUSION

CMR imaging gains an incremental role in the evaluation of diastolic dysfunction. Whilst novel relaxation parameters from CMR-FT may offer more accurate assessment of diastolic function, relaxation indices from CMR fractional area change and a reliable evaluation of left atrial contractile function represent interesting techniques to quantify the amount of diastolic dysfunction present in an individual patient. The presented novel CMR techniques promise an evaluation of diastolic function from clinically standard SSFP cine CMR images and require only minimal post-processing efforts underlining their applicability particularly for clinical routine use. 4D velocity mapping represents a promising approach to assess intraventricular

pressure gradients and might help to characterize impaired relaxation. The role of these techniques in the examination of diastolic dysfunction in HFpEF and patients with asymptomatic diastolic dysfunction however remains to be defined in future prospective clinical investigations.

#### Abbreviations

CMR: Cardiovascular magnetic resonance  
 CMR-FT: CMR feature tracking  
 DENSE: Displacement encoding with stimulated echoes  
 FAC: Fractional area change  
 HFpEF: Heart failure with preserved ejection fraction  
 LA: Left atrium  
 LV: Left ventricle  
 SENC: Strain encoded imaging  
 SR: Strain rate  
 SSFP: Steady-state free-precession sequence

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## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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