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Free-Breathing Simultaneous Cardiac Multi-Parametric Mapping: Technical Developments and Initial Clinical Experience

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1. Introduction

Cardiac magnetic resonance (CMR) parametric mapping has emerged as a promising non-invasive tool for diagnosing various cardiovascular diseases [1]. The commonly used T1 and T2 mapping approaches provide valuable diagnostic information by assessing alterations of myocardial relaxation times [2]. Edema, acute ischemia and necrosis contribute to an elevation of both T1 and T2; while scar and fibrosis result in an increase specifically in T1 values [1, 3-5]. Decrease of T1 is rare, with known causes of Fabry disease and the deposition of iron or fat [3, 6, 7]. In contrast, T1 ρ mapping employs a spin-lock radiofrequency pulse with a low frequency of several hundred Hertz to measure the longitudinal relaxation in a rotating frame. This distinctive methodology endows T1 ρ mapping with sensitivity to variations in macromolecular content [8]. Several studies have demonstrated that T1 ρ is a promising endogenous contrast for detection of focal and diffuse myocardial fibrosis [9, 10]. Compared with native T1, the increase of which is not specifically attributed to fibrosis, T1 ρ may serve as a better biomarker for myocardial fibrosis. However, T1 ρ CMR is challenging, especially for high field scanners, as the conventional T1 ρ preparation module with rectangular tip-down, spin-lock and tip-up pulses is sensitive to B0 and B1 inhomogeneities. We have designed and optimized T1 ρ preparation pulses including the adiabatically excited continuous continuous-wave spin-lock and composite spin-lock [11-13], which are robust to field inhomogeneities, making T1 ρ CMR ready for clinical application.

The combination of multiple parameters holds the potential to improve the diagnostic sensitivity and bolster diagnostic confidence for suspected cardiomyopathy, as these parameters offer complementary insights into the myocardium [2, 14]. For example, by analyzing T2 and T1 ρ together, the myocardial fibrosis index (mFI) [15] can be

derived as the difference of the two parameters, which has been shown to be a better indicator for myocardial fibrosis than T1 ρ in hypertrophic cardiomyopathy [16]. However, conventional mapping techniques measure myocardial parameters individually in separate breath-hold acquisitions and requires dummy cardiac cycles to allow for longitudinal magnetization recovery [17-19]. This practice may result in nonregistered parameter maps, prolonged scanning duration, patient discomfort, and heart rate dependency of parameter estimation.

Simultaneous multi-parametric mapping is an active research area, and numerous techniques have been proposed to improve the efficiency of data acquisition and generate co-registered parameter maps. Most simultaneous multi-parameter mapping techniques focus on cardiac T1 and T2 mapping. Among these methods, magnetic resonance fingerprinting (MRF) stands out by employing transient imaging to generate different signal evolutions for tissues with different parameter combinations and then matching the acquired signal to a simulated dictionary for parameter quantification [20-25]. Although promising, cardiac MRF relies on highly undersampled non-Cartesian trajectories due to ECG-triggering and limited breath-hold duration, which requires complex reconstruction to reduce the influence of aliasing artifacts on dictionary matching. The complex post-processing of cardiac MRF may preclude its wide clinical application. Recently, Henningsson demonstrates the feasibility of single-shot Cartesian acquisition and dictionary matching for simultaneous myocardial T1 and T2 mapping [26]. It only acquires ten time-points along the magnetization evolution and involves simplified post-processing with conventional Cartesian acquisition, and is therefore readier for clinical translation. However, the Cartesian dictionary matching based technique still requires breath-hold. A free-breathing multi-parameter mapping technique is warranted when the patients cannot

hold their breath or the acquisition time exceeds the limit of breath-hold duration.

This article introduces the techniques we recently developed for free-breathing simultaneous myocardial multi-parametric mapping and their initial clinical applications. The joint T2 and T1 ρ mapping technique was based on the conventional exponential model fitting but has been optimized regarding the order of preparation pulses [27]. Following this technique, a more efficient multi-parametric technique based on single-shot Cartesian acquisition and dictionary matching was developed and validated for free-breathing simultaneous T1, T2 and T1 ρ mapping with inhomogeneous B1 correction. To enable free-breathing acquisition, the diaphragm navigator (dNAV) was utilized for real-time slice tracking to correct the through-plane motion during acquisition, while the group-wise multi-contrast registration [29] was adopted to correct in-plane motion after acquisition.

2. Free-breathing joint myocardial T2 and T1 ρ mapping

2.1 Technical developments

The difference between myocardial T2 and T1 ρ , termed as myocardial fibrosis index, has shown to outperform other native parameters in correlating with late gadolinium enhancement in hypertrophic cardiomyopathy [15, 16]. The aim of the joint T2 and T1 ρ mapping technique is to provide co-registered T2 and T1 ρ maps to facilitate the calculation of mFI. The sequence diagram and post-processing steps are presented in Fig. 1. This method comprises seven electrocardiogram-triggered single-shot acquisitions, involving T2 preparation (T2-prep) with three echo times (TE) and T1 ρ preparation (T1 ρ -prep) with four spin-lock durations (TSL) to introduce T2 and T1 ρ sensitization. Furthermore, three dummy heartbeats were interposed between two single-shot acquisitions for signal recovery, resulting in a total acquisition time of 25 cardiac cycles. The parameters for the preparation modules were: T2-prep TEs = [0, 30, 55] ms, T1 ρ -prep TSLs = [2, 16, 30, 50] ms, and the spin-lock frequency was set to 350 Hz. To minimize the impact of incomplete longitudinal relaxation recovery on parameter quantification, the modules with shorter TE or TSL were acquired first. The interleaved acquisition of T2-prep and T1 ρ -prep images also has benefit of reducing misalignment between the T2 and

T1 ρ parameter maps.

To correct respiratory motion and enable free-breathing acquisition, real-time adjustments of the imaging plane were performed utilizing a cross-pair dNAV with an empirical tracking factor of 0.6 [30, 31]. The dNAV was applied before the T2 and T1 ρ preparation to avoid any influence of preparation pulses on the dNAV signal. The slice-tracking with dNAV effectively eliminates through-plane motion during the acquisition, and after acquisition, a group-wise registration approach was employed to correct any in-plane motion and align the multi-contrast images [29]. The T2 and T1 ρ parameter maps were derived by fitting the images to the two-parameter exponential decay model [32, 33], and mFI was calculated as the difference between T1 ρ and T2.

2.2 Clinical applications

All MR exams were performed on the 3T uMR 890 scanner (United Imaging Healthcare Shanghai, China). Figure 2 shows the parametric maps and slice-matched Late Gadolinium Enhancement (LGE) images of two patients: a 71-year-old female patient with myocardial hypertrophy; a 40-year-old male patient with hypertensive cardiomyopathy. For Patient #1, there is LGE in the inferoseptal segment, accompanied by an elevation in T2 values, thereby implying the potential manifestation of edema. Furthermore, the anterior and anterolateral segments also exhibit LGE, where the T1 ρ and mFI are increased, thereby indicating the possible presence of fibrosis. For Patient #2, no LGE is found, while conspicuous increase of T1 ρ and mFI values can be observed across the myocardium, suggesting there may be diffuse myocardial fibrosis in this patient.

3. Free-breathing simultaneous myocardial T1, T2 and T1 ρ mapping

3.1 Technical developments

The joint T2 and T1 ρ mapping technique lacks the quantification of the important parameter of T1 and requires empty cardiac cycle for signal recovery which features low acquisition efficiency. Following the two-parameter mapping technique, we developed a more efficient free-breathing multi-parametric mapping technique (FB-MultiMap) to achieve simultaneous T1, T2 and T1 ρ quantification with inhomogeneous B1 correction in a single acquisition. The framework of the proposed FB-MultiMap is shown in Fig. 3,

which includes the multi-contrast image acquisition with the optimized sequence, multi-contrast image registration, dictionary generation with Bloch simulations and parameter mapping with dictionary matching. FB-MultiMap adopts single-shot Cartesian acquisition with a 2D bSSFP readout. The inversion recovery (IR), T2-prep and T1 ρ -prep pulses are introduced in FB-MultiMap for sensitizing T1, T2 and T1 ρ , respectively.

The precision and accuracy of parameter measurements can be influenced by the configuration of the preparatory pulses [26]. Several candidate sequences were empirically designed and compared in simulations, phantom and in vivo experiments regarding estimation accuracy and precision. The optimized FB-MultiMap sequence is demonstrated in Fig. 3, where the IR pulses are played at the first and the ninth cardiac cycles; T2-preps are played in the fifth to eighth cardiac cycles with durations = [35, 45, 55, 65] ms; T1 ρ -prep with TSLs = [16, 30, 40, 50] ms are played in the 13th to 16th cardiac cycles.

The inhomogeneity of B1, particularly in high-field scanners, if not accounted for, will impact the accuracy of dictionary-based parameter estimations. Hence, besides estimating T1, T2, and T1 ρ , we also measure the B1 factor for correcting the nominal flip angle. Furthermore, a variable flip angle strategy was proposed and optimized to improve sensitization of the B1 factor. Following the optimization of angle combinations, the sequence alters the flip angle after two IR pulses, the initial T2-prep pulse and the initial T1 ρ -prep pulse, and the optimized four flip angles are 45°/35°/70°/50°.

Similar to the free-breathing joint T2 and T1 ρ mapping technique, FB-MultiMap achieved prospective respiratory motion correction by employing dNAV to adjust the imaging plane in real-time [30, 31]. To minimize the influence of the non-selective IR on the signal of the dNAV, a slice-selective IR pulse was incorporated into the sequence, aligning with the imaging position of the dNAV. Moreover, the dNAV was played before the T2-prep and T1 ρ -prep modules to avoid their interference. Subsequently, a group-wise registration method was performed to align all the multi-contrast images [29].

Parametric mapping was performed with dictionary matching, where the subject-specific dictionary was simulated with Bloch equation and the recorded R-wave

intervals and trigger delays for ranges of T1, T2, T1 ρ and B1. In contrast to MRF, where magnetization is modeled for each readout, the Cartesian sampling approach acquired a single image per cardiac cycle, with the primary contrast determined by the central region of k-space. As a result, the construction of the dictionary solely relied on the simulated transverse magnetization corresponding to the center of k-space.

3.2 Clinical applications

The proposed FB-MultiMap has been evaluated in phantoms [28], healthy subjects and several patients with different cardiac diseases. All MR images were acquired on the 3T uMR 890 scanner (United Imaging Healthcare Shanghai, China). Example T1, T2 and T1 ρ maps at three short-axis slices of a representative healthy subject are provided in Fig. 4, where good mapping quality can be observed for FB-MultiMap with no discernable motion artifacts compared with conventional mapping methods and the multi-parametric mapping performed under breath-hold (BH-MultiMap), which is possible in healthy subjects.

Fig. 5 shows the parameter maps of four patients: a 66-year-old male patient with hypertensive cardiomyopathy; a 76-year-old female patient with myocardial hypertrophy; a 31-year-old male patient with Fabry disease; a 62-year-old male patient with chronic renal disease. Except for the patient with renal disease where the administration of gadolinium contrast agent is not applicable, the LGE images were acquired for the three mentioned patients to detect any focal enhancement. For Patient #3, the left ventricle has patchy LGE regions, where increased T1 and T1 ρ values can be observed. For Patient #4, enhancement can be observed in the lateral myocardium, and the lateral T2 and T1 ρ values are higher than the septal region. The T1 values are overall increased as can be observed in both MOLLI and FB-MultiMap, albeit that there is less motion blurring in FB-MultiMap compared with MOLLI. Patient #5 has been diagnosed with Fabry disease, the T1 values of whom is around 100 ms lower than the healthy subjects, while the T2 and T1 ρ values are not obviously differed. Patient #6 has higher myocardial T1 and T1 ρ values compared with healthy subjects, while the T2 values are not elevated.

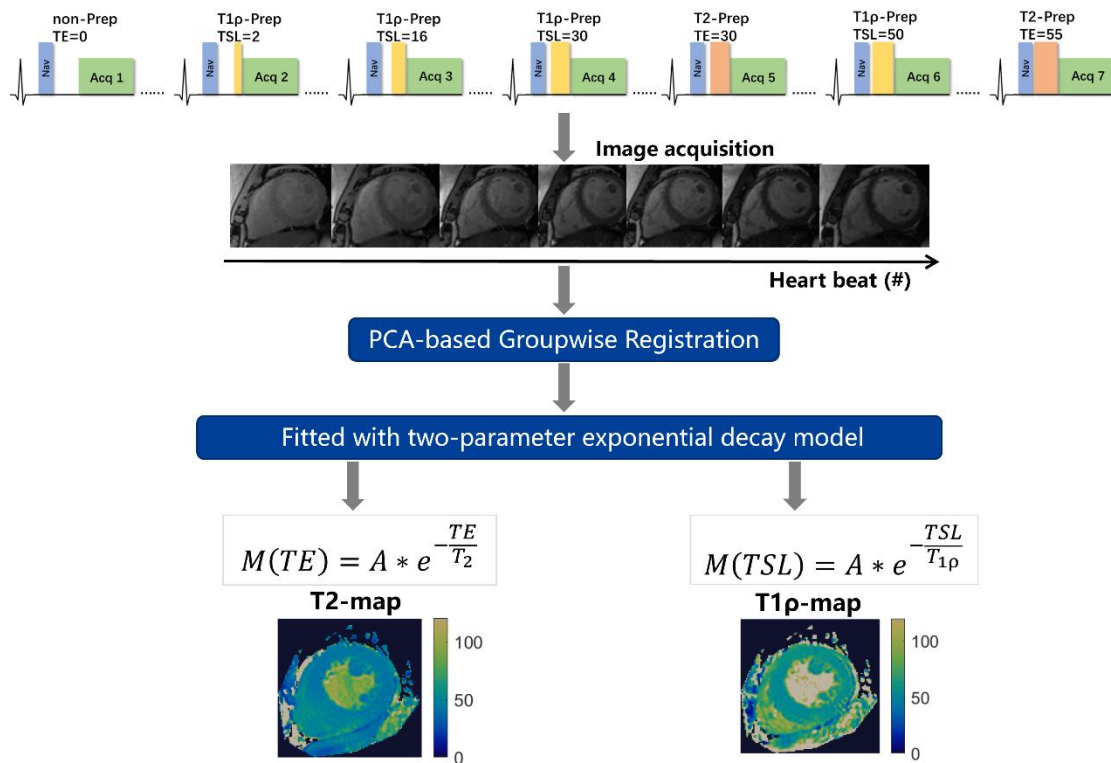


Figure 1. Sequence diagram and post-processing steps of the proposed free-breathing joint myocardial T2 and T1 ρ mapping technique. This sequence has seven ECG-triggered single-shot acquisitions, with three dummy cardiac cycles inserted between two acquisitions for signal recovery, resulting in a total of 25 cardiac cycles. The T2 and T1 ρ prepared images are acquired alternately. dNAV is employed for real-time prospective respiratory motion correction, followed by retrospective in-plane motion correction with group-wise image registration. Subsequently, the acquired images are fitted to the exponential decay model to derive T2 and T1 ρ parameter maps.

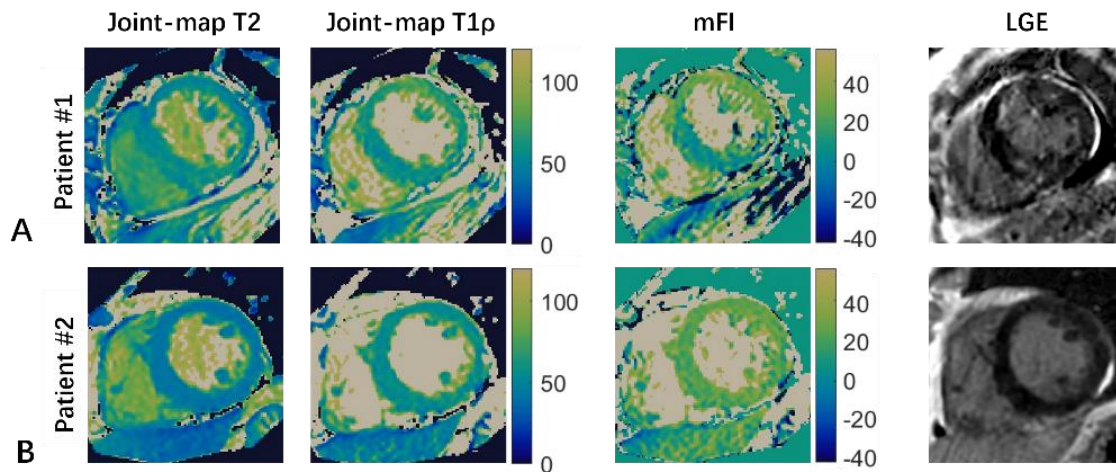


Figure 2. Parameter maps obtained with the joint T2 and T1 ρ mapping method along with the LGE images for two patients. (A) a 71-year-old female patient with myocardial hypertrophy and intramural LGE in the inferoseptal, anterior and anterolateral segments; (B) a 40-year-old male patient with hypertensive cardiomyopathy without focal LGE.

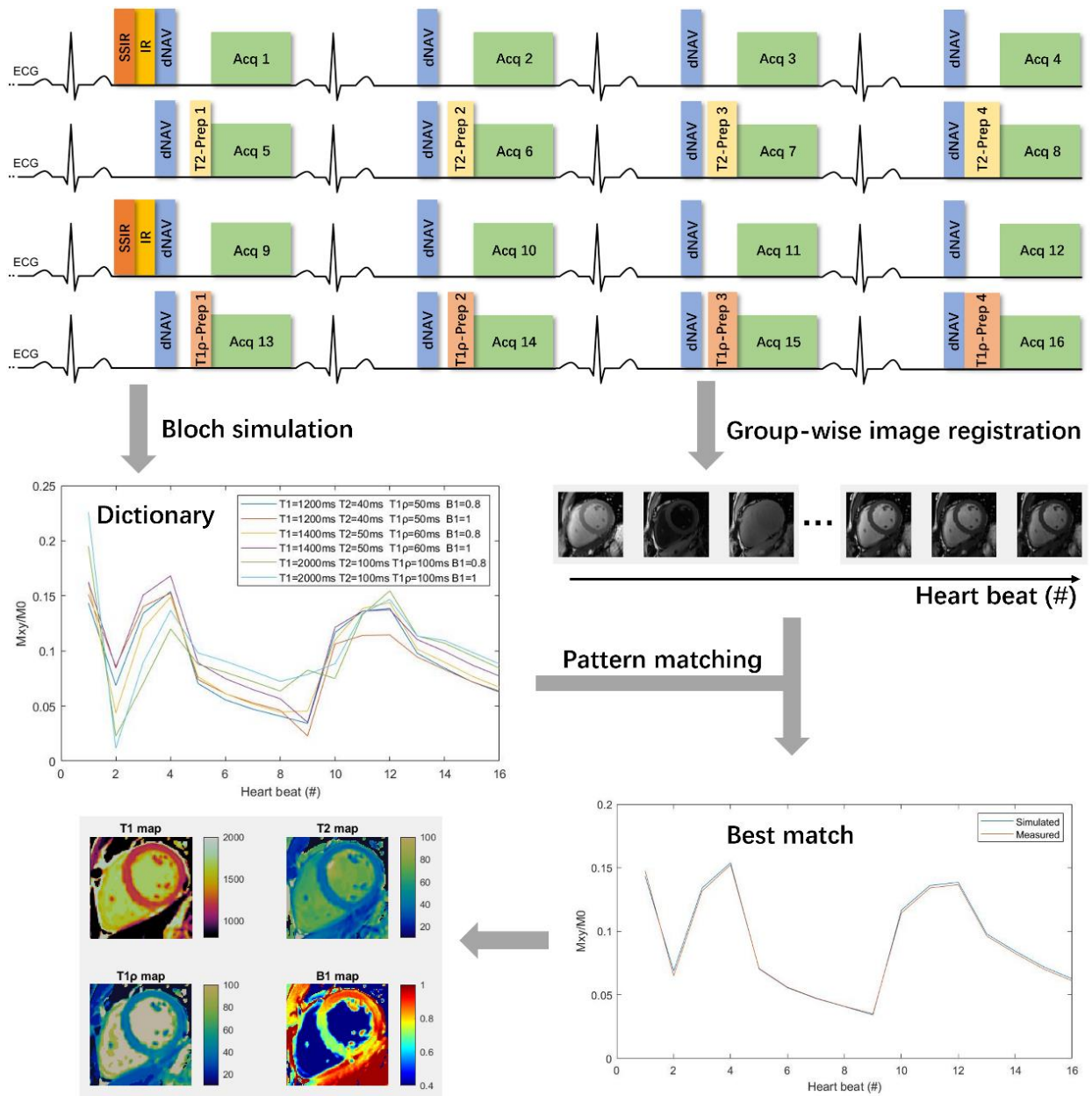


Figure 3. Sequence diagram and post-processing steps for the proposed free-breathing simultaneous myocardial T1, T2 and T1 ρ mapping technique. The sequence involves the ECG-triggered diastolic acquisition of sixteen cardiac cycles using inversion recovery (IR), T2-prep, and T1 ρ -prep pulses to introduce T1, T2, and T1 ρ sensitization. Real-time updates of the imaging plane are performed using dNAV for prospective respiratory motion correction. The slice-selective IR (SSIR) is applied to restore the diaphragm signal. Following image acquisition, retrospective correction of in-plane motion is achieved through group-wise image registration. Subsequently, dictionary matching is performed to find the dictionary entry that best matches the acquired signal at each pixel for T1, T2, T1 ρ and B1 mapping.

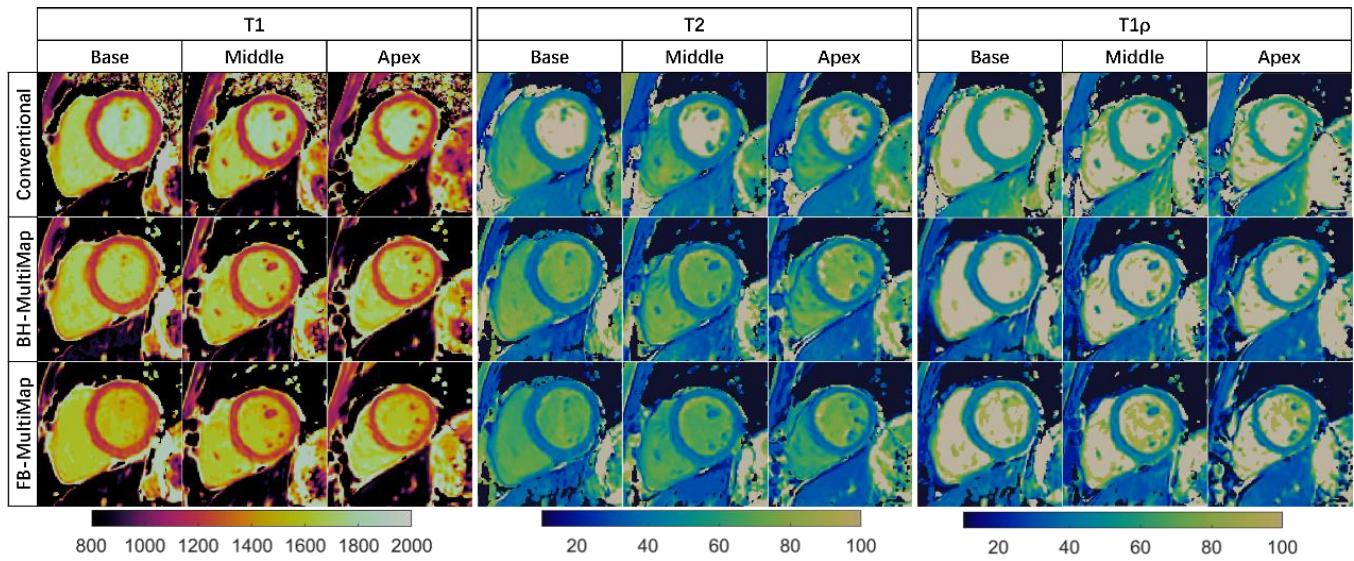


Figure 4. T1, T2, and T1ρ maps measured at three short-axis slices of a typical healthy subject using separate breath-hold mapping techniques including MOLLI, T2-prep, and T1ρ-prep bSSFP, and the proposed multi-parametric mapping technique performed under breath-hold (BH-MultiMap) and free-breathing (FB-MultiMap).

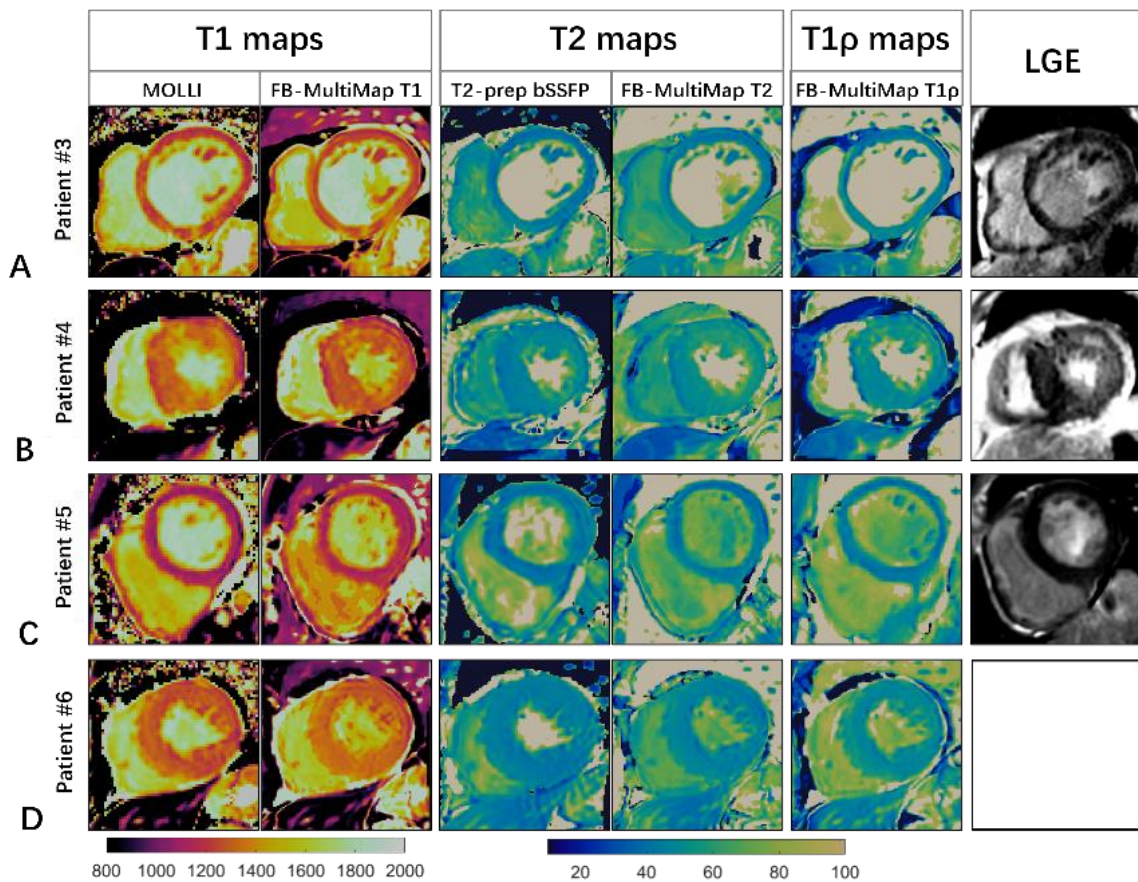


Figure 5. Parameter maps obtained with FB-MultiMap and traditional techniques of MOLLI and T2-prep bSSFP of four patients. LGE images were acquired and shown for three patients with normal renal function. (A) a 66-year-old male with hypertensive cardiomyopathy and patchy LGE; (B) a 76-year-old female patient with myocardial hypertrophy and lateral myocardial enhancement; (C) a 31-year-old male patient with Fabry disease and no obvious LGE; (D) a 62-year-old male patient with chronic renal failure.

4. Discussion and Conclusion

Cardiac MRI has unique capability of characterizing myocardial tissue non-invasively and quantitatively compared with other imaging modalities. The myocardial parameters, including T1, T2 and T1 ρ can reflect different pathological changes, and can be analyzed together to help diagnose complex cardiomyopathies. The clinical value of multi-parametric CMR has been increasingly recognized. However, for estimation of multiple parameters, conventional techniques either measure the parameters individually with separate breath-hold acquisitions, which may result in unregistered parameter maps, or estimate multiple parameters in a prolonged breath-hold acquisition, which may be intolerable to patients. To overcome these limitations, we have been developing free-breathing cardiac multi-parametric mapping techniques. Notably, the proposed FB-MultiMap can generate B1-corrected T1, T2 and T1 ρ maps in single efficient free-breathing acquisition of 16 heartbeats. The pathological alterations detected by FB-MultiMap agree with the conventional separate breath-hold measurements and also exhibit promising correspondence with LGE, which suggests the potential of FB-MultiMap in comprehensive myocardial tissue characterization without contrast agents.

For free-breathing multi-parametric mapping, the most challenging part would be to correct the respiratory motion and mitigate mapping errors caused by motion. As the two techniques introduced in this article, the dNAV was utilized for prospective motion correction by tracking the imaging slice in real time, followed by multi-contrast image registration for retrospective motion correction. The two-step motion correction strategy works well in healthy subjects and the preliminary patients. However, there is still room for improvement. Firstly, a fixed slice-tracking factor was adopted for the dNAV based through-plane motion correction. Adopting a patient- and slice-specific motion model trained in a calibration scan to characterize the heart motion relative to dNAV may help to further improve motion correction. Secondly, registering images with abrupt contrast changes is challenging. The model-based registration method [10, 34] which plug the physical model into the registration process to avoid the registration of different contrasts is worth exploring to improve the retrospective motion correction. Finally, the introduced techniques are for 2D imaging with limited resolution along the slice direction.

The 3D high-resolution free-breathing cardiac multi-parametric mapping techniques are under development.

6. Image/Figure Courtesy

All images are the courtesy of School of Biomedical Engineering, ShanghaiTech University, Shanghai, China.

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