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Citation for final published version:

Afzali, Maryam, Teh, Irvin, Coveney, Sam, Mueller, Lars, Watson, Isaac, Lwin, May, Jones, Sarah, Fasano, Fabrizio, Evans, C. John, Szczepankiewicz, Filip, Jones, Derek K. , Dall'Armellina, Erica and Schneider, Jürgen E. 2026. Dual-phase systolic and diastolic cardiac diffusion tensor imaging using higher order motion compensation spin echo sequences at 300 mT/m gradient strength. *Journal of Cardiovascular Magnetic Resonance* , 102805. 10.1016/j.jocmr.2026.102805

Publishers page: <https://doi.org/10.1016/j.jocmr.2026.102805>

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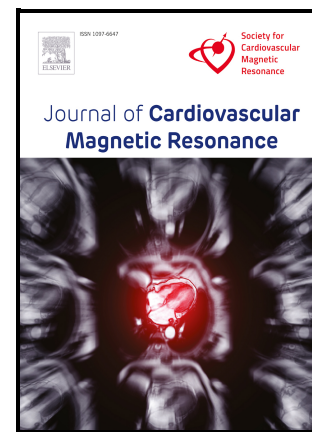
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PII: S1097-6647(26)00123-7

DOI: <https://doi.org/10.1016/j.jocmr.2026.102805>

Reference: JOCMR102805

To appear in: *Journal of Cardiovascular Magnetic Resonance*

Received date: 12 December 2025

Revised date: 9 September 2026

Accepted date: 23 September 2026

Please cite this article as: Maryam Afzali, Irvin Teh, Sam Coveney, Lars Mueller, Isaac Watson, May Lwin, Sarah Jones, Fabrizio Fasano, C John Evans, Filip Szczepankiewicz, Derek K Jones, Erica Dall'Armellina and Jürgen E Schneider, Dual-phase systolic and diastolic cardiac diffusion tensor imaging using higher order motion compensation spin echo sequences at 300 mT/m gradient strength, *Journal of Cardiovascular Magnetic Resonance*, (2026) doi:<https://doi.org/10.1016/j.jocmr.2026.102805>

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Dual-phase systolic and diastolic cardiac diffusion tensor imaging using higher order motion compensation spin echo sequences at 300 mT/m gradient strength

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Abstract

Background: Cardiac diffusion tensor imaging (cDTI) provides unique insights into myocardial microstructure and its dynamic changes during the cardiac cycle. However, motion sensitivity remains a major obstacle for spin echo (SE)-based approaches, restricting most implementations to a relatively narrow low-motion window near peak systole.

Purpose: To establish whether higher-order motion-compensated (up to 6th order) diffusion gradients beyond standard second order motion compensation (M_2) on a magnetic resonance imaging (MRI) system with a maximum gradient strength of 300 mT/m improve SE-based cDTI techniques for both systolic and diastolic acquisitions.

Methods: Ten healthy volunteers underwent free-breathing, cardiac-gated SE-cDTI acquisitions in systole and in diastole using diffusion gradients with up to second- (M_2), fourth- (M_4), and sixth-order (M_6) motion compensation. Success rate (percentage of left ventricular voxels with $(1.1 < MD < 1.9) \times 10^{-3} \text{mm}^2/\text{s}$) and diffusion measures including mean diffusivity, fractional anisotropy, helix angle, and secondary eigenvector angle were quantified and compared between both cardiac phases.

Results: Second-order motion compensation was sufficient for systolic cDTI, whereas fourth-order motion compensation was required for successful diastolic acquisitions in all participants. Mean diffusivity values in systole were (1.53 ± 0.06) , (1.60 ± 0.07) , and $(1.62 \pm 0.06) \times 10^{-3} \text{mm}^2/\text{s}$ for M_2 , M_4 , and M_6 respectively, and in diastole were (2.26 ± 0.67) , (1.73 ± 0.19) , and $(1.71 \pm 0.12) \times 10^{-3} \text{mm}^2/\text{s}$. No significant differences in cDTI-derived parameters were observed between M_4 and M_6 for systolic and diastolic acquisitions.

Conclusion: This study demonstrates the feasibility of dual-phase SE-based cDTI techniques enabled by 300 mT/m gradients. This method will allow reliable quantification of myocardial microstructural changes between systole and diastole and represents a step towards clinical translation of dynamic cDTI.

Keywords: cardiac MRI, diffusion tensor imaging, systole, diastole, higher order motion compensation

List of abbreviations:

$b_{\max}$	maximum b-value
bSSFP	balanced steady state free precession
cDTI	cardiac diffusion tensor imaging
cDWI	cardiac diffusion-weighted imaging
CC	circumferential cardiomyocyte
DTI	diffusion tensor imaging
DWI	diffusion-weighted imaging
E2A	secondary eigenvector angle
ECG	electrocardiogram / electrocardiographic
EPI	echo-planar imaging
FA	fractional anisotropy
$G_{\max}$	maximum gradient strength
GRE	gradient recalled echo
HA	helix angle
LHC	left-handed helical cardiomyocyte
M_2	second-order motion compensation
M_4	fourth-order motion compensation
M_6	sixth-order motion compensation
$M_0M_1M_2M_3M_4M_5M_6$	zeroth- to sixth-order gradient moments/motion compensation orders
MD	mean diffusivity
MR	magnetic resonance
MRI	magnetic resonance imaging
NOW	Numerical Optimization of gradient Waveforms (toolbox)
PNS	peripheral nerve stimulation
RF	radiofrequency
RHC	right-handed helical cardiomyocyte
RR	R-wave to R-wave (cardiac) interval
RWLS	robust weighted least squares
SD	standard deviation
SE	spin echo
SNR	signal-to-noise ratio

SPAIR spectral attenuated inversion recovery

STEAM stimulated echo acquisition mode

T2 transverse (transversal) relaxation time

TA transverse angle

TE echo time

TR repetition time

ZOOM ZOnally-magnified Oblique Multislice

Journal Pre-proof

Introduction

Diffusion-weighted imaging (DWI) enables non-invasive investigation of tissue microstructure by sensitizing the measured signal to the random motion of water molecules in the tissue (8). In the heart, DWI and diffusion tensor imaging (DTI) have been extensively applied to explore myocardial architecture and its alterations in health and disease (48; 37; 24; 18; 17).

Myocardial microstructure exhibits dynamic changes in orientation and organization throughout the cardiac cycle. To investigate this, Chen et al. (10) compared ex vivo pig hearts arrested in diastole and then fixed in systole, revealing marked differences in sheetlet orientation between the two cardiac phases (10). These findings were later supported by other studies (25; 29; 21) which demonstrated significant differences in helix angle and sheet angle distributions between systole and diastole. Building on these fundamental insights, subsequent studies extended this line of inquiry to pathological conditions, showing how sheet architecture is altered in disease states such as focal myocardial fibrosis and progressive cardiomyopathies (12; 11).

In vivo cardiac DTI is performed using two main types of pulse sequences: diffusion-weighted stimulated echo acquisition mode (STEAM) sequences (55; 40; 20; 42; 41; 27; 49) and motion-compensated spin echo (SE) sequences. While early work incorporated first order motion compensated diffusion gradients (22; 54), it is now commonly accepted that second order motion compensation (M_2) is required for a successful application of spin echo cDTI in systole (36; 50; 5; 2; 17). Each approach presents distinct advantages and limitations: spin echo methods offer improved signal-to-noise ratio and reduced sensitivity to motion-induced phase errors (4) but require higher gradient amplitudes to achieve the required diffusion weighting within the shortest possible echo time for application in the moving heart (2). Higher gradient strengths also shorten the diffusion-encoding duration, thereby reducing the temporal window during which the diffusion measurement is susceptible to bulk cardiac motion. In contrast, STEAM sequences can be implemented using standard clinical MRI hardware and can, in principle, be applied in different cardiac phases, but they exhibit lower inherent signal-to-noise ratio and approximately twofold longer acquisition times (per echo-planar imaging (EPI) readout). STEAM sequences are also more susceptible to heart rate variations during acquisition as highlighted in the recent cDTI consensus paper (17). Furthermore, breath-holding is typically required which may compromise data consistency and patient comfort (40; 33; 38; 21; 32; 45).

Recently, Afzali et al. demonstrated spin echo-based cDTI on a magnetic resonance (MR) system equipped with maximum gradient strength of $G_{\max} = 300, \text{mT/m}$, achieving third-order motion

compensation (M3) with echo times comparable to those used in standard clinical scanners for second-order motion compensation (2). However, that study was limited to systolic acquisitions. More recently, Wen et al. evaluated the feasibility of extending third-order motion-compensated DTI to the diastolic phase, although their work revealed signal instability and dropout across certain trigger time windows (57). Coveney et al. previously demonstrated the benefits of higher order motion compensation (up to sixth order) in cDTI, but this was limited to systolic phase (14).

In this study, we sought to utilise higher-order motion-compensated spin echo diffusion encoding on an MRI system with $G_{\max} = 300 \text{ mT/m}$ to enable robust dual-phase (i.e. systolic and diastolic) in vivo cardiac DTI acquisitions (1; 3). We focused on characterizing differences in helix angle and secondary eigenvector angle (E2A) between systole and diastole in the human heart in vivo. To the best of our knowledge, this is the first study to demonstrate in vivo cardiac DTI in the diastolic phase using spin echo fourth- (M_4) and sixth-order motion-compensated (M_6) diffusion encoding and strong gradient system.

Methods

Cardiac diffusion-weighted images (cDWI) were acquired on a Connectom 3T research only MRI system equipped with a gradient system of 300 mT/m and a slew rate of 200 T/m/s , in combination with an 18-channel body receive coil and a 32-channel spine receive coil (Siemens Healthcare, Forchheim, Germany). Ten healthy volunteers (without known previous cardiac conditions) were recruited for this study (age range 20.1 ± 1.6 years (18-22 years), weight range $64 \pm 12 \text{ kg}$ (54-94 kg), six females). The study was approved by the local institutional review board and all subjects gave their written consent.

Routine gradient recalled echo (GRE) (59) and balanced steady state free precession (bSSFP) (43) sequences were used for cardiac planning and cine imaging, while cDWI was performed with a prototype pulse sequence that enabled diffusion encoding with user-defined gradient waveforms (53; 35). The cine images were acquired in short-axis orientation for apical, middle, and basal slices. cDWI was performed at the same location and orientation as the cine imaging. The phase encoding direction was systematically rotated in scout diffusion weighted images (step size 30°). The rotation that provided the best image quality, assessed visually based on reduced field of view wrap, minimal distortion, and improved anatomical delineation, was chosen for the full cDWI acquisition in each subject.

Diffusion gradient waveforms were designed using the numerical optimization of gradient waveforms (NOW) toolbox (47; 52) (<https://github.com/jsjol/NOW>) to provide up to second-, fourth-, and sixth-order motion compensated (i.e. $M_0M_1M_2 = 0$, $M_0M_1M_2M_3M_4 = 0$, $M_0M_1M_2M_3M_4M_5M_6 = 0$) waveforms (52; 6) that can reach a specific b-value in the shortest echo time. Here, $M_0 - M_6$ denote both gradient moment orders and motion-compensation orders. The maximum gradient strength used in this study for the acquisition of symmetric in time M_2 , M_4 and M_6 compensation to generate the b-value of 450 s/mm^2 was 257.3, 261.9 and 279.5 mT/m and the maximum slew-rate was 67.8, 74.5 and 73.6 T/m/s which resulted in an echo time of 56, 66, and 76 ms (Figure 1) (slew-rate is limited due to peripheral nerve stimulation (PNS) and cardiac stimulation limits, see (2) for more details).

The motion-compensated waveforms are defined by three coupled constraints: gradient timing (which determines the motion-compensation order), target diffusion weighting (b-value), and hardware limits (maximum gradient strength and slew rate). These parameters cannot, in general, be independently fixed without over-constraining the problem. In our implementation, the gradient timing was treated as a fixed constraint, as it is essential to preserve the desired motion-compensation properties of the waveform. We also aimed to maintain a consistent target b-value across encoding schemes to ensure comparability. Consequently, the waveform was first optimized offline under fixed timing and hardware limits to identify the achievable diffusion weighting. During sequence execution, small adjustments in gradient amplitude and slew rate were permitted within hardware constraints to ensure that the prescribed b-value was achieved while strictly preserving the predefined timing structure. This approach ensured that motion compensation was maintained consistently, while allowing exact b-value matching across encoding schemes. Other cDTI acquisition parameters were: repetition time (TR) = 3 R-wave to R-wave (cardiac) (RR) intervals, field of view = $320 \times 120 \text{ mm}^2$ using ZOnally-magnified Oblique Multislice (ZOOM, tilted radiofrequency (RF): excitation, tilt angle: 15° , tilted slice thickness: 20 mm) (35; 51), in-plane resolution = $2.5 \times 2.5 \text{ mm}^2$, slice thickness = 8 mm, 3 short axis slices (basal, middle and apical), partial Fourier factor = 7/8, bandwidth = 2354 Hz/pixel, no parallel imaging. Each complete dataset consisted of two b-values [$b = 100$ and 450 s/mm^2] in 3 and 18 directions, respectively, repeated 4 times. Data was acquired with electrocardiogram (ECG)-gating and under free-breathing (19). The relatively short diffusion encoding duration and motion-compensated gradient waveforms were relied upon to mitigate the impact of respiratory motion on the acquired signal. In another work, not reported here, we compared the images with breath-hold and free-breathing for motion

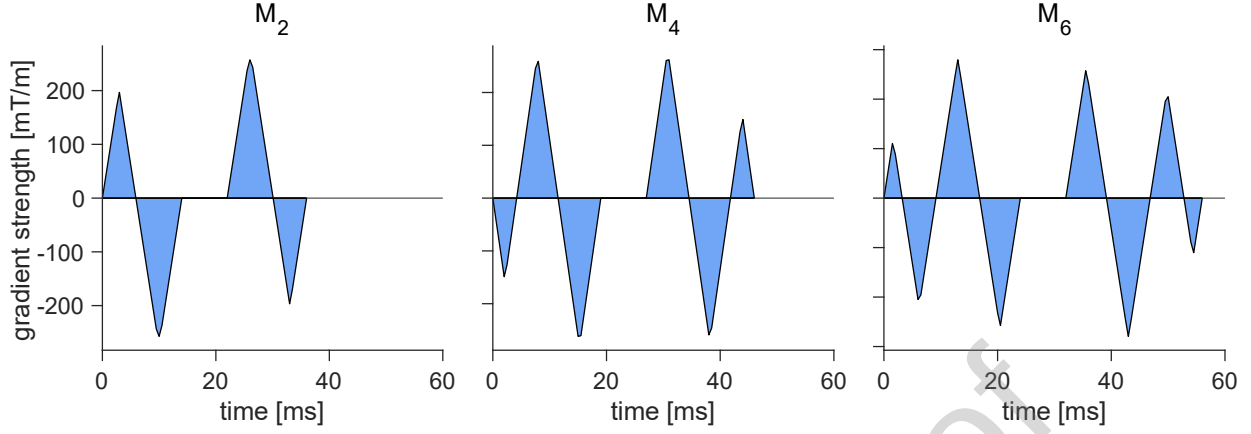


Figure 1: Numerically optimized second, fourth, and sixth order motion compensated waveform for maximum b-value, $b_{\max} = 450 \text{ s/mm}^2$, maximum gradient strength, $G_{\max} = 257.3, 261.9$ and 279.5 mT/m and maximum slew rate of $67.8, 74.5$ and 73.6 T/m/s (lower than the technical limit to reduce peripheral nerve stimulation (PNS) and avoid cardiac stimulation).

compensated spin echo acquisitions and we found no significant difference between the cDTI maps. Saturation bands were placed around the heart to further suppress any signal from outside the volume of interest. Fat suppression was performed using the spectral attenuated inversion recovery (SPAIR) method (28). The trigger delay was adjusted for cDWI acquisition based on the timing of peak systole and diastole in the cine images, respectively. For systolic acquisition, the trigger time was set to be equal to 85% of peak systole time, and for diastolic acquisition, a trigger time equal to 200% of the peak systole time was used. The total acquisition time was less than one hour where the nominal scan time of the DTI protocols was 25.2 minutes at 60 beats per minute heart rate. The scan time is around 4.2 minutes for each motion encoding scheme and each cardiac phase (systole or diastole). Across all volunteers, the acquisition time for one shot was 1 ± 0.29 seconds (mean $\pm$ standard deviation) and the heart rate was 63 ± 16 beats per minute. The trigger time was $274 \pm 16 \text{ ms}$ for systolic acquisitions and $640 \pm 54 \text{ ms}$ for diastolic acquisitions.

Data analysis

Cardiac diffusion weighted images were first interpolated using zero filling (factor of 2). For this purpose, both magnitude and phase data were acquired for each volunteer and used to generate

the complex data. A Fourier transform was then applied to transfer the image from the spatial domain into the frequency domain, where it was then zero padded to twice its original size. A Butterworth filter (cutoff frequency of 2 and the filter order of 3) was applied and the data was inverse Fourier transformed back to the spatial domain. An in-house developed toolbox was used for post-processing (13; 23). For each slice, all low b-value images were first registered to one user-specified low b-value image. All images were then registered to the mean of the co-registered low b-value images. The 2D registration was performed slice-wise with SimpleITK (30) with rigid transformation. For systolic data analysis, M_2 -compensated images were registered first, and then M_4 and M_6 compensated images were registered to the same reference image as the M_2 -compensated images. For diastolic data, images acquired with M_4 motion compensation were used as the reference. Registration was first performed within the M_4 dataset to obtain a reference image, after which the M_2 - and M_6 -compensated images were registered to this same reference, ensuring all datasets were aligned consistently. This choice was made based on visual inspection of image quality in systolic and diastolic acquisition with different orders of motion compensation. Next, a robust weighted least squares (RWLS) method was used to fit the tensor (15) to the data from each motion compensation scheme in both systole and diastole. Diffusion metrics such as fractional anisotropy (FA), mean diffusivity (MD), helix angle (HA) and secondary eigenvector angle (E2A) were calculated for each subject.

Helix angles were defined as positive for a right-handed helical orientation (found in the sub-endocardium) and negative for a left-handed helical orientation (found in the sub-epicardium). To aid comparison between systole and diastole, myocardial tissue voxels were binned into left-handed helical cardiomyocyte (LHC): $HA < -30^\circ$, circumferential cardiomyocyte (CC): $-30^\circ < HA < 30^\circ$, and right-handed helical cardiomyocyte (RHC): $HA > 30^\circ$ (25), respectively.

The left ventricular myocardium was segmented manually in each slice (13). Areas corrupted by susceptibility-related distortions (typically between the myocardium, deoxygenated blood, and air, particularly around the posterior vein) were manually excluded for the calculation of global metrics. To quantify the quality of the images acquired using different motion compensation orders, we calculated the percentage of voxels with $1.1 \times 10^{-3} < MD < 1.9 \times 10^{-3} \text{mm}^2/\text{s}$ after exclusion of susceptibility corrupted voxels. Reported values of mean diffusivity in the literature for healthy human heart using spin echo acquisitions is around $(1.5 \pm 0.2) \times 10^{-3} \text{mm}^2/\text{s}$ (17), therefore, we considered a range based on mean $\pm$ two standard deviation.

We report global E2A values as absolute values because E2A is a signed angular metric; averaging

signed values across the myocardium can lead to cancellation between positive and negative angles, resulting in a mean that does not reflect the underlying magnitude of sheetlet orientation. Using absolute values therefore provides a more representative measure of the overall E2A magnitude at the global level.

Bland–Altman plots were used to compare the mean FA, MD, and $|E2A|$ obtained from different motion compensation orders (M_2 , M_4 , M_6) in both systolic and diastolic acquisitions. To determine the statistical significance between parameters, the Wilcoxon signed-rank test was used; a p-value less than or equal to 0.05 was considered statistically significant.

SNR was computed voxel-wise as the mean signal at $b=100$ s/mm² divided by the noise standard deviation, where the latter was estimated from a separate acquisition without RF excitation (256 repetitions) at the same slice location.

The uncertainty values were estimated using image-level repetition bootknife approach described by Coveney et al. (16). Briefly, repeated diffusion-weighted images were resampled at the image level to generate multiple realisations of the acquired dataset, and the diffusion tensor was refitted for each realisation. The corresponding cDTI metrics (MD, FA and $|E2A|$) were then calculated for each realisation. The uncertainty was quantified from the resulting distributions as the standard deviation for MD and FA, and the circular standard deviation for the angular metric E2A. This produced voxel-wise uncertainty maps, from which the median uncertainty within the left ventricular mask was calculated.

Results

Figure 2 shows representative cardiac diffusion-weighted images acquired using M_2 , M_4 , and M_6 at two b-values: 100 and 450 s/mm². Data is shown for both systole and diastole across three short-axis slices (apical, mid-ventricular, and basal). Visual inspection demonstrates some signal dropouts in the second-order motion-compensated diastolic acquisitions. The image quality in fourth and sixth order motion compensated diastolic images is similar while the SNR in M_6 is slightly lower than the one obtained with lower motion compensation orders ($SNR_{M_2} = 40 \pm 16$, $SNR_{M_4} = 38 \pm 10$, $SNR_{M_6} = 32 \pm 10$) as a consequence of the increasing echo time (TE) (i.e. 56, 66, and 76 ms for M_2 , M_4 , and M_6 , respectively). The image quality in systolic images is visually better in M_2 compared to M_4 and M_6 . Similarly, increasing the motion-compensation order reduces the SNR in systolic images

($\text{SNR}_{M_2} = 44 \pm 13$, $\text{SNR}_{M_4} = 36 \pm 8$, $\text{SNR}_{M_6} = 28 \pm 8$). Example SNR maps are provided in the Supplementary Information (Figure S1).

Quantitative diffusion maps derived from the tensor model are shown in Figure 3, including MD,

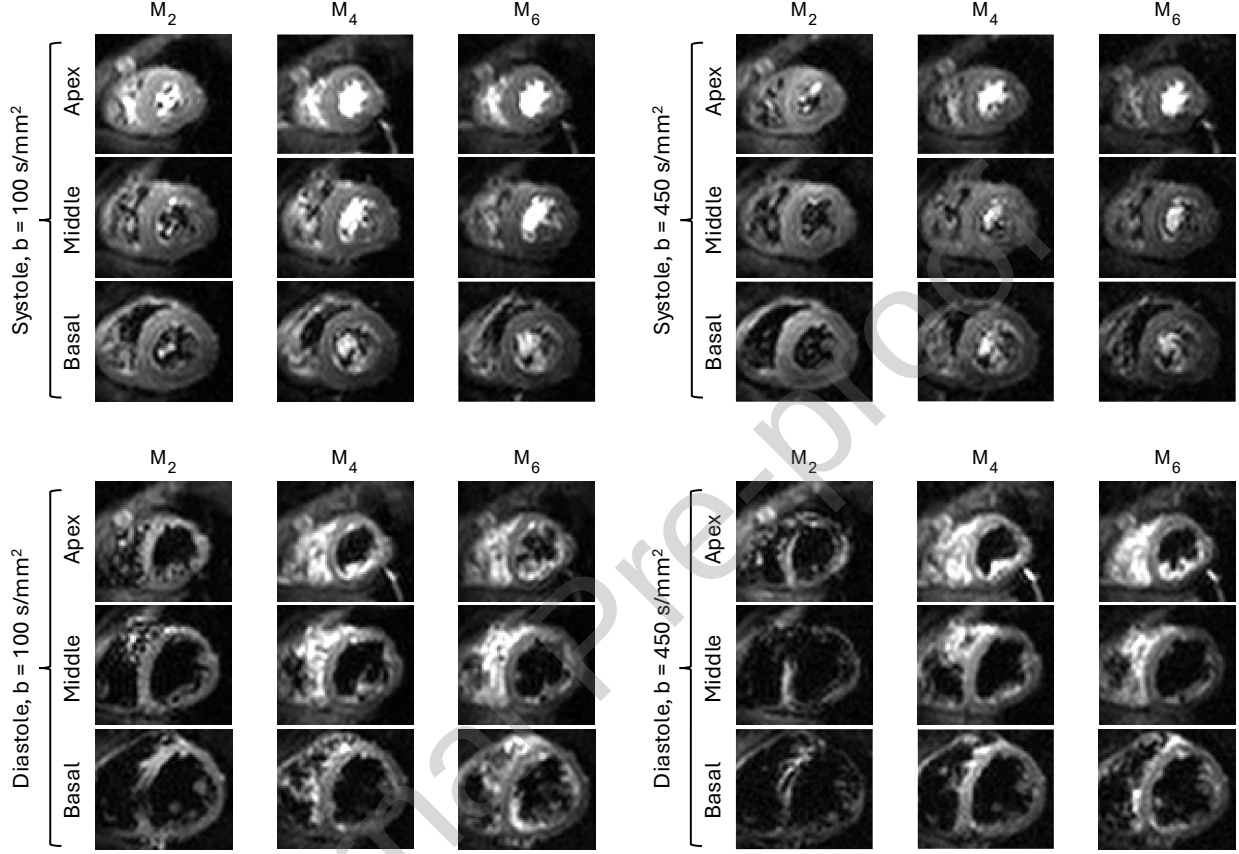


Figure 2: Representative diffusion weighted images acquired using second, fourth, and sixth order motion compensation (M_2 , M_4 , and M_6) for $b = 100$ and 450 s/mm^2 in systolic and diastolic phase of the cardiac cycle.

FA, HA, and E2A. These maps are displayed for M_2 , M_4 , and M_6 encoding schemes in both systole and diastole. HA maps display the characteristic transmural helix angle gradient, which is preserved in both cardiac phases. Among the tested encoding schemes, M_2 in systole and M_4 in diastole appear to provide the best overall depiction of this pattern. Notably, E2A maps capture the expected transmural variation in sheetlet orientation, which differs between systole and diastole, reflecting the dynamic nature of sheetlet reorientation during contraction and relaxation. The use of higher-order motion compensation (particularly M_4) appeared to enhance the consistency and clarity of angular

metrics in the diastolic phase, where lower-order compensation (M_2) is more vulnerable to motion artifacts.

The percentage of voxels over the left ventricular mask with $(1.1 < MD < 1.9) \times 10^{-3} \text{mm}^2/\text{s}$ in the systolic phase using M_2 , M_4 , and M_6 were 98%, 91%, and 86%, respectively. This percentage was lower for the diastolic phase 23%, 82% and 74% for M_2 , M_4 , and M_6 respectively (Figure 4). Despite differences in motion-compensation performance, all datasets achieved sufficient SNR and myocardial coverage to enable reliable diffusion tensor estimation in every subject.

Figure 5 summarizes the effects of different orders of motion compensation (M_2 , M_4 , M_6) on the cDTI metrics in the systolic and diastolic phases of the cardiac cycle. Median values are presented for (A) MD, (B) FA, and (C) absolute secondary eigenvector angle ($|E2A|$) in both systolic and diastolic phases. Table 1 lists the global myocardial median and %95 confidence intervals of MD, FA and $|E2A|$ for second, fourth and sixth order motion compensation (M_2 , M_4 , and M_6) in both systolic and diastolic phases of the cardiac cycle averaged over the ten volunteers. Increasing the motion compensation order in the systolic acquisition, leads to higher MD values from $(1.51 [1.48, 1.58]) \times 10^{-3} \text{mm}^2/\text{s}$ (M_2) to $(1.62 [1.57, 1.66]) \times 10^{-3} \text{mm}^2/\text{s}$ (M_6), while FA $(0.32 [0.30, 0.33])$ and E2A $(30 [27, 34])$ values are not much affected by increasing the motion compensation order. In the diastolic phase, increasing the motion compensation order from M_2 to M_4 reduces the MD values from $(2.23 [1.90, 2.56]) \times 10^{-3} \text{mm}^2/\text{s}$ (M_2) to $(1.67 [1.57, 1.81]) \times 10^{-3} \text{mm}^2/\text{s}$ (M_4) consistent with the improvement in MD map quality. The MD values and the quality of MD maps in the diastolic acquisition is consistent between M_4 $(1.67 [1.57, 1.81]) \times 10^{-3} \text{mm}^2/\text{s}$ and M_6 $(1.72 [1.61, 1.79]) \times 10^{-3} \text{mm}^2/\text{s}$. FA values also decrease from M_2 $(0.34 [0.31, 0.38])$ to M_4 $(0.30 [0.28, 0.32])$ in the diastolic phase, while the change is negligible from M_4 to M_6 $(0.30 [0.28, 0.35])$. Similar trend is observed for E2A in diastolic acquisition, where E2A decreases from M_2 $(28 [26, 33]^\circ)$ to M_4 $(20 [16, 23]^\circ)$ and remains unchanged from M_4 to M_6 $(22 [18, 24]^\circ)$.

Table 2 summarizes the median uncertainty values (16) of MD, FA and $|E2A|$ within the left ventricular mask for M_2 , M_4 and M_6 in systole and diastole. In systole, uncertainty values were low and comparable across all motion-compensation orders, with MD uncertainty of $0.04 \times 10^{-3} \text{mm}^2/\text{s}$ for both M_2 and M_4 , and $0.03 \times 10^{-3} \text{mm}^2/\text{s}$ for M_6 . FA uncertainty was 0.01 for all three encodings, while $|E2A|$ uncertainty was 2° throughout. In diastole, uncertainty values were generally higher, particularly for M_2 , which showed an MD uncertainty of $0.10 \times 10^{-3} \text{mm}^2/\text{s}$, FA uncertainty of 0.02, and $|E2A|$ uncertainty of 5° . These values were reduced for M_4 $(0.05 \times 10^{-3} \text{mm}^2/\text{s}, 0.01, 2^\circ)$ and M_6 $(0.04 \times 10^{-3} \text{mm}^2/\text{s}, 0.01, 3^\circ)$, indicating lower uncertainty for higher-order motion compensation

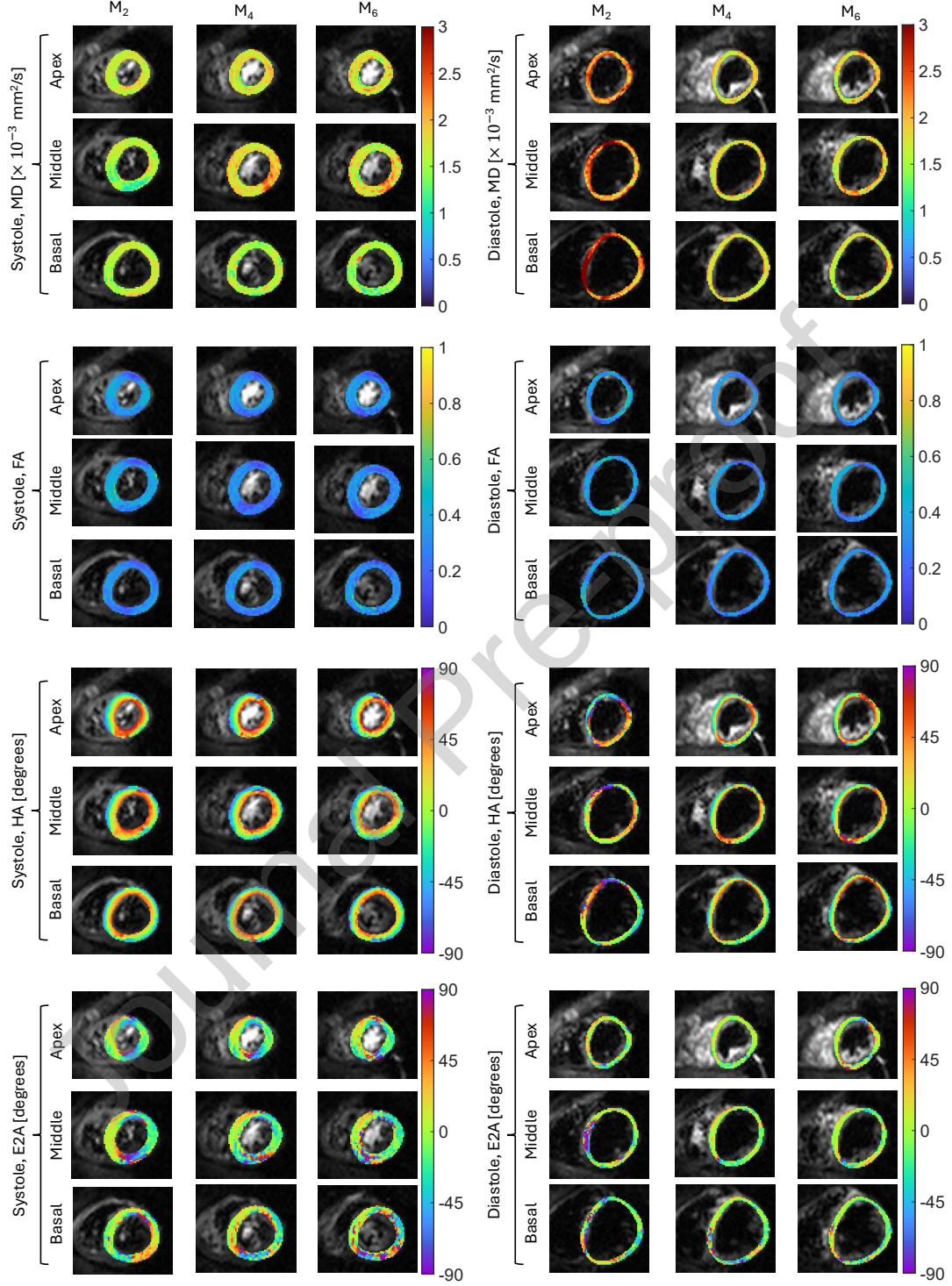


Figure 3: Representative mean diffusivity (MD, fractional anisotropy (FA), helix angle (HA), and secondary eigenvector angle (E2A) calculated for up to second, fourth, and sixth order motion compensation (up to M_2 , M_4 , and M_6) in systolic and diastolic phase of the cardiac cycle.

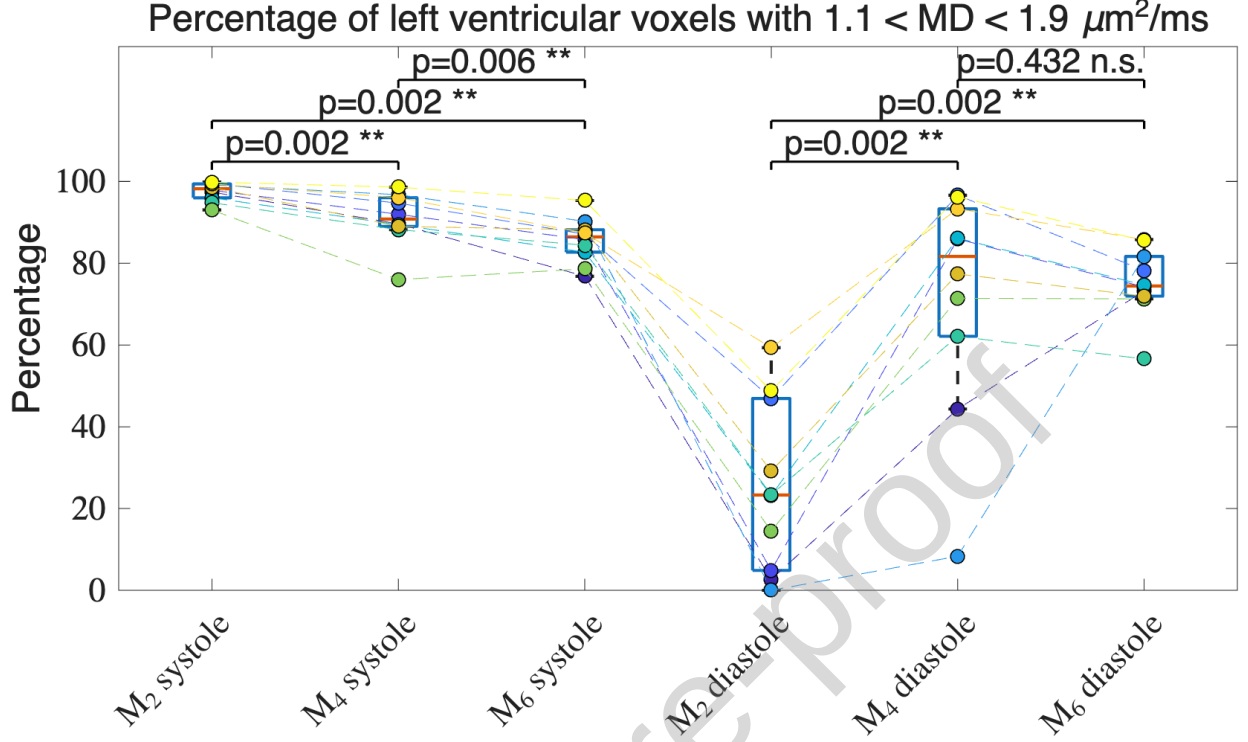


Figure 4: Percentage of left ventricular voxels with $(1.1 < MD < 1.9) \times 10^{-3} \text{ mm}^2/\text{s}$ for second, fourth, and sixth order motion compensation (M_2 , M_4 , and M_6) in systolic and diastolic phase of the cardiac cycle (different colors show different subjects). Abbreviations: MD, mean diffusivity; n.s., not significant. ** denotes a statistically significant difference ($p < 0.05$).

in diastole.

For MD (Table 3), the largest difference between systolic and diastolic values was observed with second-order motion compensation (M_2), showing a mean difference of $(-0.73 \pm 0.64) \times 10^{-3} \text{ mm}^2/\text{s}$ ($p = 6e-3$), indicating significantly lower MD in systole compared to diastole. This difference decreased with increasing motion compensation order: M_4 yielded a smaller, non-significant difference of $(-0.12 \pm 0.18) \times 10^{-3} \text{ mm}^2/\text{s}$ ($p = 0.06$), and M_6 showed the lowest difference at $-0.09 \pm 0.10 \times 10^{-3} \text{ mm}^2/\text{s}$ ($p = 0.02$) (Table 3).

For FA (Table 3), differences between cardiac phases were not statistically significant in any motion compensation order, although M_2 again exhibited the largest difference $(-0.06 \pm 0.12, p = 0.14)$, with M_4 and M_6 showing minimal differences $(-6e-3 \pm 0.02$ and $-5e-3 \pm 0.03$, respectively).

For $|E2A|$ (Table 3), the systole–diastole differences showed a distinct pattern: M_2 yielded only a

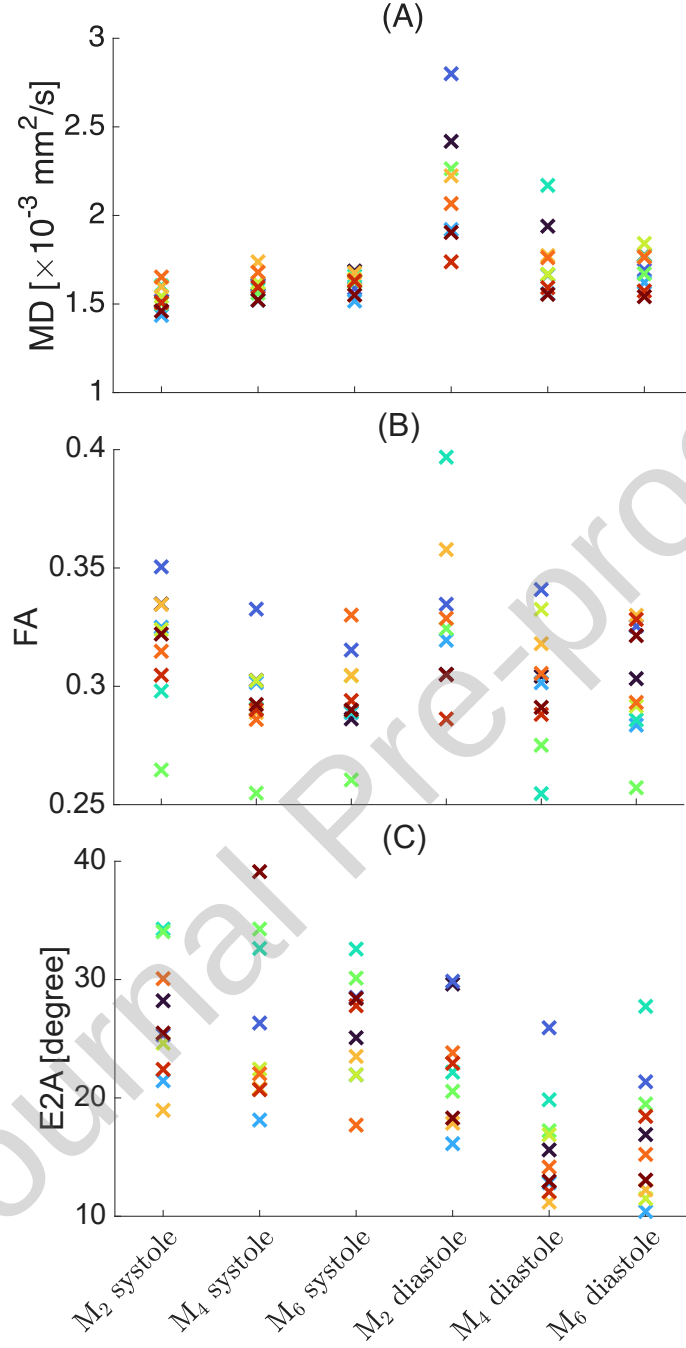


Figure 5: Median of the parameters derived from cDTI over the left ventricle plotted for all subjects (crosses coloured by subject (N = 10)). (A) mean diffusivity (MD), (B) fractional anisotropy (FA) and (C) absolute secondary eigenvector angle (E2A) in systolic and diastolic phases of the cardiac cycle using different orders of motion compensation (M₂, M₄, and M₆).

Table 1: Median and %95 confidence interval of mean diffusivity (MD), fractional anisotropy (FA) and absolute secondary eigenvector angle ($|E2A|$) for second, fourth and sixth order motion compensation (M_2 , M_4 , and M_6) for both systolic and diastolic phases of the cardiac cycle, inside a left ventricle mask and then averaged over ten volunteers.

Systole	MD [$\times 10^{-3}$ mm ² /s]	FA	$ E2A $ (degrees)
M_2	1.51 [1.48, 1.58]	0.32 [0.30, 0.33]	30 [27, 34]
M_4	1.59 [1.56, 1.65]	0.29 [0.28, 0.30]	29 [26, 34]
M_6	1.62 [1.57, 1.66]	0.30 [0.29, 0.31]	31 [27, 34]
Diastole	MD [$\times 10^{-3}$ mm ² /s]	FA	$ E2A $ (degrees)
M_2	2.23 [1.90, 2.56]	0.34 [0.31, 0.38]	28 [26, 33]
M_4	1.67 [1.57, 1.81]	0.30 [0.28, 0.32]	20 [16, 23]
M_6	1.72 [1.61, 1.79]	0.30 [0.28, 0.35]	22 [18, 24]

negligible difference ($0 \pm 8^\circ$, $p = 0.97$), while both M_4 and M_6 revealed significant increases in $|E2A|$ in systole relative to diastole ($9 \pm 6^\circ$, $p = 1e-3$ and $10 \pm 3^\circ$, $p = 8e-6$, respectively).

To assess the impact of motion compensation order on myocardial microstructural measurements, we examined the distribution of helix angle (HA) and E2A values across the left ventricular myocardium in both systole and diastole (Figure 6, 7 and 8). The HA distributions display the expected left-right transmural gradient, consistent with known myocardial microarchitecture.

Figure 6, panels (A-C) show the histogram of HA values for different motion compensation orders (M_2 , M_4 , M_6). Using M_2 (Figure 6, (A)), diastolic HA values have high standard deviation and high frequency of relatively larger angles, most likely due to the artifacts in the diffusion weighted images. Diastolic HA values improve by increasing the motion compensation order to M_4 and M_6 (Figure 6 (B-C)). HA values in systolic acquisitions are similar between different motion compensation orders (Figure 6 (A-C)). An increase in LHC in diastole compared to systole is observed using all motion compensation orders, however, this increase is not statistically significant. The proportion of circumferential cardiomyocytes is higher in systole using M_2 , while this is lower using M_4 and M_6 , where the difference is statistically significant using M_6 ($p = 0.03$; note that diastolic acquisitions using M_2 are not reliable due to uncompensated residual motion). A decrease in RHC is observed in diastole for all three motion compensation orders (M_2 , M_4 , M_6) but is only statistically significant for M_4 ($p = 0.04$)(Figure 6).

Table 2: Median of uncertainty values for mean diffusivity (MD), fractional anisotropy (FA) and absolute secondary eigenvector angle ($|E2A|$) for second, fourth and sixth order motion compensation (M_2 , M_4 , and M_6) for both systolic and diastolic phases of the cardiac cycle, inside a left ventricle mask.

Systole	MD [$\times 10^{-3}$ mm ² /s]	FA	$ E2A $ (degrees)
M_2	0.04	0.01	2
M_4	0.04	0.01	2
M_6	0.03	0.01	2
Diastole	MD [$\times 10^{-3}$ mm ² /s]	FA	$ E2A $ (degrees)
M_2	0.10	0.02	5
M_4	0.05	0.01	2
M_6	0.04	0.01	3

In Figure 7 (A), using M_2 , systolic and diastolic acquisitions show similar distributions of E2A angles, while a reduction in absolute E2A values is expected in diastole compared to systole. By increasing motion compensation order to M_4 and M_6 , this reduction in absolute E2A angles is observed (Figure 7 (B-C)). Systolic E2A angles are similar in all motion compensation orders (Figure 7 (A-C)). In addition, we have also reported the histograms for the transverse angles. Diastolic transverse angles using M_2 showed high frequency in relatively large angles (Figure 8 (A)), while increasing the motion compensation order to M_4 and M_6 reduced the frequency of large angles (Figure 8 (B-C)). Systolic transverse angles have similar trend in all motion compensation orders (Figure 8 (A-C)). Bland–Altman analyses are summarized in Figures 9–11 and Table 4.

For MD, inter-method comparisons within systole (Figure 9 (A-C) and Table 4) further showed M_2 differed significantly from M_4 and M_6 ($(-0.07 \pm 0.05) \times 10^{-3}$ mm²/s, $p = 9e-4$; and $(-0.09 \pm 0.07) \times 10^{-3}$ mm²/s, $p = 2e-3$, respectively), while M_4 and M_6 were in close agreement ($(-0.02 \pm 0.06) \times 10^{-3}$ mm²/s, $p = 0.37$). The same trend continued in diastole (Figure 9(D-F) and Table 4), with significant differences between M_2 and both M_4 ($(0.53 \pm 0.52) \times 10^{-3}$ mm²/s, $p = 0.01$) and M_6 ($(0.54 \pm 0.68) \times 10^{-3}$ mm²/s, $p = 0.03$), but negligible difference between M_4 and M_6 ($(0.01 \pm 0.17) \times 10^{-3}$ mm²/s, $p = 0.82$).

FA values in systole differed significantly between M_2 and M_4 (0.02 ± 0.01 , $p = 1e-3$). Comparisons between M_2 and M_6 (0.01 ± 0.02 , $p = 0.08$) and between M_4 and M_6 ($-7e-3 \pm 0.02$, $p = 0.24$) did not

Table 3: Mean difference $\pm$ standard deviation between global mean values of MD, FA, and absolute E2A calculated using DTI fit to systolic and diastolic data acquired using second, fourth, and sixth order motion compensation (M_2 , M_4 , and M_6) inside a left ventricle mask (* shows the statistical significance).

MD [$\times 10^{-3}$ mm ² /s]	
MD _{M₂ systole} - MD _{M₂ diastole}	-0.73 $\pm$ 0.64 (p = 6e-3)*
MD _{M₄ systole} - MD _{M₄ diastole}	-0.12 $\pm$ 0.18 (p = 0.06)
MD _{M₆ systole} - MD _{M₆ diastole}	-0.09 $\pm$ 0.10 (p = 0.02)*
FA	
FA _{M₂ systole} - FA _{M₂ diastole}	-0.06 $\pm$ 0.12 (p = 0.14)
FA _{M₄ systole} - FA _{M₄ diastole}	-6e-3 $\pm$ 0.02 (p = 0.28)
FA _{M₆ systole} - FA _{M₆ diastole}	-5e-3 $\pm$ 0.03 (p = 0.62)
E2A [degree]	
E2A _{M₂ systole} - E2A _{M₂ diastole}	0 $\pm$ 8 (p = 0.97)
E2A _{M₄ systole} - E2A _{M₄ diastole}	9 $\pm$ 6 (p = 1e-3)*
E2A _{M₆ systole} - E2A _{M₆ diastole}	10 $\pm$ 3 (p = 8e-6)*

reach significance. Similar trends were seen in diastole, although none of the differences reached statistical significance (Figure 10(D-F)).

For |E2A|, no significant inter-method differences were observed in systole (Figure 11 (A-C) and Table 4). However, in diastole, M_2 |E2A| was observed higher compared to both M_4 and M_6 ($9 \pm 6^\circ$, $p = 1e-3$ and $9 \pm 9^\circ$, $p = 9e-3$), whereas M_4 and M_6 remained in close agreement ($0 \pm 4^\circ$, $p = 0.97$) (Figure 7(D-F)).

Discussion

This is the first study to demonstrate the feasibility of acquiring dual-phase (systolic and diastolic) in vivo human cDTI using higher-order motion-compensated spin echo sequences on an MRI system with 300 mT/m gradient strength. SE-based cDTI is typically performed at end-systole where the heart is in a more quiescent phase (33). Using higher order motion compensation (i.e. M_4) made

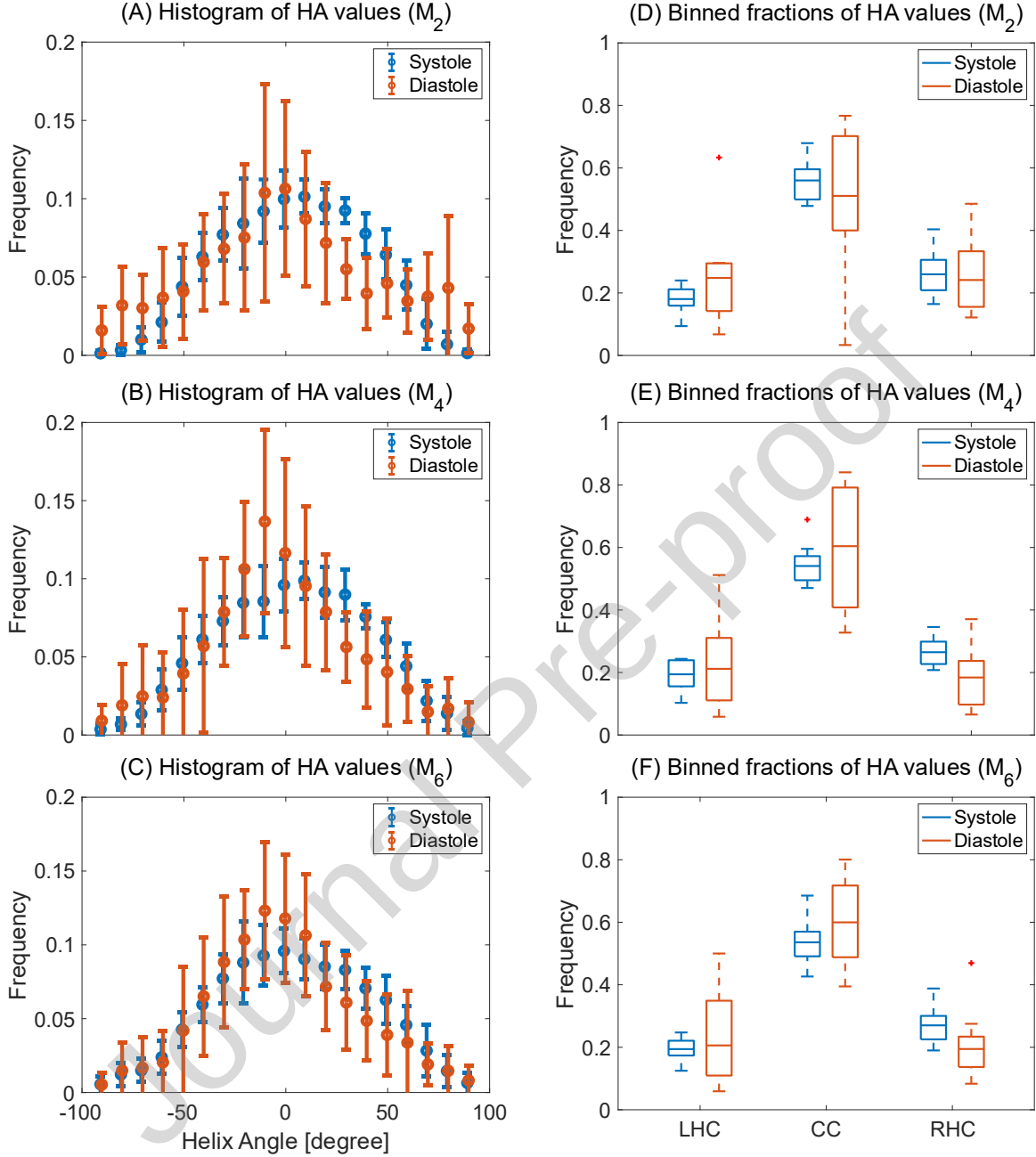


Figure 6: Histogram of helix angle (HA) values in systole and diastole ($n = 10$ hearts), using second, fourth and sixth order of motion compensation (M_2 , M_4 , and M_6). Systole and diastole results are shown in blue and red respectively. All data shown as mean $\pm$ standard deviation. (D-F) Binned fractions of left-handed helical cardiomyocyte (LHC): $HA < -30^\circ$, circumferential cardiomyocyte (CC): $-30^\circ < HA < 30^\circ$, and right-handed helical cardiomyocyte (RHC): $HA > 30^\circ$ using second, fourth and sixth order motion compensation (M_2 , M_4 , and M_6)).

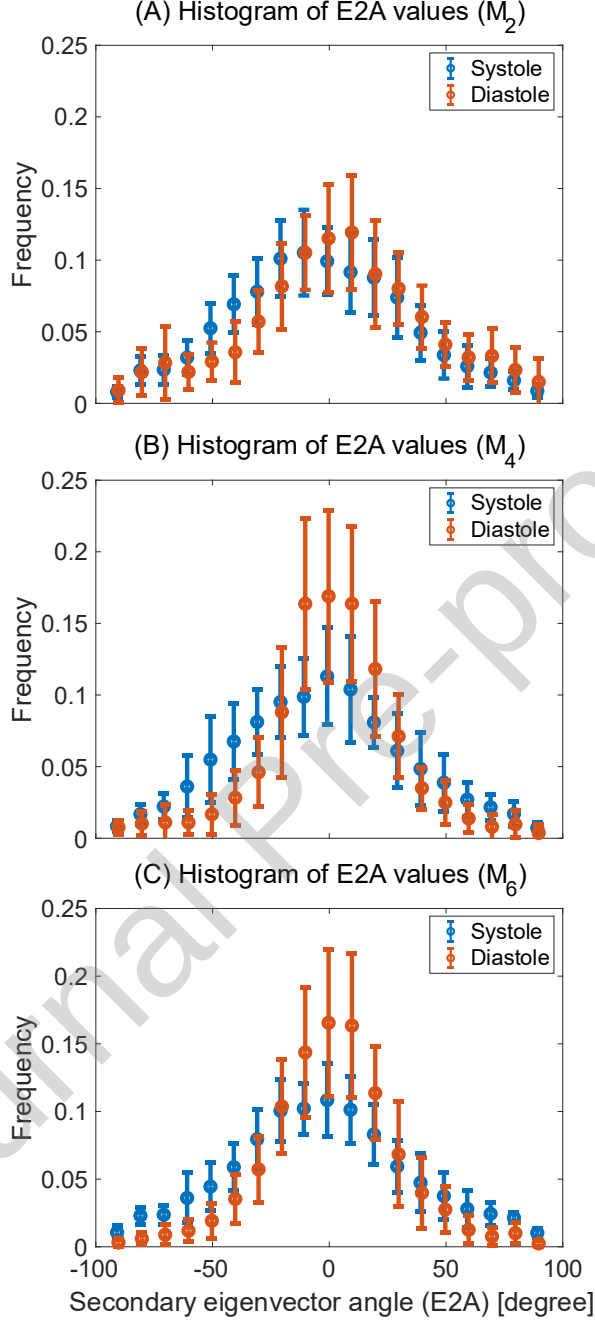


Figure 7: Histogram of secondary eigenvector angle (E2A) values in systole and diastole ($n = 10$ hearts), using second, fourth and sixth order of motion compensation (M_2 , M_4 , and M_6). Systole and diastole results are shown in blue and red respectively. All data shown as mean $\pm$ standard deviation.

the diastolic acquisition feasible using a diffusion-weighted spin echo sequence. We successfully implemented up to second-, fourth-, and sixth-order motion-compensated diffusion encoding to enable

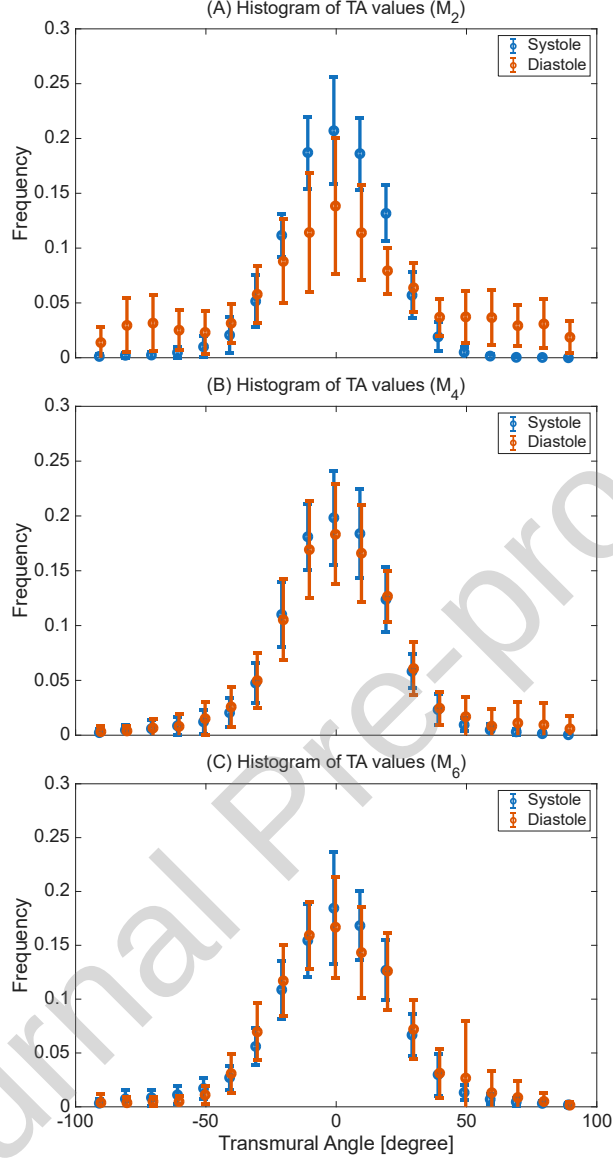


Figure 8: Histogram of transverse angles (TA) in systole and diastole ($n = 10$ hearts), using second, fourth and sixth order of motion compensation (M_2 , M_4 , and M_6). Systole and diastole results are shown in blue and red respectively. All data shown as mean $\pm$ standard deviation.

detailed characterization of myocardial microstructure across the cardiac cycle.

The diffusion-encoding gradient waveforms used in this work are designed to be both time- and $G_{\max}$ -optimal under the specified system constraints, following the general framework described in (47; 52). Specifically, the optimization maximizes gradient amplitude usage while minimizing encoding time for the prescribed b-value and motion moments. The apparent difference, compared to the waveforms presented by Welsh et al. (56), arises from the hardware constraints. In our case,

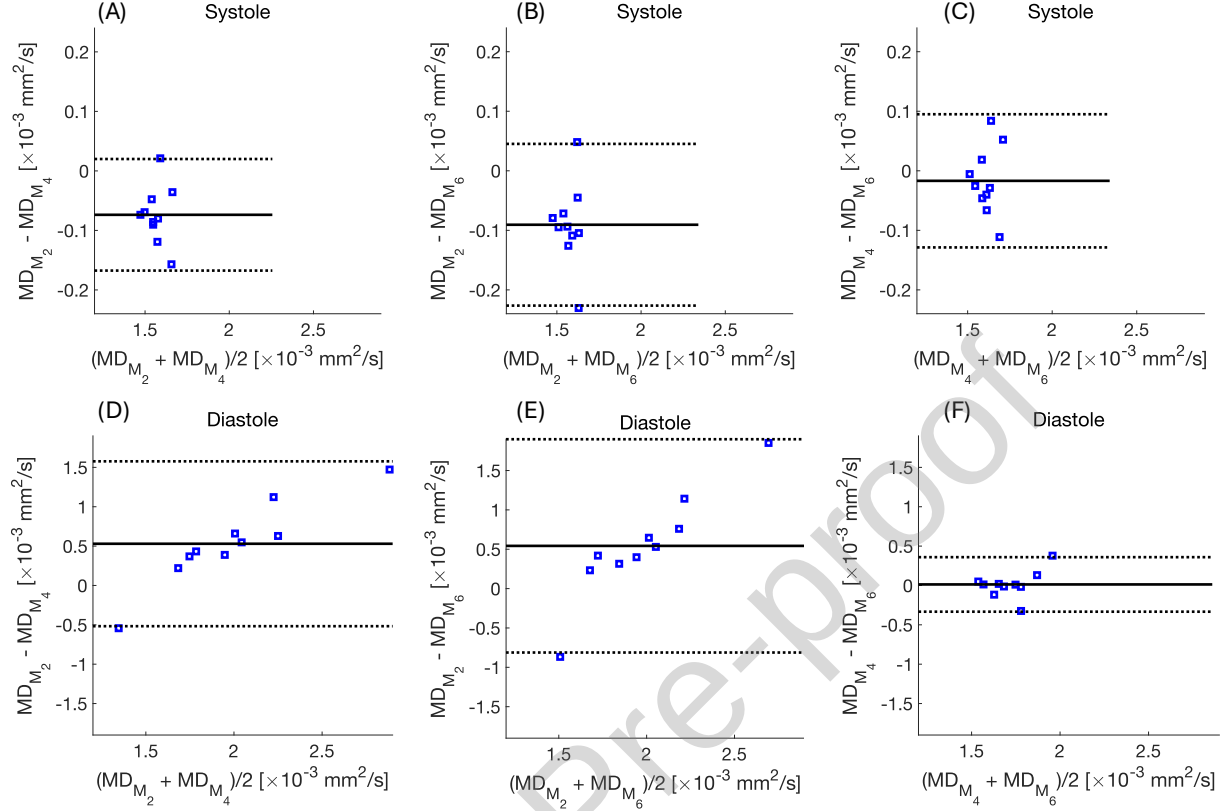


Figure 9: Bland–Altman plots, comparing the mean diffusivity (MD) (A–C) in systole between M_2 , M_4 , and M_6 , (D–F) comparing MD in diastole between M_2 , M_4 , and M_6 . Mean difference ± 1.96 standard deviation (SD) is given by solid and dashed black lines, respectively ($N = 10$ subjects).

although a high gradient strength (300 mT/m) is available, the slew rate was limited to approximately 80 T/m/s due to peripheral nerve stimulation and cardiac stimulation constraints (see (2)). Combined with a relatively moderate target b-value (450 s/mm²), this leads to a regime in which the gradients are primarily slew-rate limited. As a result, the time-optimal solution consists of triangular waveforms that ramp up and down at the maximum allowed slew rate without requiring a plateau at $G_{\max}$. In contrast, for less restrictive slew-rate limits the time-optimal solution includes extended periods at $G_{\max}$, resulting in trapezoidal waveforms as reported in (56).

Coveney et al., (14) reported the feasibility of performing M_6 on a clinical scanner ($G_{\max} = 80 \text{ mT/m}$) with echo time of 113 ms, maximum b-value of 350 s/mm² and voxel size of $2.5 \times 2.5 \times 8 \text{ mm}^3$ for systolic acquisition. In this work, the implementation of high-order motion-compensated encoding was facilitated by using an MRI system with gradient strength of 300 mT/m,

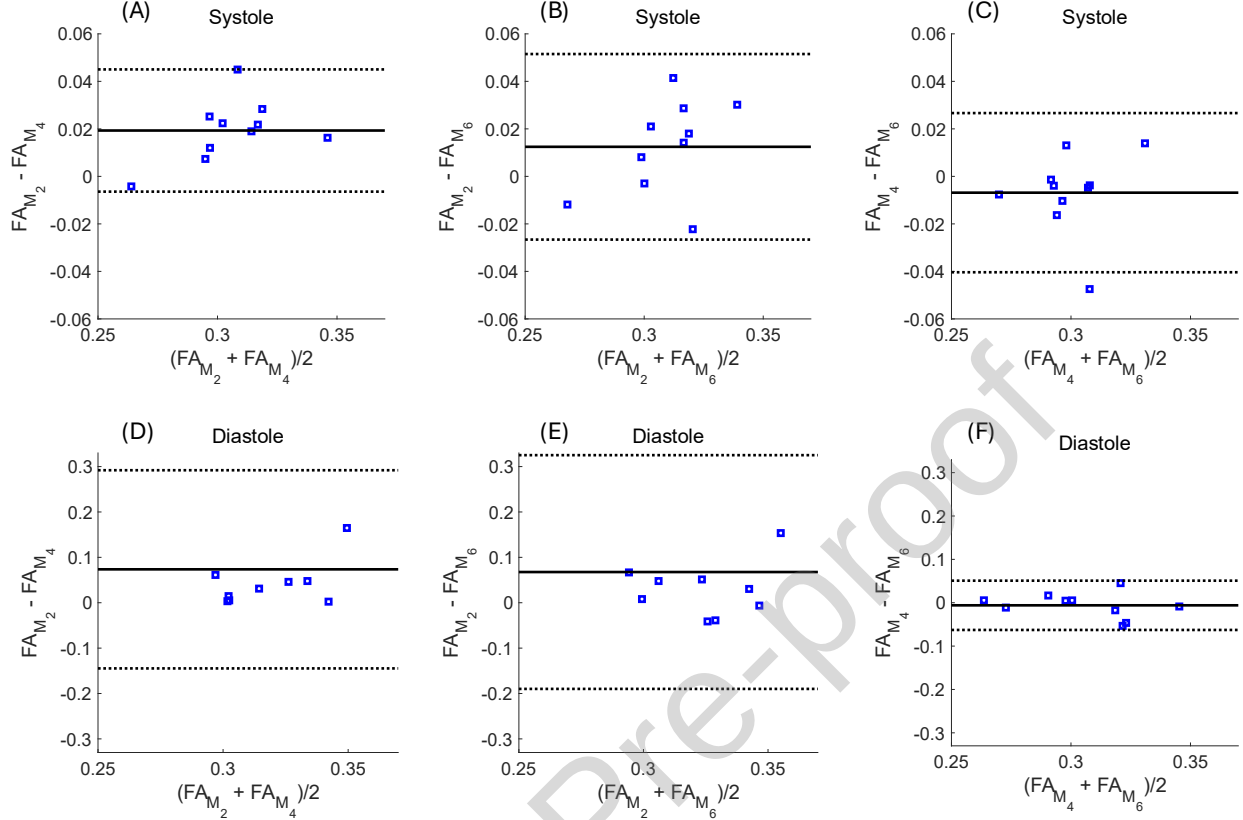


Figure 10: Bland–Altman plots, comparing the fractional anisotropy (FA) (A–C) in systole between M_2 , M_4 , and M_6 , (D–F) comparing FA in diastole between M_2 , M_4 , and M_6 . Mean difference ± 1.96 standard deviation (SD) is given by solid and dashed black lines, respectively ($N = 10$ subjects).

allowing short echo times even for sixth-order encoding ($TE = 76\text{ms}$). This technical capability overcomes one of the main barriers that has hampered the application of spin echo-based DTI in the heart, particularly in diastole. Our results build on the recent demonstration of third-order systolic imaging on this platform (2), extending feasibility to higher-order encoding and dual-phase assessment.

The observed differences in the blood pool signal intensities between cardiac phases and motion-compensation orders likely reflect differing sensitivities of the diffusion-encoding gradients to intracardiac flow. However, the underlying mechanisms were not investigated in this study and warrant further investigation. Higher-order motion compensation enabled diffusion imaging in diastole, where previous studies have reported signal instability and dropout using lower-order methods. Consistent with prior observations (57), second-order motion compensation (M_2) led to pronounced

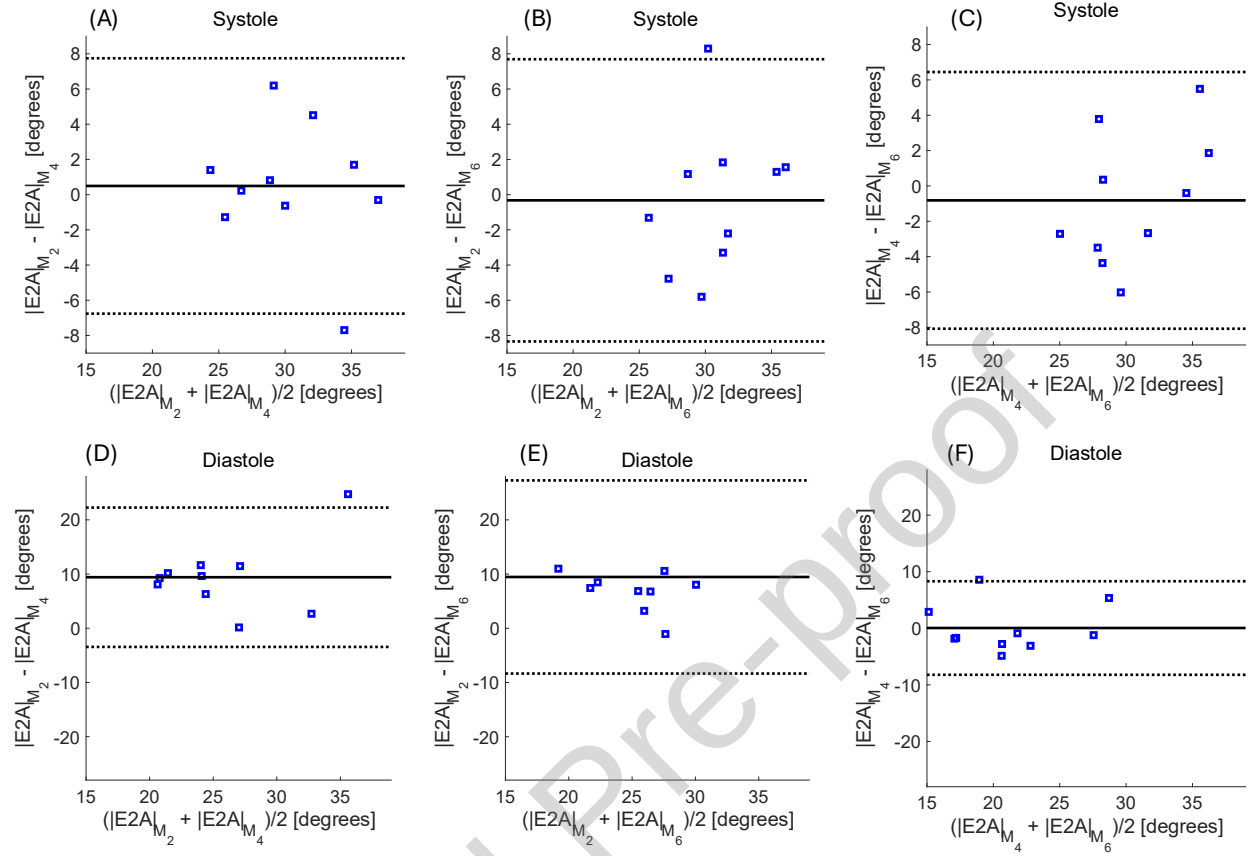


Figure 11: Bland–Altman plots, comparing the absolute secondary eigenvector angle ($|E2A|$) (A–C) in systole between M_2 , M_4 , and M_6 , (D–F) comparing $|E2A|$ in diastole between M_2 , M_4 , and M_6 . Mean difference ± 1.96 standard deviation (SD) is given by solid and dashed black lines, respectively ($N = 10$ subjects).

signal degradation in diastolic acquisitions, reflected in elevated and highly variable MD and FA values. The application of fourth-order motion compensation (M_4) substantially improved image quality and quantitative consistency in diastole, with minimal further improvement using sixth-order compensation (M_6), suggesting that M_4 represents an optimal trade-off between motion robustness and echo time on the current gradient platform.

In systole, the effects of motion compensation order were less pronounced. Afzali et al. (2) previously showed that third order motion compensation (M_3) increased MD, most likely due to the time-dependent diffusion in the tissue, whereas FA did not change significantly in different orders of motion compensations. In this work, M_2 encoding yielded the best image quality and most sta-

ble MD, FA, HA, and E2A metrics in systole, while increasing motion compensation order to M_4 and M_6 introduced longer echo times that led to reduced SNR and slight degradation in MD map quality. This phase-specific dependence likely reflects the greater challenge of compensating residual myocardial motion during diastole compared with the systolic imaging window. These results highlight the need for phase-specific optimization of diffusion encoding strategies (52).

The progressively lower MD estimates observed with increasing order of motion compensation may, in part, indicate improved compensation of cardiac motion. Importantly, our data show that angular diffusion metrics, particularly E2A, are sensitive to phase-dependent myocardial microstructural changes (Figure 5 (C)). The transmural variation in E2A observed in both cardiac phases (Figure 7) is consistent with histological and ex vivo DTI findings (10; 25), supporting the concept of sheetlet reorientation during the cardiac cycle. While HA maps showed the expected transmural gradient in both phases (Figure 6), E2A exhibited pronounced phase-dependent variation, reflecting the dynamic reorientation of myocardial sheetlets during contraction and relaxation. The observed reduction in E2A from systole to diastole is qualitatively consistent with previous STEAM-based cDTI studies, which have similarly reported larger E2A values in systole than diastole (46). However, direct quantitative comparison should be interpreted with caution, as STEAM and spin-echo cDTI differ substantially in their diffusion encoding mechanisms, motion sensitivity, strain effects, and diffusion times (46). Despite these methodological differences, the preservation of the expected systolic-diastolic E2A trend suggests that high-order motion-compensated spin-echo cDTI is capable of capturing physiologically meaningful changes in myocardial laminar architecture across the cardiac cycle. This reinforces the growing recognition that secondary eigenvector metrics may offer unique value for probing myocardial mechanical function and disease-related alterations (12; 11).

In the systolic phase, MD increased with order of motion compensation, suggesting that second order motion compensation is sufficient for systolic acquisition. In diastole, the transition from M_2 to M_4 markedly reduced MD and improved consistency, but further gains from M_4 to M_6 were minimal. The pronounced reduction in MD from M_2 to M_4 likely reflects more accurate suppression of complex residual motion during the longer diastolic window. FA values were more stable across motion compensation schemes (Figure 9 and Table 4).

The absolute secondary eigenvector angle ($|E2A|$), which reflects sheetlet orientation, showed the clearest phase-dependent differences. At higher orders (M_4 and M_6), $|E2A|$ was significantly higher in systole compared to diastole, consistent with known sheetlet reorientation during contraction. However, M_2 failed to capture this physiological variation, showing no significant difference be-

tween phases (Table 3). These results suggest that accurate E2A quantification is particularly sensitive to motion artifacts, and that at least fourth-order compensation in diastole is required to resolve the expected contraction-dependent changes in sheetlet orientation.

The E2A mobility observed in this study is lower than values reported in prior literature using STEAM (39; 45) and spin-echo (34). However, using spin-echo acquisition in (45) showed similar E2A mobility as our reported values (Fig. 7, Panel b in (45), M2-SE systole vs M2-SE diastole, the difference between absolute E2A angles seems around 10 degrees). Direct comparison between our results and the ones reported in the literature should be made with caution. Previous studies have demonstrated systematic differences between STEAM and spin-echo acquisitions, with STEAM generally yielding higher E2A values in systole (44; 45; 46). Furthermore, while diastolic measurements using lower-order motion compensation (e.g., M2) reported larger mobility in some works (34), our results and prior work (5; 57) suggest that such acquisitions may be more susceptible to motion-induced bias. In addition, E2A measurements are sensitive to the precise timing of acquisition within the cardiac cycle. Small variations in trigger delay relative to peak systole or diastole can lead to differences in the estimated E2A angles and, consequently, the derived mobility. Therefore, differences in cardiac phase definition and timing across studies may further contribute to the variability in reported E2A mobility. Overall, the lower E2A mobility reported here likely reflects a combination of methodological differences, and sensitivity to cardiac timing.

Helix angle distributions further support these observations. The expected epicardial-to-endocardial progression of HA remained evident, although the HA histograms exhibited small shifts between conditions. However, differences in the proportions of cardiomyocyte subpopulations (LHC, CC, RHC) were detected in systole and diastole. In particular, left-handed helical cardiomyocytes counted higher in diastole than systole while the trend was opposite for right-handed helical cardiomyocytes (Figure 6) similar to the trend observed by (25).

While sixth-order compensation yielded marginal improvements over M_4 in some metrics, the longer echo time ($TE = 76$ ms) required for M_6 compared to M_4 ($TE = 66$ ms) reduced the signal-to-noise ratio by 20% ($((\exp(-76/46) - \exp(-66/46)) / \exp(-66/46))$, assuming transversal relaxation time (T_2) = 46 ms (26)).

Given the lack of statistically significant improvement in most parameters between M_4 and M_6 , we conclude that M_4 offers the best compromise between motion robustness and SNR in diastole and M_2 in systole. This was consistent with our previous findings examining M_2 - M_6 motion compensation during systole (14).

While this study focused on second-, fourth-, and sixth-order motion compensation, third-order (M_3) encoding represents a potential intermediate solution. Previous studies have demonstrated the feasibility of M_3 in diastole, although with reported sensitivity to trigger timing and associated signal instability (57). As such, M_3 may offer a compromise between motion robustness and SNR, and future work should investigate whether it represents an optimal balance for cardiac diffusion imaging.

ZOOM was used to reduce the field-of-view in the phase-encoding direction (51; 58; 35). To shorten the acquisition time, undersampling strategies may be employed including parallel imaging (7) or compressed sensing (31). Further reduction of scan time could also be achieved by combining the proposed method with simultaneous excitation of multiple slices and subsequent unfolding using parallel imaging principles (9).

Some limitations should be acknowledged. First, the study was conducted in a small cohort of healthy young volunteers, and findings need to be extended to a larger cohort including older subjects and patients with heart disease. Second, manual segmentation and exclusion of susceptibility-affected regions, while necessary for analysis, introduces operator variability. Third, while higher-order motion compensation improved diastolic image quality, it comes at the cost of increased gradient demand and longer echo times, which can be challenging on standard clinical scanners. We demonstrated how higher order motion compensation can be facilitated by next-generation MRI scanners with strong gradient systems. In practice, the usable gradient performance in this study was limited by PNS and cardiac stimulation constraints rather than the hardware limits. At high gradient amplitudes, these physiological limits restrict the achievable slew rate to similar levels for both 300 mT/m and 200 mT/m systems. As a result, the effective operating regime is comparable, with higher gradient capability primarily offering increased flexibility in waveform design rather than a direct performance advantage.

Conclusions

In conclusion, this study demonstrates the feasibility of dual-phase in vivo cDTI using high-order motion-compensated spin echo sequences on an MRI system with gradient strength of 300 mT/m. Higher-order motion compensation substantially improved the robustness of diastolic acquisitions by reducing motion-related signal dropout and bias in diffusion tensor metrics. While conventional second-order motion compensation led to elevated MD and FA values in diastole, these differences

were markedly reduced with fourth- and sixth-order motion compensation, indicating improved suppression of residual cardiac motion. Furthermore, angular diffusion metrics, particularly E2A, revealed systematic differences between systole and diastole that were preserved across M_4 and M_6 , supporting their sensitivity to dynamic changes in myocardial microstructure. These findings establish a framework for more reliable assessment of cardiac microstructure throughout the cardiac cycle using spin-echo cDTI.

Acknowledgments

This research was funded in whole, or in part, by Wellcome Trust Investigator Award (219536/Z/19/Z) and British Heart Foundation (PG/19/1/34076; PG/24/12118; PG/25/12504; RE/24/130031). For the purpose of open access, the author has applied a CC BY public copyright license to any Author Accepted Manuscript version arising from this submission.

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Table 4: Mean difference $\pm$ standard deviation between global mean values of MD, FA, and absolute E2A calculated using DTI fit to systolic and diastolic data acquired using second, fourth, and sixth order motion compensation (M_2 , M_4 , and M_6) inside a left ventricle mask (* shows the statistical significance).

MD [$\times 10^{-3}$ mm ² /s], systole	
MD _{M₂ systole} - MD _{M₄ systole}	-0.07 $\pm$ 0.05 (p = 9e-4)* (Figure 9(A))
MD _{M₂ systole} - MD _{M₆ systole}	-0.09 $\pm$ 0.07 (p = 2e-3)* (Figure 9(B))
MD _{M₄ systole} - MD _{M₆ systole}	-0.02 $\pm$ 0.06 (p = 0.37) (Figure 9(C))
MD [$\times 10^{-3}$ mm ² /s], diastole	
MD _{M₂ diastole} - MD _{M₄ diastole}	0.53 $\pm$ 0.52 (p = 0.01)* (Figure 9(D))
MD _{M₂ diastole} - MD _{M₆ diastole}	0.54 $\pm$ 0.68 (p = 0.03)* (Figure 9(E))
MD _{M₄ diastole} - MD _{M₆ diastole}	0.01 $\pm$ 0.17 (p = 0.82) (Figure 9(F))
FA, systole	
FA _{M₂ systole} - FA _{M₄ systole}	0.02 $\pm$ 0.01 (p = 1e-3)* (Figure 10(A))
FA _{M₂ systole} - FA _{M₆ systole}	0.01 $\pm$ 0.02 (p = 0.08) (Figure 10(B))
FA _{M₄ systole} - FA _{M₆ systole}	-7e-3 $\pm$ 0.02 (p = 0.24) (Figure 10(C))
FA, diastole	
FA _{M₂ diastole} - FA _{M₄ diastole}	0.07 $\pm$ 0.11 (p = 0.07) (Figure 10(D))
FA _{M₂ diastole} - FA _{M₆ diastole}	0.07 $\pm$ 0.13 (p = 0.14) (Figure 10(E))
FA _{M₄ diastole} - FA _{M₆ diastole}	-6e-3 $\pm$ 0.03 (p = 0.53) (Figure 10(F))
E2A [degree], systole	
E2A _{M₂ systole} - E2A _{M₄ systole}	0 $\pm$ 4 (p = 0.68) (Figure 11(A))
E2A _{M₂ systole} - E2A _{M₆ systole}	0 $\pm$ 4 (p = 0.81) (Figure 11(B))
E2A _{M₄ systole} - E2A _{M₆ systole}	-1 $\pm$ 4 (p = 0.50) (Figure 11(C))
E2A [degree], diastole	
E2A _{M₂ diastole} - E2A _{M₄ diastole}	9 $\pm$ 6 (p = 1e-3)* (Figure 11(D))
E2A _{M₂ diastole} - E2A _{M₆ diastole}	9 $\pm$ 9 (p = 9e-3)* (Figure 11(E))
E2A _{M₄ diastole} - E2A _{M₆ diastole}	0 $\pm$ 4 (p = 0.97) (Figure 11(F))

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Jurgen E. Schneider reports financial support was provided by Wellcome Trust. Jurgen E. Schneider reports financial support was provided by British Heart Foundation. Maryam Afzali reports financial support was provided by British Heart Foundation. Filip Szczepankiewicz reports a relationship with Random Walk Imaging AB that includes: equity or stocks. Fabrizio Fasano reports a relationship with Siemens that includes: employment. Irvin Teh has patent issued to University of Leeds. Filip Szczepankiewicz has patent issued to Random Walk Imaging. none If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Diffusion gradient waveforms

