Diffusion tensor cardiovascular magnetic resonance with a spiral trajectory: An in vivo comparison of echo planar and spiral stimulated echo sequences

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Running head: Diffusion tensor cardiovascular magnetic resonance with a spiral trajectory

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Abstract

Purpose:
Diffusion tensor cardiovascular magnetic resonance (DT-CMR) using stimulated echo acquisition mode (STEAM) with echo-planar-imaging (EPI) readouts is a low signal-to-noise-ratio (SNR) technique and therefore typically has a low spatial resolution. Spiral trajectories are more efficient than EPI and could increase the SNR. The purpose of this study was to compare the performance of a novel STEAM spiral DT-CMR sequence with an equivalent established EPI technique.

Methods:
A STEAM DT-CMR sequence was implemented with a spiral readout and a reduced field-of-view. An in-vivo comparison of DT-CMR parameters and data quality between EPI and spiral was performed in 11 healthy volunteers imaged in peak-systole and diastasis at 3T. The SNR was compared in a phantom and in-vivo.

Results:
There was a >49% increase in the SNR in-vivo and in the phantom measurements (in-vivo septum, systole: SNR_{EPI}=8.0±2.2, SNR_{spiral}=12.0±2.7; diastasis: SNR_{EPI}=8.1±1.6, SNR_{spiral}=12.0±3.7). There were no significant differences in helix angle gradient (systole: HAG_{EPI}=-0.79±0.07°/%; HAG_{spiral}=-0.74±0.16°/%; P=0.11; diastasis: HAG_{EPI}=-0.63±0.05°/%; HAG_{spiral}=-0.56±0.14°/%; P=0.20), mean diffusivity in systole (MD_{EPI}=0.99±0.06×10^{-3} mm^2/s, MD_{spiral}=1.00±0.09×10^{-3} mm^2/s, P=0.23) and secondary eigenvector angulation (systole: E2A_{EPI}=61±10°; E2A_{spiral}=63±10°; P=0.77; diastasis: E2A_{EPI}=18±11°; E2A_{spiral}=15±8°; P=0.20) between the sequences. There was a small difference (≈20%) in fractional anisotropy (systole: FA_{EPI}=0.49±0.03, FA_{spiral}=0.41±0.04; P<0.01; diastasis: FA_{EPI}=0.66±0.05, FA_{spiral}=0.55±0.03; P<0.01) and mean diffusivity in diastasis (10%; MD_{EPI}=1.00±0.12×10^{-3} mm^2/s, MD_{spiral}=1.10±0.09×10^{-3} mm^2/s, P=0.02).
Conclusion:
This is the first study to demonstrate DT-CMR STEAM using a spiral trajectory. SNR was increased by using a spiral rather than the more established EPI readout and DT-CMR parameters were largely similar between the two sequences.
Introduction

Diffusion tensor cardiovascular magnetic resonance (DT-CMR) is a unique technique providing non-invasive measures of myocardial microstructure including orientation of cardiomyocytes (1, 2) and aggregates of cardiomyocytes known as sheetlets (3). This information holds great potential for gaining new insights into the structure and function of the normal myocardium and in diseases including cardiomyopathies (3-6) and myocardial infarction (7-9).

DT-CMR is frequently performed using a stimulated echo acquisition mode (STEAM) technique (2, 10, 11) and has demonstrated interesting clinical results when performed in both systole and diastasis (3). The STEAM technique uses diffusion encoding at identical positions in two consecutive cardiac cycles to provide a long mixing time (one cardiac cycle) with short diffusion encoding gradients and therefore minimizes bulk motion effects. However, it acquires only one image every other cardiac cycle. Calculating the diffusion tensor requires a minimum of seven images with sufficient signal to noise ratio (SNR) and acquiring several averages to bolster SNR is time consuming.

DT-CMR acquisitions typically use echo planar imaging (EPI) readouts to rapidly acquire single shot data (10, 11). The maximum readout duration is restricted by off-resonance artifacts, T2/T2* and cardiac motion. The short T_2 of myocardial tissue of ~47 ms (12) means that minimizing the echo time (TE) is important in maximizing SNR. A symmetric EPI readout samples half of k-space before reaching the centre of k-space and limiting the minimum TE. For a centre-out spiral, TE does not depend on resolution or FOV. Several studies have investigated spiral trajectories in neurological DTI (13, 14). Spirals have also been widely used in cardiac MRI research due to their efficient k-space coverage and motion resilience (15, 16) and Zhong et al. (17) used a spiral trajectory with a stimulated echo in a cine DENSE sequence for strain measurements. In this study we build on pilot work presented at ISMRM (18, 19) and aim to
demonstrate the equivalence of the DT-CMR results obtained using STEAM with both an EPI and a spiral readout performed in diastasis and at peak systole. We measured the SNR in vivo and in a phantom with the aim of demonstrating SNR improvements using a spiral readout with a view to future improvements in spatial resolution.

Methods

Pulse Sequence Design
The single-shot diffusion-weighted STEAM sequence used in this work is shown with an EPI and spiral readout in Figure 1. Spirals were designed as slew rate limited Archimedean trajectories (20, 21). The spiral readout duration is shortened by reducing the field of view (FOV) that contributes to the stimulated echo (the stimulated echo FOV) by applying slice-selective gradients in orthogonal directions during the three radio-frequency (RF) pulses. For the EPI sequence the stimulated echo FOV is reduced in the phase-encode and slice directions, as a reduction in the read FOV would not shorten the readout. TE is reduced for the spiral sequence due to its centre-out nature and by using asymmetric RF pulses. The peak of the first RF pulse was located at 81% of the duration and the second RF pulse was a time-reversed copy of the first. For both sequences the three RF pulses had phases 90°, 0° and 0°.

Data acquisition, reconstruction and processing
All data were acquired on a clinical 3 T scanner (Skyra Siemens Healthcare, Erlangen Germany) with a maximal gradient strength and slew rate of 43 mT/m and 180 T/m/s respectively. An 18 element anterior coil and 8-12 elements of a posterior spine coil were used. A second order shim was performed before the first acquisition with each of the sequences. Each average of the EPI DT-CMR acquisition required 18 cardiac cycles; two cardiac cycles for each of the following: EPI phase correction lines, parallel imaging reference data, a so called “b0” (b=34s/mm²) image and diffusion weighted images (with
b_{main}=600 \, \text{s/mm}^2 \text{ or } b_{ref}=150 \, \text{s/mm}^2) \text{ encoded in 6 diffusion encoding directions. Each spiral average requires } 16 \text{ cardiac cycles, two for each of the following: a dummy cycle to drive the transverse magnetization into a steady-state, a “b}_0\text{” image and similarly to the EPI, 6 diffusion weighted images. For both sequences an acquired resolution of } 2.8\times2.8\times8 \, \text{mm}^3 \text{ and the same b-values were used. For the spiral acquisitions a readout FOV of } 120\times120 \, \text{mm}^2 \text{ and stimulated echo FOV of } 80 \% \text{ of the readout FOV was used; for the EPI sequence the FOV was } 360\times135 \, \text{mm}^2 \text{ (readout x phase encode)}. \text{ The readout duration was } 13 \, \text{ms and } 14 \, \text{ms, TE was } 23 \, \text{ms and } 11 \, \text{ms and dwell time was } 1.6 \, \mu\text{s and } 2.8 \, \mu\text{s for the EPI and the spiral sequences respectively. Parallel imaging with SENSE x2 was used with EPI (22).}

The spiral data was reconstructed offline using the GNUFFT algorithm (23) in MATLAB (Mathworks, Natick, MA, USA) and data from the receive coils was combined using the maximized SNR technique (24) using coil sensitivity maps obtained from the dummy cycle and “b}_0\text{” images.

The EPI data was reconstructed online using the standard product reconstruction. Images from both sequences were reconstructed to a 1.4x1.4 mm$^2$ resolution.

**Phantom SNR measurements**

A cylindrical agar phantom (11 cm long, 12 cm diameter, long axis aligned along the scanner bore) with an agar concentration of 40 g/L was imaged with both sequences.

Spiral and EPI DT-CMR data for SNR measurements were acquired with 60 averages for each of the 6 directions at b=150 s/mm$^2$ and b=600 s/mm$^2$ using the protocols described above. A simulated ECG period of 1000 ms was used. The SNR was calculated pixel wise for the unaveraged magnitude images for each of the directions individually (25, 11) via:

$$
\text{SNR} = \frac{\overline{X}}{\sigma} = \frac{\frac{1}{N} \sum_{i=1}^{N} x_i}{\left(\frac{1}{N} \sum_{i=1}^{N} [x_i - \overline{X}]^2\right)^{1/2}} = \frac{\sqrt{N}}{\sqrt{\sum_{i=1}^{N} [x_i - \overline{X}]^2}}
$$
with the signal intensity in one of the averages $x_i$, mean signal intensity averaged over the $N$ averages $\bar{x}$ and standard deviation over the $N$ averages $\sigma$. This mean SNR was calculated within a ROI for each direction and subsequently the mean over all 6 directions was taken.

**In vivo imaging**

Mid-ventricular single slice short-axis breath-hold DT-CMR was performed in 11 healthy volunteers (4 female, mean age 33 [range 21-52] years, heart rate 60 [49-71] bpm). The study was conducted in accordance with National Research Ethics Service approval. DT-CMR was performed at peak systole and diastasis in each of the volunteers using both the EPI and spiral sequences. Timings were determined from cine images in the same plane as the DT-CMR. To minimize bias in the results due to the acquisition order, the four data sets ($EPI_{systole}$, $spiral_{systole}$, $EPI_{diastasis}$, $spiral_{diastasis}$) were acquired in a random order. To minimize artifacts from residual unsuppressed tissue outside the imaging FOV in the spiral acquisition, four spatial saturation bands were positioned around the FOV.

8 averages in 8 breath-holds were acquired for each cardiac phase and sequence with $b_{main}=600$ s/mm$^2$ and a 9th breath-hold was performed to obtain reference images with $b_{ref}=150$ s/mm$^2$ in each of the 6 directions. Post-processing was performed using in-house MATLAB software (3). The pixel wise diffusion tensor was calculated using a linear least-squares algorithm using the $b_{ref}=150$ s/mm$^2$ and $b_{main}=600$ s/mm$^2$ data to minimize perfusion effects (26). The b-values were corrected for the length of the cardiac cycles giving $b_{main}=611$ [509-741] s/mm$^2$ and images were included in the tensor calculation without averaging.

Sequences were compared using measures of mean left ventricular (LV) fractional anisotropy (FA), mean diffusivity (MD), eigenvalues, transmural helix angle (HA) gradient (HAG) transverse angle (TA) and median absolute secondary eigenvector angulation (E2A), excluding the papillary muscles and the septo-marginal trabeculations of the right ventricle. SNR maps were calculated for each of the directions using Eq [1] and the SNR was measured in a ROI in the septal wall and over the LV for each
diffusion direction and the median was calculated. To quantify HA, the mean HAG was calculated (°/± myocardial wall thickness) by linear regression of transmural HA line profiles from endocardium to epicardium. Only line profiles with a negative slope and an $R^2 \geq 0.3$ were included in the HAG measurement. The sheetlet orientation was quantified via E2A (defined in (3)).

A comparison of the data quality was performed using the $R^2$ value and root-mean-square error (RMSE) of the linear regression of HAG. In healthy volunteers the TA, the angle between the projection of the main eigenvector into the short axis and the circumferential direction, is approximately zero in a mid-slice (27) and therefore its standard deviation within each subject was used as another data quality measure. A non-parametric statistical analysis was performed with a Wilcoxon signed rank test. A threshold of $P<0.05$ was considered significant.

**Results**

**Phantom SNR measurements**

Phantom T1 was measured as 1075±25 ms (typical myocardial T1 1169-1315 ms (28, 29)) using inversion recovery sequences and T$_2$ was 48±1 ms (typical myocardial T2 = 47 ms, (12)) using multiple spin-echo acquisitions. The phantom MD was 1.2±0.04x10$^{-3}$ mm$^2$/s using a product Stejskal-Tanner spin-echo EPI sequence. Signal intensity in the phantom demonstrated a small drift (~2 % over 13 minutes) during the acquisition, which was corrected using a linear fit. SNR was 74±13 and 120±38 (62% increase) for $b=150s/mm^2$ and 41±7 and 66±21 (61% increase) for $b=600 s/mm^2$ for the EPI and the spiral sequences respectively. The theoretical SNR increase due to the shorter spiral TE is 29% (T2=47ms).

**In vivo measurements**

The acquisition time including planning, and both sequences in both cardiac phases was 40-60 minutes. One subject was excluded from the
analysis due to arrhythmia, causing both sequences to fail, for a second subject the diastasis data was excluded due to a sub-optimal selection of the trigger time. Pixel wise diffusion tensors and the associated parameter maps were calculated from all other acquisitions. Figure 2 shows the diffusion images from all 6 directions for a typical volunteer (full FOV images and both b-values shown in Supporting Figure S1) and the FA, MD, HA, E2A and SNR maps for both sequences in both cardiac phases are shown in Figure 3. There is a reasonable correspondence of the visual appearance of the maps between the EPI and spiral sequences. Figure 4 plots the mean LV HAG, median E2A and TA; and Figure 5 the mean FA, MD and median SNR in the septum (LV SNR is provided in Supporting Figure S2) for each subject using both sequences in both cardiac phases. The segment-wise (anterior, lateral, inferior, septal) percentage of profiles accepted for the HAG calculation for systolic EPI is: 95, 93, 93, 99%, systolic spiral: 95, 84, 87, 99%, diastasis EPI: 95, 86, 88, 97% and diastasis spiral: 66, 70, 78, 90%. The in vivo SNR comparison for b=600s/mm\(^2\) images showed an increase from (median±interquartile range) 8.0±2.2 using EPI to 12.0±2.7 using spiral (51%) in systole and from 8.1±1.6 to 12.0±3.7 (49%) in diastasis. The SNR in the LV increased from 6.0±1.3 using EPI to 10.2±1.9 using spiral (69%) in systole and from 5.9±1.8 to 8.1±1.4 (38%) in diastasis.

A comparison of DT-CMR results between the sequences and with literature is provided in Supporting Tables S1 and S2. There were no significant differences between sequences in either phase of the cardiac cycle for E2A (\(P=0.77/0.20\), systole/diastasis), HAG (\(P=0.11/0.20\), systole/diastasis) or for systolic MD (\(P=0.23\)) and diastasis TA (\(P=0.30\)). However, there were small differences in FA in systole and diastasis (\(P<0.004\)), MD in diastasis (\(P=0.02\)) and TA in systole (\(P=0.01\)).

The lower FA using the spiral are the result of higher secondary (\(P=0.06/0.004\), systole/diastasis) and tertiary eigenvalues (\(P=0.002/0.004\), systole/diastasis). The primary eigenvalue showed no significant difference between sequences at either phase (\(P=0.19/1.00\),
systole/diastole). A subject wise comparison of the eigenvalues is shown in Supporting Figure S3.

Supporting Figure S4 shows the data quality analysis including $R^2$ and RMSE for the HAG calculation and the standard deviation of the TA (stdTA). The circumferential distribution of the $R^2$ and RMSE values is also shown. The highest $R^2$ was found in the septal wall for both sequences and phases. The lowest RMSE was found in the anterior wall for the EPI and in the lateral wall for the spiral in both phases. The data quality comparison showed no significant difference between the sequences for stdTA ($P=0.28/0.73$ systole/diastasis), systolic RMSE ($P=0.56$) and systolic $R^2$ ($P=0.43$). In diastasis there was an 18% drop of the $R^2$ and a 36% increase of the RMSE using the spiral readout.

**Discussion and Conclusion**

This is the first demonstration of the use of a spiral trajectory in DT-CMR. Here we have shown that spiral STEAM DT-CMR can be used to produce largely similar DT-CMR parameters to those obtained with a more typical EPI trajectory.

This work has shown that the SNR can be increased by replacing the EPI readout of a STEAM sequence by a spiral; the measured increase was over 61 % in a phantom and over 49 % in vivo in the septum where the SNR is minimally affected by artefacts. An increase in SNR was expected due to the TE differences between the sequences; assuming $T2=47$ ms the TE reduction of 23 ms to 11 ms should result in a SNR increase of 29 %. The larger improvement in SNR observed is likely to be the result of differences in the sequence and in the reconstruction methods used.

The SNR measurement was performed on the $b_{main}$ images, because there are fewer “$b_0$” and $b_{ref}$ images. In addition, the spiral “$b_0$” images frequently demonstrate wrap artefacts from structures outside the stimulated echo FOV. This artefact is the result of the free induction decay (FID) signal from the third RF pulse of the stimulated echo. While this
signal is spoiled by the diffusion gradients in the $b_{\text{main}}$ images, the spoiling is insufficient in the “$b_0$” images. As the TE of the EPI sequence is more than twice that of the spiral sequence, it is likely that the T2* decay of the FID signal substantially attenuates this artefact in the EPI data. This artefact would result in misleading SNR values for the “$b_0$” spiral images. Whilst we matched imaging parameters where possible, the differences between the two techniques means that there are inherent differences in the type and severity of artefacts such as blurring that may affect SNR and in imaging parameters such as receiver bandwidth, the use of parallel imaging and reconstruction pipelines.

E2A and HAG in both cardiac phases and MD and TA in diastasis were similar between the sequences ($p>0.05$). However, for the spiral sequence FA was lower while diastolic MD and systolic TA were lower for the EPI data. While we have used the established STEAM EPI sequence as our reference in this study, it does not provide ground truth results. Studies considering the effects of noise on diffusion tensor data have demonstrated artifactual increases in FA (30, 31) due to eigenvalue repulsion (32), which could explain the reduced spiral FA. While the spiral MD in diastasis is higher, the difference is small ($0.10 \times 10^{-3} \text{ mm}^2/\text{s}$) being the same as the inter-centre difference measured using the STEAM EPI sequence in a multi-centre study (33) and unsubstantial when compared to the increase MD observed in disease (7). The trigger times of both sequences were matched, which ensured a similar diffusion encoding time. However, this means that the central k-space data is acquired slightly earlier in the cardiac cycle for the spiral. In the time between diffusion encoding and acquiring the central k-space data, the diffusion encoded tissue could be rotated around the LV long axis by the cardiac motion. The rotation of the diffusion-encoded tissue relative to the diffusion encoding direction could lead to an artifactual change in TA for the EPI sequence. This change is more likely to be seen in systole where the heart is more dynamic.
We found similar values of the data quality measures between sequences, except for a reduction in the $R^2$ and an increase in RMSE using the spiral sequence in diastasis. We attribute this difference to off-resonance artifacts including blurring, which were more evident using the spiral sequence as no off-resonance correction was used. As the myocardium is thinner in diastasis than in systole, a similar sized artefact affects a larger proportion of the transmural thickness.

Supporting Tables S1 and S2 provide a summary of the results obtained here compared with those from previous studies using STEAM EPI acquisitions. FA and MD obtained with the spiral lie within the range reported in the literature (2, 11, 33-37). E2A reported here is similar to that described in the literature (3, 6) and the higher diastolic value in Ferreira et al. (3) is a consequence of using the median here rather than the mean over the LV. HAG is lower than other studies using °/°% units (35, 37), particularly in diastasis, although comparatively lower values have been quoted using °/mm (38). Mean TA values are not widely reported, although our values are higher than in Stoeck et al. (37).

Parallel imaging was used with the EPI sequence in order to reduce the readout duration. In order to minimize background noise and match the noise distribution between the sequences we estimated coil sensitivity maps from the spiral data and performed a coil weighted reconstruction. Nevertheless the image reconstruction is intrinsically different between the sequences. While strategies, such as partial Fourier, low-high phase encode ordering and further reductions in the phase field of view, may be used to reduce the EPI TE further, we chose to use an established EPI protocol (26, 31), optimized in earlier work (11) and compare to our current optimal spiral protocol with a smaller FOV. Due to the challenges in recruiting older healthy subjects, our cohort was relatively young and future work will investigate the performance of the two techniques in older and diseased cohorts.
Future work will address the remaining challenges in spiral DT-CMR, particularly in diastole, by using an off-resonance correction or shorter spiral readouts in combination with parallel imaging. Spatial resolution may be increased via parallel imaging (39) and segmented acquisitions using variable density spirals (40). These improvements in spatial resolution may be valuable in understanding LV microstructure in thin myocardium due to myocardial infarction or dilated cardiomyopathy and in the right ventricle.

In conclusion, this initial proof of concept study demonstrates the first use of a spiral trajectory in combination with STEAM to obtain DT-CMR data to interrogate cardiac microstructure. DT-CMR results were largely similar between sequences with increased SNR and similar data quality in systole using the spiral sequence. In future taking full advantage of the increased SNR and features of spiral trajectories to increase spatial resolution may enable greater transmural detail in clinical DT-CMR studies and may provide novel diagnostic information in new patient cohorts and the right ventricle.
Figures:

Figure 1: Sequence diagram for the STEAM EPI a) and STEAM spiral b) sequences. The stimulated echo field of view is reduced via slice-selective excitation RF pulses, as only the region that experiences all three RF pulses contributes to the stimulated echo. For the EPI sequence the stimulated echo FOV is only reduced in the phase encode direction since a reduction in the frequency encode direction would not lead to a substantially shorter readout length unlike for the spiral where it is reduced in both in-plane directions. Asymmetric RF pulses are used in the spiral sequence for the first two pulses in order to further reduce the TE. The asymmetries are 81% and 19% for the first and second pulses respectively.
Figure 2: Magnitude images for an example volunteer for both sequences in systole and diastasis with $b_{\text{main}}=600$ s/mm$^2$ in all 6 diffusion directions.
Figure 3: Example DT-CMR parameter maps from the same volunteer shown in Figure 2 in systole and diastasis: FA, MD, HA, E2A and SNR maps are shown for the EPI and the spiral sequences.
Figure 4: Subject wise comparisons of a) HAG, b) E2A and c) TA are shown. The individual subjects are color-coded and the medians and interquartile ranges are plotted in black. The p-values above or below the data indicate the results of Wilcoxon signed rank test between the EPI and spiral data for both cardiac phases.

Figure 5: Subject wise comparisons of a) FA, b) MD and c) septal SNR are shown with color coding and labelling as in Figure 4.
Supporting Material:

Supporting Figure S1: Magnitude images for an example volunteer from both sequences. A full acquired FOV and an extract are shown for all 6 diffusion directions and both diffusion weightings for the EPI and the spiral acquisition.
Supporting Figure S2: Subject wise comparison of LV SNR is shown with color coding and labelling as in Figures 4 and 5.
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<th>FA diast.</th>
<th>MD [x10⁻³ mm²/s] syst.</th>
<th>MD [x10⁻³ mm²/s] diast.</th>
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**Supporting Table S1:** Comparison of the EPI and the spiral readout results for the mean diffusivity (MD) and fractional anisotropy (FA). The median and the interquartile range are shown. A Wilcoxon signed rank test with a threshold of P<0.05 was used. The DT-CMR parameter values measured in this work were compared with those measured with STEAM in the existing literature. The values quoted from Stoeck et al. (37) are mean values given before strain correction obtained with encoding in 10 directions. Stoeck et al. (37), von Deuster et al. (27), Reese et al. (2), Tseng et al. (41), and Wu et al. (9) used a 1.5T magnet, all other works were performed at 3T. Von Deuster et al. (27) used 12 diffusion directions and scanned in mid systole as did Wu et al. (9). Tseng et al. (41) reported results in the free wall and the septum respectively.
Supporting Table S2: Comparison of the EPI and the spiral readout results for the helix angle gradient (HAG), secondary eigenvector angulation (E2A) and transverse angle (TA). As in Supporting Table S1, the median and the interquartile range and the Wilcoxon test results are shown. The DT-CMR parameter values measured in this work were compared with those measured with STEAM in the existing literature. The values quoted from Stoeck et al. (37) are mean values given before strain correction obtained with encoding in 10 directions.

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Supporting Table S2: Comparison of the EPI and the spiral readout results for the helix angle gradient (HAG), secondary eigenvector angulation (E2A) and transverse angle (TA). As in Supporting Table S1, the median and the interquartile range and the Wilcoxon test results are shown. The DT-CMR parameter values measured in this work were compared with those measured with STEAM in the existing literature. The values quoted from Stoeck et al. (37) are mean values given before strain correction obtained with encoding in 10 directions.
Supporting Figure S3: A subject-wise comparison of the primary (a), secondary (b) and tertiary (c) eigenvalues (EV) for both cardiac phases for the EPI and spiral readouts.
Supporting Figure S4: Quality analysis of the data using $R^2$ and RMSE values of the HAG and the standard deviation of the TA (stdTA). The median circumferential variation over all subjects of $R^2$ and RMSE is shown circumferentially in (a) and (b) respectively. The printed values are the median over the myocardial segments. A subject wise comparison of these values is shown in (c) and (d) and the subject wise comparison of the stdTA is demonstrated in (e).
References