

Imperial College London
National Heart & Lung Institute

Development of novel magnetic resonance methods for advanced parametric mapping of the right ventricle

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Abstract

The detection of diffuse fibrosis is of particular interest in congenital heart disease patients, including repaired Tetralogy of Fallot (rTOF), as clinical outcome is linked to the accurate identification of diffuse fibrosis.

In the Left Ventricular (LV) myocardium native T₁ mapping and Diffusion Tensor Cardiac Magnetic Resonance (DT-CMR) are promising approaches for detection of diffuse fibrosis. In the Right Ventricle (RV) current techniques are limited due to the thinner, mobile and complex shaped compact myocardium. This thesis describes technical development of RV tissue characterisation methods.

An interleaved variable density spiral DT-CMR method was implemented on a clinical 3T scanner allowing both *ex* and *in vivo* imaging. A range of artefact corrections were implemented and tested (gradient timing delays, off-resonance and T₂* corrections). The off-resonance and T₂* corrections were evaluated using computational simulation demonstrating that for *in vivo* acquisitions, off-resonance correction is essential.

For the first-time high-resolution Stimulated Echo Acquisition Mode (STEAM) DT-CMR data was acquired in both healthy and rTOF ex-vivo hearts using an interleaved spiral trajectory and was shown to outperform single-shot EPI methods.

In vivo the first DT-CMR data was shown from the RV using both an EPI and an interleaved spiral sequence. Both sequences provided were reproducible in healthy volunteers. Results suggest that the RV conformation of cardiomyocytes differs from the known structure in the LV.

A novel STEAM-SAturation-recovery Single-sHot Acquisition (SASHA) sequence allowed the acquisition of native T₁ data in the RV. The excellent blood and fat suppression provided by STEAM is leveraged to eliminate partial fat and blood signal more effectively than Modified Look-Locker Imaging (MOLLI) sequences. STEAM-SASHA T₁ was validated in a phantom showing more accurate results in the native myocardial T₁ range than MOLLI. STEAM-SASHA demonstrated good reproducibility in healthy volunteers and initial promising results in a single rTOF patient.

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Abbreviations

Adenosine Tri Phosphate (ATP)

Analog-Digital (A-D)

Apparent Diffusion Coefficient (ADC)

balanced Steady State Free Precession (bSSFP)

Cardiac Magnetic Resonance (CMR)

Coefficient Of Variation (COV)

Coil Sensitivity (CS)

Coil Sensitivity Map (CSM)

Computed Tomography (CT)

Congenital Heart Disease (CHD)

Contrast Enhanced Magnetic Resonance Angiography (CEMRA)

Diffusion Spectrum Imaging (DSI)

Diffusion Tensor Cardiac Magnetic Resonance Imaging (DT-CMR)

Diffusion Tensor Imaging (DTI)

Diffusion Weighted Imaging (DWI)

Dilated Cardiomyopathy (DCM)

Echo Planar Imaging (EPI)

Electrocardiogram (ECG)

Extra Cellular Matrix (ECM)

Extra Cellular Volume Fraction (ECV)

Fast Fourier Transform (FFT).

Field Map (FM)

Field Of View (FOV)

Fractional Anisotropy (FA)

Free Induction Decay (FID)

Frequency Encode (FE)

Gadolinium Based Contrast Agent (GBCA)

Generalised Auto Calibrating Partial Parallel Acquisition (GRAPPA)

Gradient Echo (GRE)

Gradient Impulse Response Function (GIRF)

Graphical User Interface (GUI)

Helix Angle (HA)

Helix Angle Gradient (HAG)

Hypertrophic Cardiomyopathy (HCM)

Inclination Angle (IA)

Integrated Development Environment for Applications (IDEA)

Inter Quartal Range (IQR)

Inversion Recovery (IR)

Late Gadolinium Enhancement (LGE)

Left Ventricle (LV)

Mean Diffusivity (MD)

Modified Look-Locker Imaging (MOLLI)

Motion Compensated Spin Echo (MCSE)

Myocardial Infarction (MI)

Non-Uniform Fast Fourier Transform (NUFFT)

Nuclear Magnetic Resonance (NMR)

Peripheral Nerve Stimulation (PNS)

Periodically Rotated Overlapping Parallel Lines with Enhanced Reconstruction (PROPELLER)

Phase Encode (PE)

Proton Density (PD)

Pulmonary Regurgitation (PR)

Point Spread Function (PSF)

Radio Frequency (RF)

repaired Tetralogy of Fallot (rTOF)

Right Ventricle (RV)

Right Ventricular Outflow Tract (RVOT)

Root Mean Square (RMS)

Root Mean Square Error (RMSE)

SAturation-recovery Single-sHot Acquisition (SASHA)

Short Axis (SAX)

Self-Navigated Interleaved Spirals (SNAILS)

Sensitivity Encoding (SENSE)

Signal Noise Ratio (SNR)

Situs Inversus Totalis (SIT)

Spin Echo (SE)

Stimulated Echo Acquisition Mode (STEAM)

Sum Of Squares (SOS)

Tetralogy of Fallot (TOF)

Transverse Angle (TA)

Repetition Time (TR)

Ventricular Septal Defect (VSD)

1 Cardiac Anatomy and Function

This chapter provides an introduction to cardiac anatomy and function in normal humans.

1.1 Macrostructure

The heart located at the centre of the thorax acts as the driving force behind human blood circulation. While only measuring about the size of two clasped hands, it is able to pump about 7200 litres of blood per day enabling the transportation of oxygen, carbon dioxide, nutrients and waste throughout the body [1].

The heart is organized into two major parts, the left and the right (Figure 1) and even across a healthy spectrum, the physical orientation can vary depending on height, body mass and other factors [1]. Thus, even for healthy people the following definition of left and right is based on function rather than on physical location:

- The right heart pumps deoxygenated blood to the lungs and, after gas exchange takes place, oxygenated blood returns to the left heart.
- The left heart pumps oxygenated blood to the rest of the body.

A different anatomical structure is needed in the left and right heart to carry out these two different functions. A far greater mechanical force is required to pump blood throughout the body, reaching all the extremities, rather than just to the lungs which are located near to the heart. The right side is therefore less muscular, with compact muscle measuring approximately 4-5 mm [2]–[5] across the wall, while the left side is comprised of approx. 9-11 mm of compact myocardium [6]–[10].

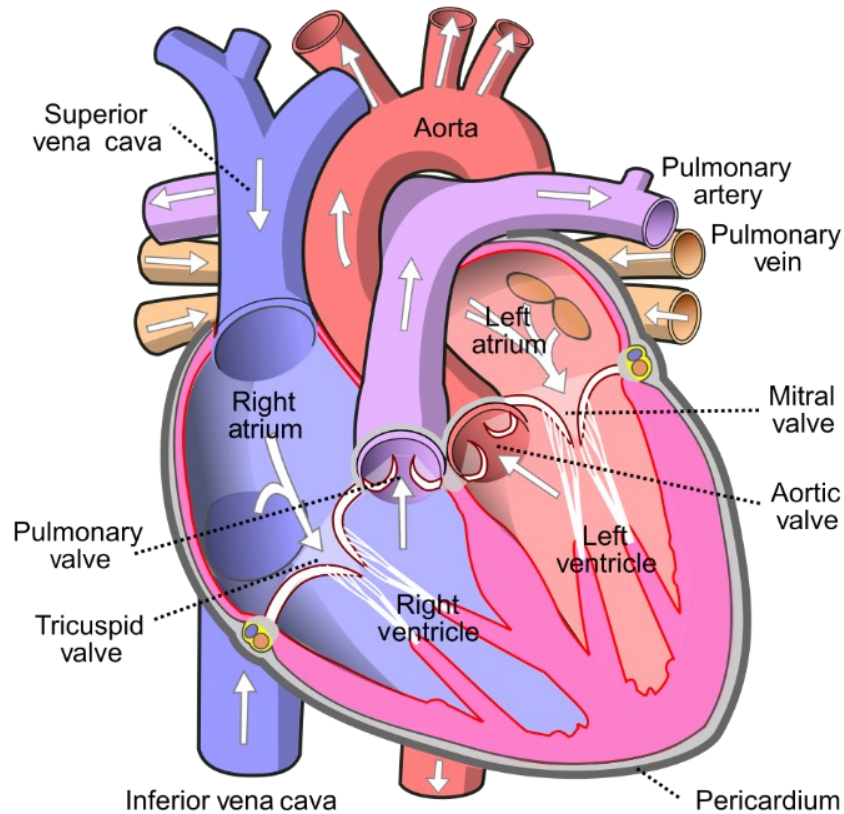


Figure 1: Diagram of the left and right side of the heart including the major vessels and direction of blood (white arrows). Taken from [1]

Both sides are further separated into two chambers, the smaller atria, and the bigger ventricles (Figure 1). The venous blood enters the atria from either the vena cava (right) or pulmonary veins (left) and the atria contract first during the cardiac cycle to complete the filling of the ventricles before the mitral (left) and tricuspid (right) valves close. The ventricles then contract, pumping blood out of the heart through the pulmonary valve on the right side and the aortic valve on the left. [1], [12]

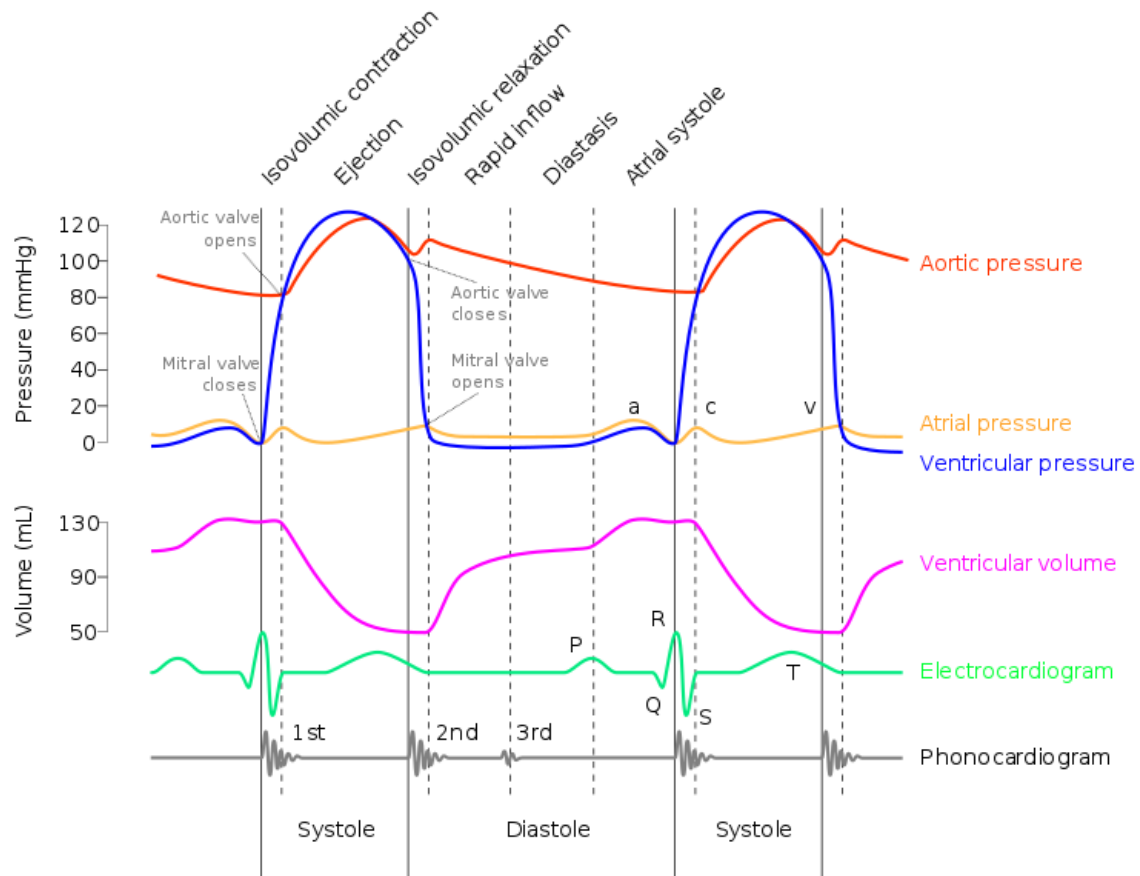


Figure 2: Wiggers diagram showing the cardiac cycle in terms of different measurements. Green shows the electrical signal that can be obtained with an electrocardiogram (ECG) and is defined through the PQRST waves. Pink shows the change in ventricular volume. Orange, yellow and blue respectively show the aortic, atrial, and ventricular pressure. Grey the acoustic measurements taken by a phonocardiogram. Taken from [11]

Through this cycle the volume and pressure within the ventricle and connected vessels changes and can be described by a so-called Wiggers diagram shown in Figure 2. In green here the electric signal captured by an Electrocardiogram (ECG) is shown, with the P wave indicating the depolarisation of the atria, the QRS corresponding to the depolarisation of the ventricle and the T wave the repolarisation of the ventricle. The diagram shows the increase in ventricular pressure in blue coinciding with the QRS complex. When a threshold left ventricular pressure is reached the aortic valve opens and then there is a respective increase in the aortic pressure shown in red. Similarly, the fluctuations of atrial pressure are shown in yellow and the overall ventricular volume is provided in the pink line.

1.1.1 Right Ventricular Macrostructure

While commonly depicted to be similar in diagrams (such as Figure 1) the anatomy of the Right Ventricle (RV), differs from the thicker walled Left Ventricle (LV). These differences originate in the embryological beginnings where the RV develops from a different field of cells than the LV [13]. The RV forms a triangular shape when viewed in the sagittal plane and in the short-axis can be described as concave in the free wall and convex in the septum (Figure 3) [1]. Additionally, the RV is sometimes sub-divided into the sinus and the infundibulum, as shown in Figure 3.

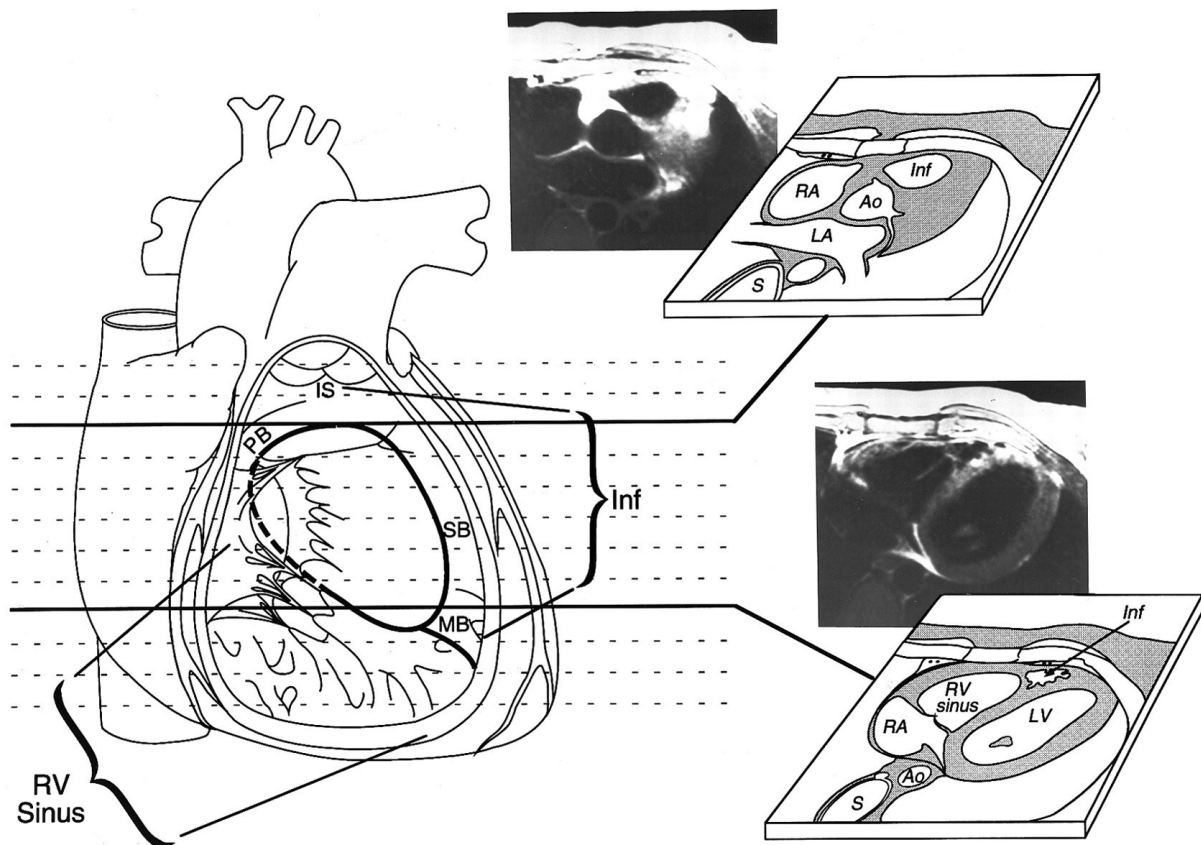


Figure 3: Diagram of the RV with accompanying illustrations of the RV Sinus, RV Infundibulum (Inf), the Right Atrium (RA), the Left Ventricle (LV), Left Atrium (LA), Spine (S), Aorta (Ao), Moderator Band (MB), Septal Band (SB), Parietal Band (PB) and Infundibular Septum (IS). Taken from [14]

Figure 4 shows example measures of the RV thickness compared to the septum in systolic and diastolic cardiac phases from a typical healthy human. While the septum measures 9mm and 12mm in diastole and systole respectively, the RV free wall measures only 3-4 mm and 4-5 mm.

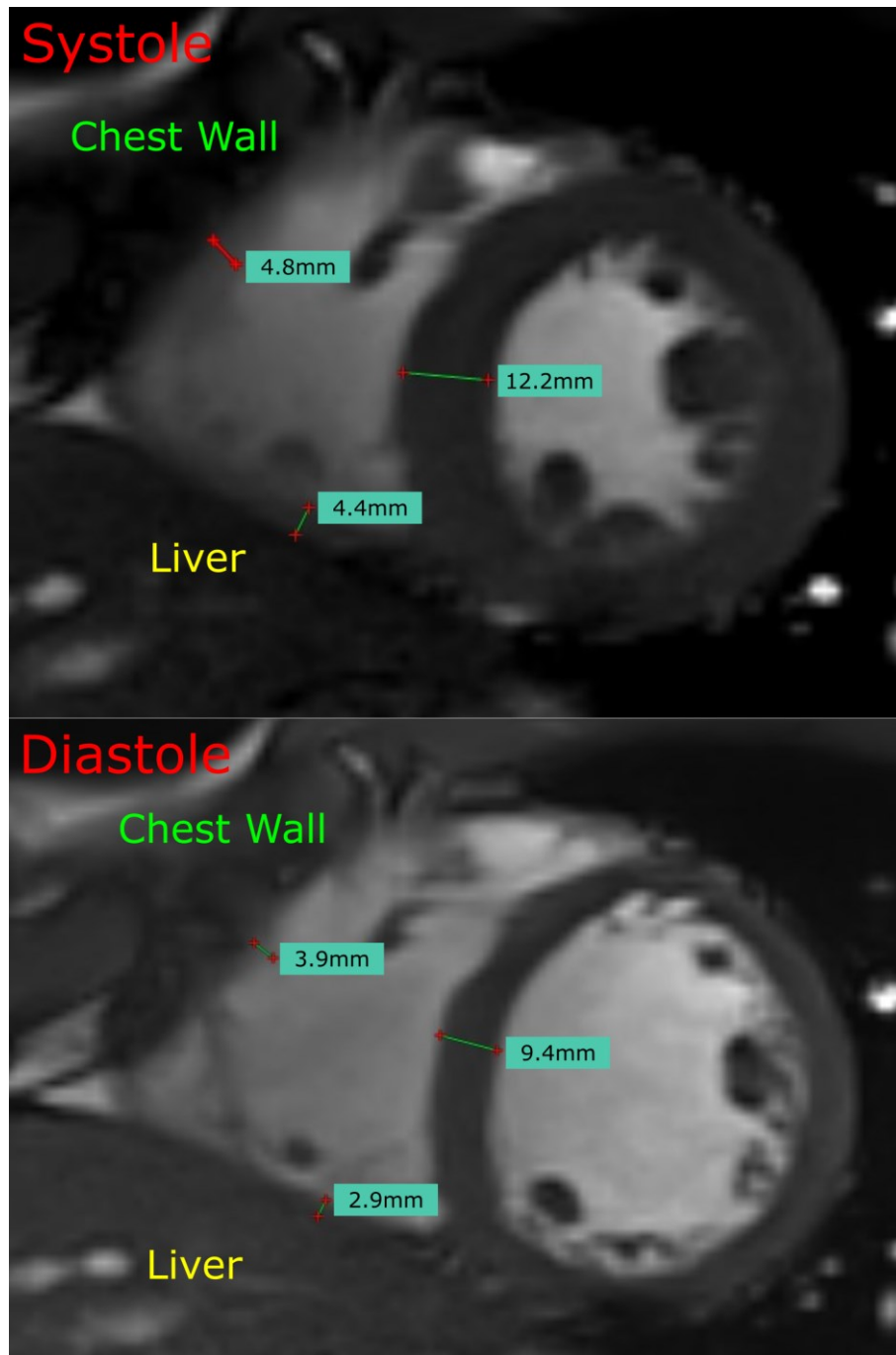


Figure 4: Systolic and diastolic cardiovascular MRI images from one healthy volunteers imaged in the right ventricular short axis plane. Images show manual measurements of the wall thickness in the septum, inferior and anterior RV.

These anatomical differences and the variations in physiological workload result in quite different contraction mechanisms in the RV compared to the LV. The major RV motion during contraction is longitudinal from inlet to outlet and is sometimes described as a ‘bellowing’ motion originating in the free wall towards the septum [1]. Consequentially haemodynamic loading is very different, especially in Congenital Heart Disease (CHD) patient groups [15].

Despite these differences, the left and right heart should not be considered independent, as LV and RV share the septum, coronary supply, and a common myocyte type (covered below). As a consequence there is a functional interdependence, with experimental work attributing >50 % of RV mechanical work to the contraction of the LV [16], [17].

1.2 Microstructure

1.2.1 Cardiomyocytes

Cardiomyocytes are muscle cells that make up approximately 75 % of the myocardial volume [12] and are the driver for the mechanical forces inside the heart. There are subtle differences between the ventricular and the atrial cardiomyocytes. While the atrial cells are smaller, measuring about 5-6 μm in diameter and 20 μm in length, the ventricular cells are roughly 10-25 μm thick and 50-100 μm long [12]. Atrial cells are more elliptical in shape compared to the long and narrow shape of the ventricular cells. Myocytes are enclosed by an external membrane called the sarcolemma which contains a vast tubular network (T-tubules) penetrating deep into the cells and filled with extracellular fluid [1], [12].

Within a cardiomyocytes there is at least one, sometimes more, cell nuclei and several types of organelle, of which the most prominent are myofibrils and mitochondria [12]. Mitochondria, are responsible for producing Adenosine Triphosphate (ATP), the main source of energy within the cell, and are packed close to the main energy consumer the myofibril (Figure 5) [12].

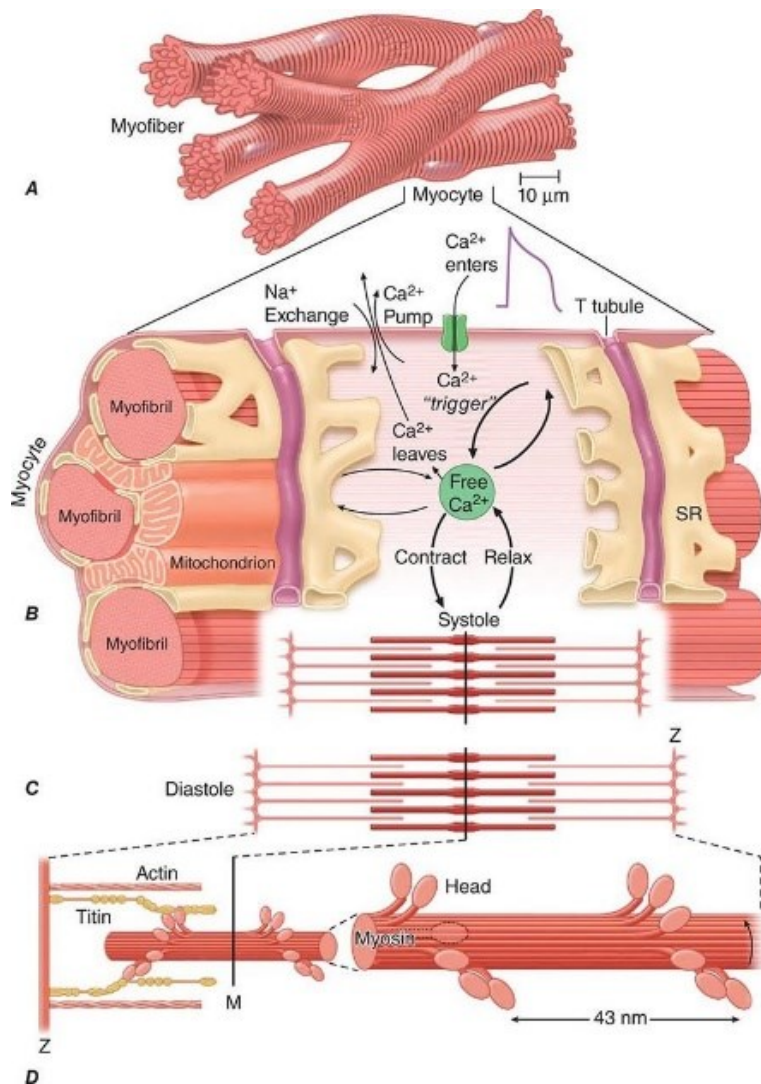


Figure 5: Makeup of the individual cardiomyocyte and the underlying contraction pathway. (A) depicts the branching structure of the myocyte with connection to other myocytes. (B) shows the myocyte on a cellular level with the most prominent organelles (Myofibril, Mitochondria and T tubule). The activation pathway for contraction is also displayed, with ion pumps moving calcium into the cell and triggering the change between the two states shown in (C) which shows the reorganisation of the Actin and Myosin filaments between systole and diastole in the myofibril. In (D) the individual molecules (Actin, Titin, Myosin) present in the makeup of the myofibril are shown. While the Actin is fixed to the Z bands the Myosin is located between the Actin filaments. During contraction the heads of the Myosin interact with the Actin and pull it towards the Z band and relax when ATP binds to them during relaxation. The Titin in this setup acts as a molecular spring and as placeholder for the Myosin. Taken from [12]

The myofibrils, which make up approximately 50 % of the cell volume, are responsible for the contraction - relaxation process that defines the myocytes most prominent function [12]. As shown in Figure 5 the myofibril is made up of many sarcomeres that attach to the next group of sarcomeres at the so-called z-bands (see Figure 5) [18]. The actin filaments and titin molecules within each sarcomere are perpendicularly attached to these z-bands [18]. While the actin filaments reach far into each sarcomere the titin is attached to filaments of myosin that are located in the centre of each sarcomere [18]. When the wave of electrical depolarisation reaches a cardiomyocyte, the change in membrane potential activates ion pumps that increase Ca^{2+} concentration within the cell [18]. The increase in cytosolic calcium results in the myosin filaments being pulled towards the z band [18]. While none of the filaments themselves actually contract, the sliding mechanism of the actin over myosin filaments generates the mechanical force that shortens and thickens the cardiomyocytes, resulting in the ejection of blood from the heart [12].

While we continue to learn new information about their exact makeup, a group of myocytes is often described as being held together by connective tissue to form a functional group, often cited as a myofiber in standard textbooks ([1], [12], [18], Figure 5). Modern research suggests however that these myofibers do not exist [19], as when investigating the microscopic architecture of the heart cells are highly interconnected, making the concept of a “fiber” highly subjective. Instead throughout this thesis the assessment of the microstructure will be based on the cardiomyocytes themselves.

1.2.2 Helix Angle

Cardiomyocytes contract along their long axis. The orientation of the cardiomyocyte long axis is both transmurally varying and approximately parallel to the local myocardial walls (Figure 7). This transmural variation in cardiomyocyte orientation was observed as far back as 1864, by Pettigrew (see Figure 6) [20] and the orientation of the cardiomyocyte with respect to an axial plane in the LV (or short axis) is commonly measured via the Helix Angle(HA).

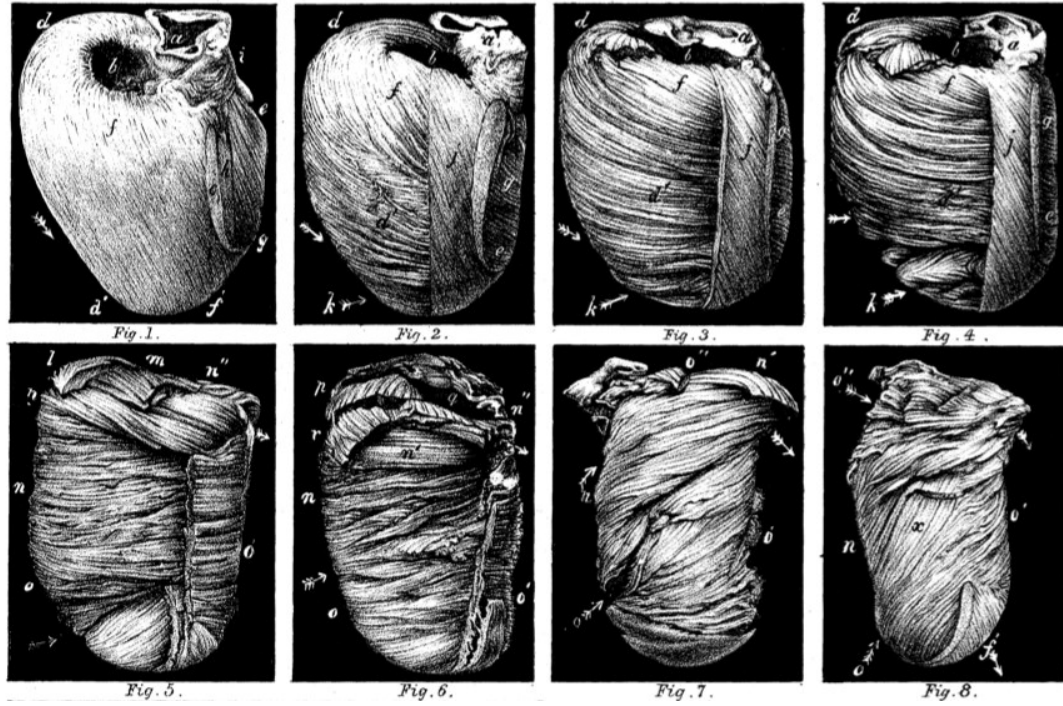


Figure 6: Drawing of a dissected heart and the visible macroscopic aggregations of cardiomyocytes that can be seen when “peeling” layer after layer of the heart (boiled in water). Taken from [20]

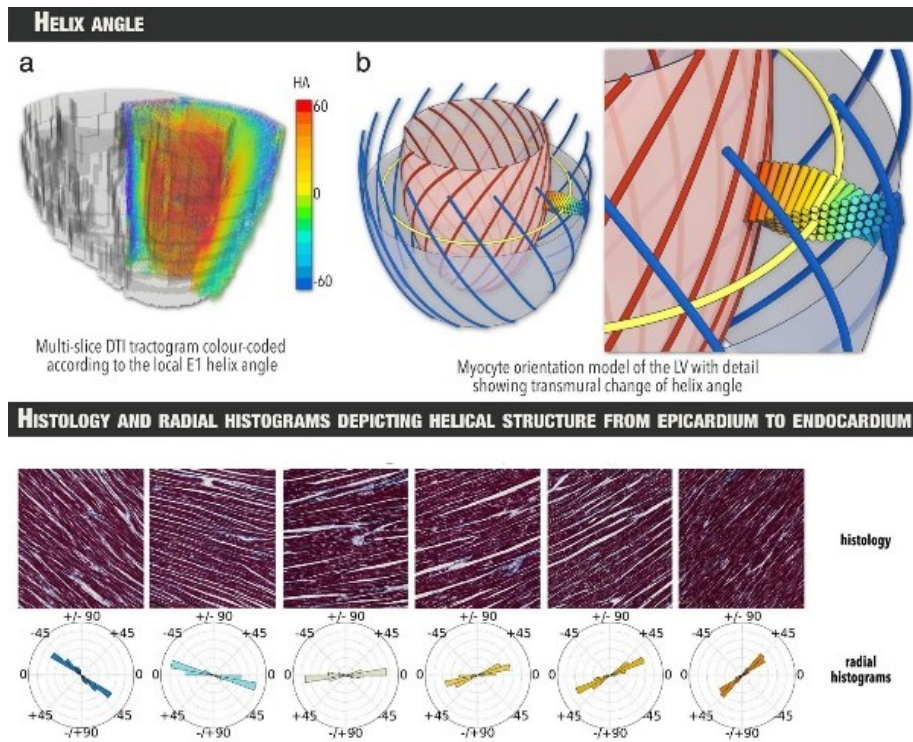


Figure 7: Diagram showing a tractogram based on multislice data from an ex vivo heart imaged with DTI in (a), with the colour scale indicating HA. (b) a simplified model of the primary direction of cardiomyocytes in the HA model. The bottom panel shows histology images from endo to epicardium with the corresponding radial histograms (rose plots) showing the transmural change in HA. Taken from [19]

Histology studies on mammalian hearts were conducted by Streeter et al. [21] and Sands et al. [22] who found the HA to be -60° and -70° respectively in at the epicardium and $+60^\circ$ and $+70^\circ$ in the endocardium. Streeter used a light microscopy technique and conducted the study on canine LV tissue [21]. Sands et al. developed a 3D confocal microscopy approach and applied this in a specimen of rat LV tissue [22]. Similarly, Tezuka [23] used a histology-based approach in normal human hearts and found that the HA varies from -72° in the epicardium to 63° in the endocardium.

Nielsen-Vallespin et al. [24] used a different approach to measure this change in HA *in vivo*. Diffusion Tensor Cardiac Magnetic Resonance (DT-CMR) was used to find a change (median [Inter Quartal Range (IQR)]) from (systole: $-57[-57$ to $-54]^\circ$; diastole: $56[-61$ to $-54]^\circ$) in the epicardium to (systole: $33[31$ to $35]^\circ$; diastole: $40[35$ to $43]^\circ$) in the endocardium in humans (more in Chapters 4+5).

1.2.3 Sheetlets

Sheetlets are groups of [25] [26] approximately 4-12 cardiomyocytes thick, with a poorly defined size in the perpendicular dimensions. The cardiomyocytes within the sheetlet are connected to each other by collagenous perimysium which is part of the extracellular matrix of the heart (Figure 8). Sheetlets are separated by collagen lined, fluid filled shear layers, allowing slippage as described in the next section. It was first understood that the perimysium connections between these groups of cardiomyocytes form stacked sheets spanning around the heart [26]. This view has since been refined and extended through various microscopy and DT-CMR studies [27]–[33]. Nowadays it is believed that these sheetlets are not only more complex in terms of sheetlets branching off or ending abruptly, but that their construction may differ between heart regions [34].

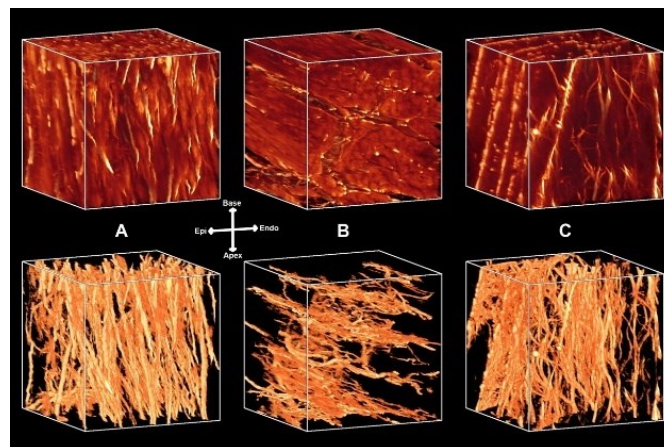


Figure 8: Subepicardial (A), midwall (B), and subendocardial (C) cardiac tissue blocks from a rat ($300\ \mu\text{m} \times 300\ \mu\text{m}$). The top row shows myocytes (red) and collagen (white/orange) and the bottom row collagen only. Taken from [25]

The sheetlets are orientated obliquely to the local epicardial wall tangent plane and the orientation changes during the cardiac cycle (Figure 9). At peak systole the sheetlets tend to be more perpendicular to the local wall tangent plane with a high sheetlet angle, while in diastole they tend to be more parallel to the local wall tangent plane and have a small sheetlet angle. This information was obtained mainly by histological and DT-CMR studies such as [21], [22], [33], [35]–[41], [24]–[28], [30]–[32].

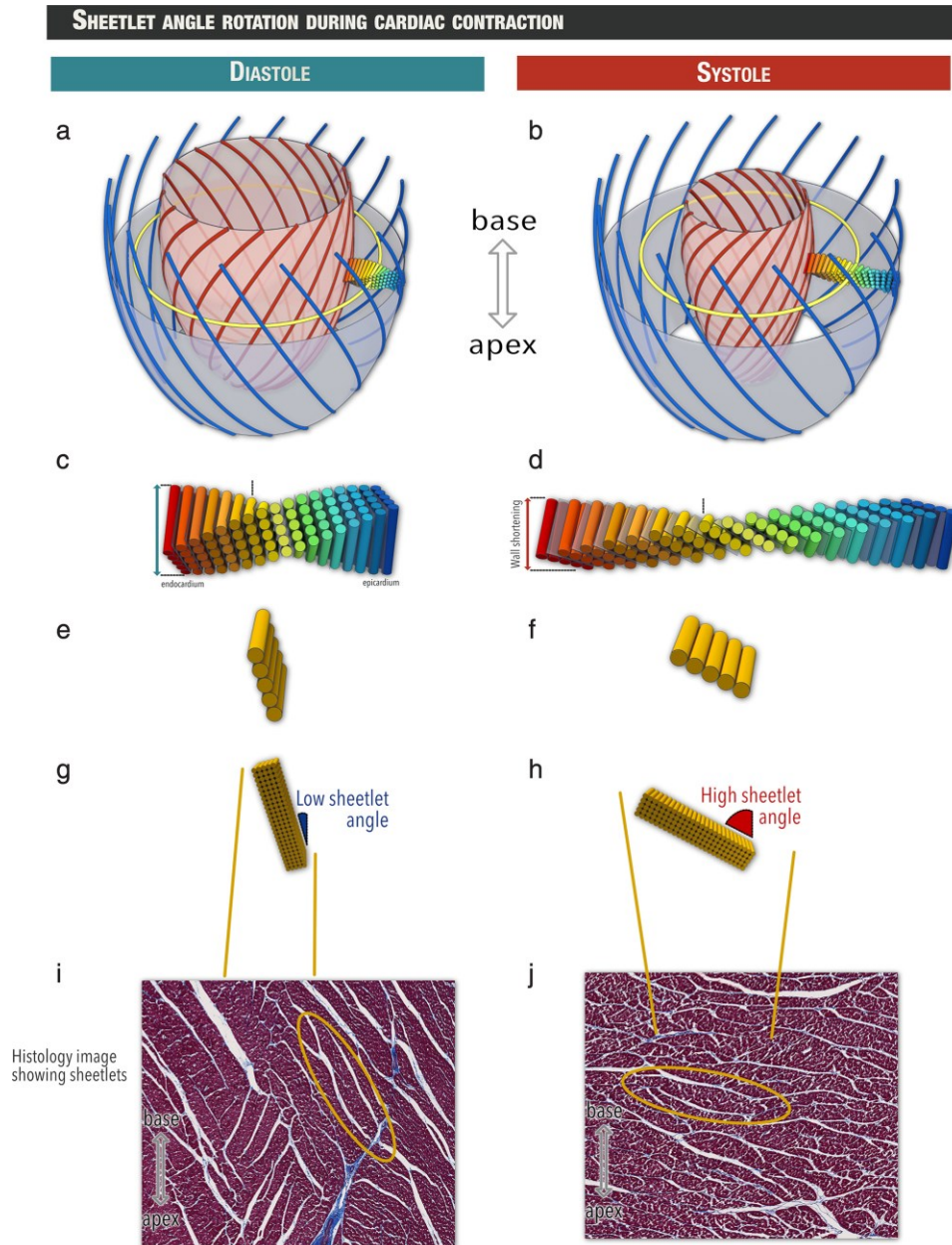


Figure 9: Display of sheetlet orientation during systole and diastole. (a) and (b) show a model of the whole LV and the wall thickening/thinning. (c) and (d) respectively show the underlying arrangement of helically arranged cardiomyocytes, within sheetlets in diastole and systole. (e) and (f) show a model of an individual sheetlet and the change in angle between systole and diastole (g), (h). While (i) and (j) show the sheetlet structure in a histological sample. Taken from [19]

1.2.4 Sheetlet Slippage

A number of studies [35], [37], [38], [41]–[44] have noted that the thickening of the myocardial wall during contraction cannot simply be explained by the contraction of cardiomyocytes in their transmurally varying helical arrangement alone, but a secondary mechanism has to be involved. While cardiomyocytes expand in diameter by approximately 8-15 % the myocardial wall thickens radially by 30-40 % [45], [46].

The secondary mechanism is provided by the reorientation of sheetlets (as described above) with fluid filled shear layers between them, which are believed to allow for the sheetlets to slip over each other [31]. This concept avoids the conflict due to neighbouring cardiomyocytes of differing helical angle simultaneously contracting and allows greater wall thickening than without the mechanism [19].

A study conducted by Costa et al. [41] used live canines with surgically implanted radiopaque markers in the anterior left ventricular free wall. Following *in vivo* imaging using biplane radiography, the hearts were arrested and underwent histology. A 10-20° change in sheet angulation from systole to diastole was observed, allowing for a description of the shear and rearrangement processes that accounted for the wall thickening mechanisms described. A study, using a similar approach, that supported these findings was performed by Harrington et al. [28].

However, while studies like those described above provide insights into the underlying mechanisms of cardiac contraction and provide evidence for sheetlet slippage, there is not yet a general consensus on the exact mechanisms that relates the contraction of cardiomyocytes to the reorientation of sheetlets. One key reason that changes in sheetlet conformation during contraction are not better understood is the currently inadequate range of methods available to visualize the cardiac microstructure. While there have been improvements in microscopy (e.g. [22]), high-resolution Magnetic Resonance Imaging (MRI) of hearts infused with contrast agent [30] and synchrotron X-ray phase-contrast imaging [47] which are enabling a better understanding of the relevant structures, these *ex vivo* methods cannot be used to investigate changes found *in vivo*. As a consequence, new methods for *in vivo* imaging are being developed. One such tool that already has shown to be valuable for studying the microstructure *in vivo* is DTI ([24], [27], [31]–[33], [36], [48]–[50]) which, in contrast to the bi-plane radiography methods using radiopaque opaque markers, can be performed *in vivo* in humans.

1.2.5 Right Ventricular Microstructure

Given the thin compact myocardial wall and the complex shape of the RV, as well as a general trend to focus on the LV, the scientific knowledge of the RV microstructure is limited. The few existing *ex vivo* studies that have included an investigation of the RV microstructure are described in the following.

A study from Teh et al. [51] investigated the microstructure of *ex vivo* rabbit hearts arrested in different contraction states. An *ex vivo* DT-CMR approach was used which allows for the underlying structures to be visualised via the principal eigenvectors [v_1 (for cardiomyocyte long axis orientation), v_3 (for sheetlet normal)], normally noted as $\hat{e}$ in this thesis, (covered in detail in Chapter 4). Then for both v_1 and v_3 the HA and Transverse Angle (TA) are used to describe the eigenvectors orientation (Figure 10, Figure 11) [51] and their variation with transmural depth (endocardium $x < 0$ mm to epicardium $x > 0$ mm), Figure 12. HA v_1 consistently increases from negative to positive angle values, from epicardium to endocardium. While not as consistent, it can be seen in the HA v_3 that there is an increase in this parameter when moving from endo to epicardium. TA v_1 and v_3 are less stable, but TA v_1 can be interpreted as having less angular change across the transmural depth (Figure 12).

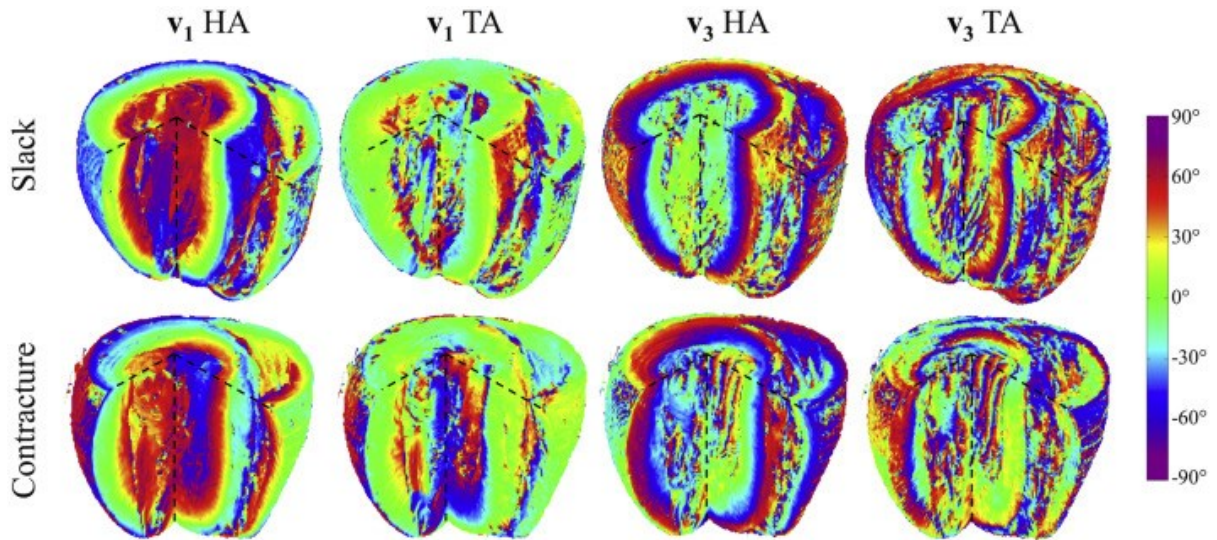


Figure 10: HA and TA from whole-heart *ex vivo* DTI in rabbit hearts acquired in two states of contraction. v_1 corresponds to the orientation of the cardiomyocyte long axis and v_3 , the orientation of the normal vector for the sheetlet plane. Taken from [51]

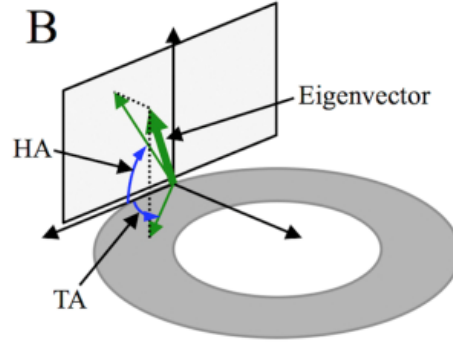


Figure 11: The definition of HA and TA for an eigenvector used in [51]. For HA, the eigenvector is projected into the wall-tangent plane and the angle between the projection and the short-axis plane is calculated. For TA, the eigenvector is projected into the short-axis plane and the angle between the projection and the tangential plane is calculated. Taken from [51]

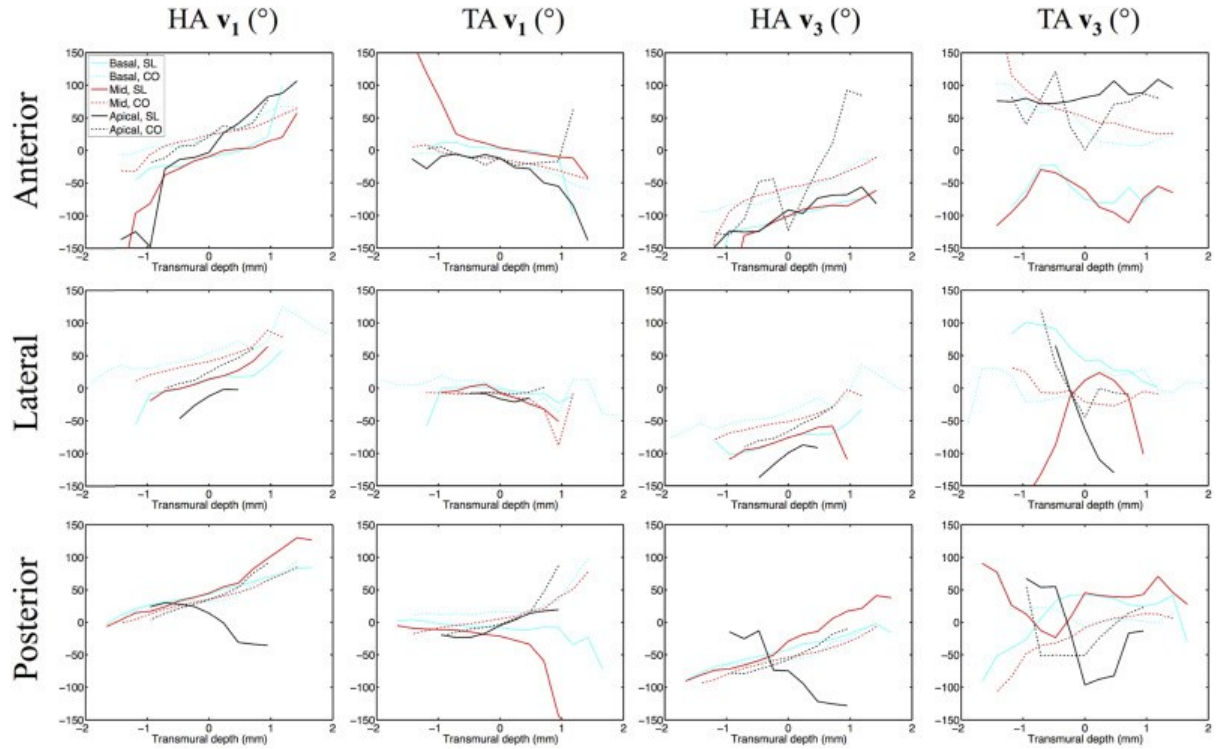


Figure 12: Transmural profiles of measures of cardiomyocyte and sheetlet orientation in three segments (anterior, lateral, posterior) of the RV wall in terms of HA [v_1 , v_3] and TA [v_1 , v_3]. Obtained from ex vivo rabbit heart DTI in slack (SL) and contracted (CO) states of arrest. The transmural depth is centred on the midline $x=0$ mm and is reaching the epicardium and endocardium respectively at $x < 0$ mm and $x > 0$ mm. Taken from [51]

Another study conducted by Gilbert et al. [30] in *ex vivo* rat hearts was performed using a 3D high-resolution gadolinium contrast enhanced MRI approach to image both the RV and LV. By infusing the excised hearts with contrast agent and then imaging at very high-resolution, the extracellular spaces appear brighter than the cells. The images allow clear delineation of the sheetlet cleavage planes and myolaminae (sheetlets) as shown in Figure 13. While this study focused on the LV, the images and videos supplied include the RV and so allow an initial visualisation of sheetlet structure within the RV. The sheetlets appear in general in a less organized way compared to the LV and are in parts difficult to make out. In areas where the sheetlets appear, the change from endocardium to epicardium shows a less gradual change than in the LV and instead appear to be divided into two major directional populations.

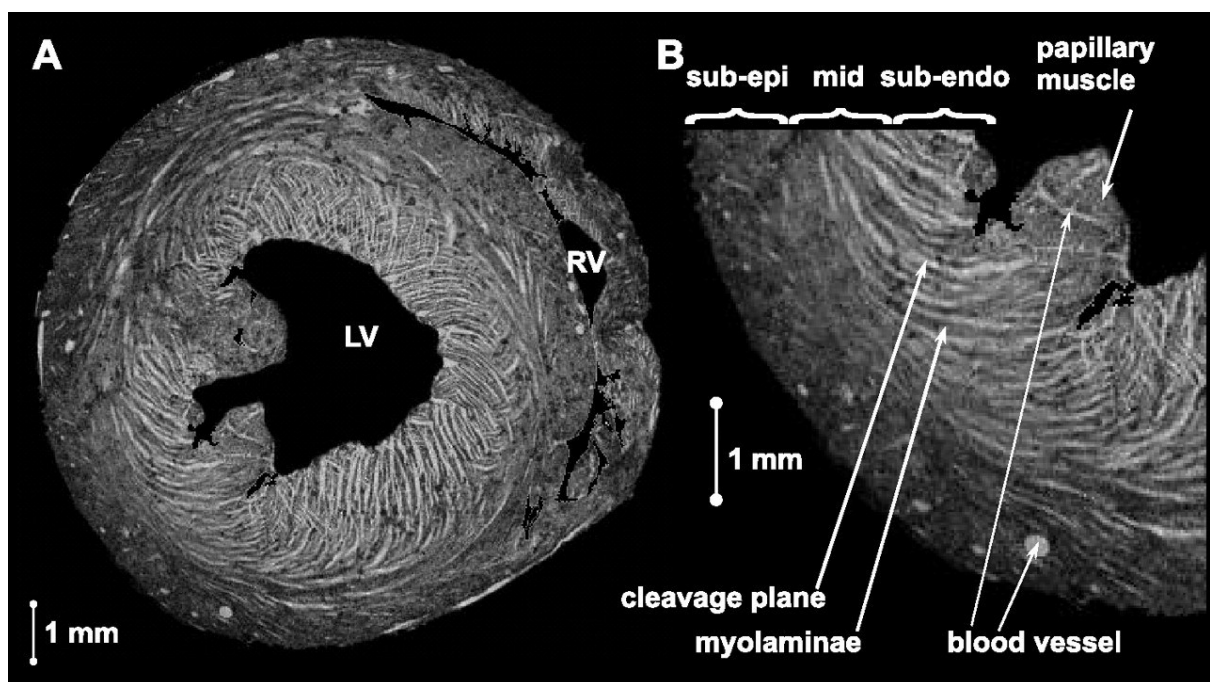


Figure 13: The sheetlet and shear layer architecture obtained using an *ex vivo* gadolinium enhancement MRI approach. (A) shows a slice of the resulting images depicting the LV and RV. (B) display of the transmural depth of the LV and the features such as blood vessel, papillary muscle, myolaminae(sheetlets) and cleavage planes(sheetlet shear layer). Taken from [30]

Garcia et al. [47] conducted a synchrotron X-ray phase-contrast study on two formalin-fixed fetal hearts. One presenting with complex CHD and a right isomerism, while the other heart was a control heart. The results were analysed in terms of HA, as shown in Figure 14. These angles were further investigated at the 4 positions shown in Figure 14 and plotted as histograms for the RV and LV as shown in Figure 15. A substantial change in the distribution of angles shown in the histogram between the base and the apex in the normal hearts is evident, while this does not show in the CHD heart. Furthermore, the number of cardiomyocytes orientated in a circumferential direction is higher in CHD than it is in the control. One important factor to bear in mind is, however, that these are developing hearts. While there might be patterns and trends that will also be found in fully developed specimens, these cannot be assumed and require a study in their own right.

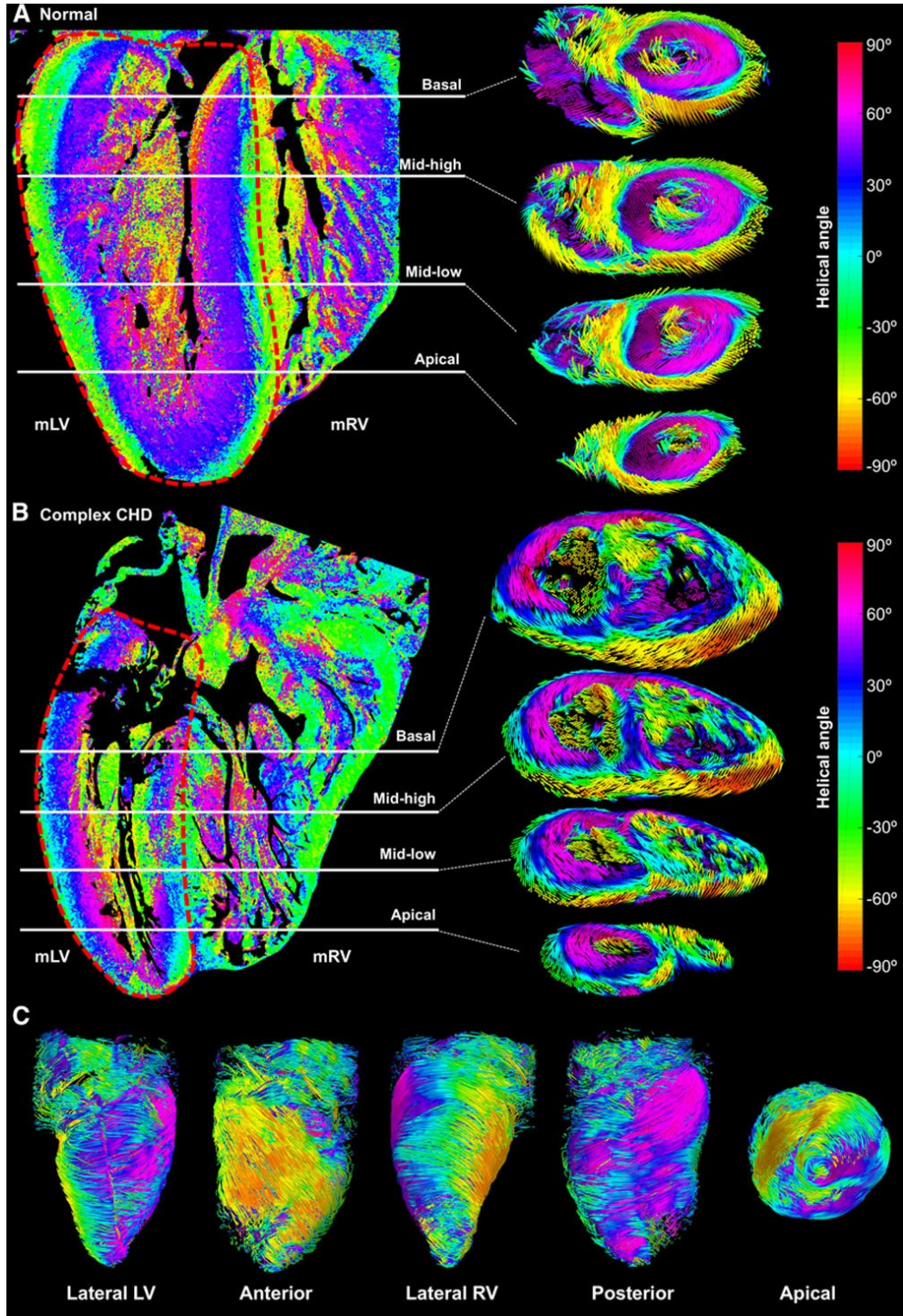


Figure 14: The microstructure in normal (A) and complex CHD (B) fetal hearts. The colormaps show HA. Both (A) and (B) are shown as long axis images and then a color-coded visualisation of the primary eigenvector is shown in four short axis slice positions. (C) shows the data presented as tractograms of the cardiomyocyte orientation. Taken from [47].

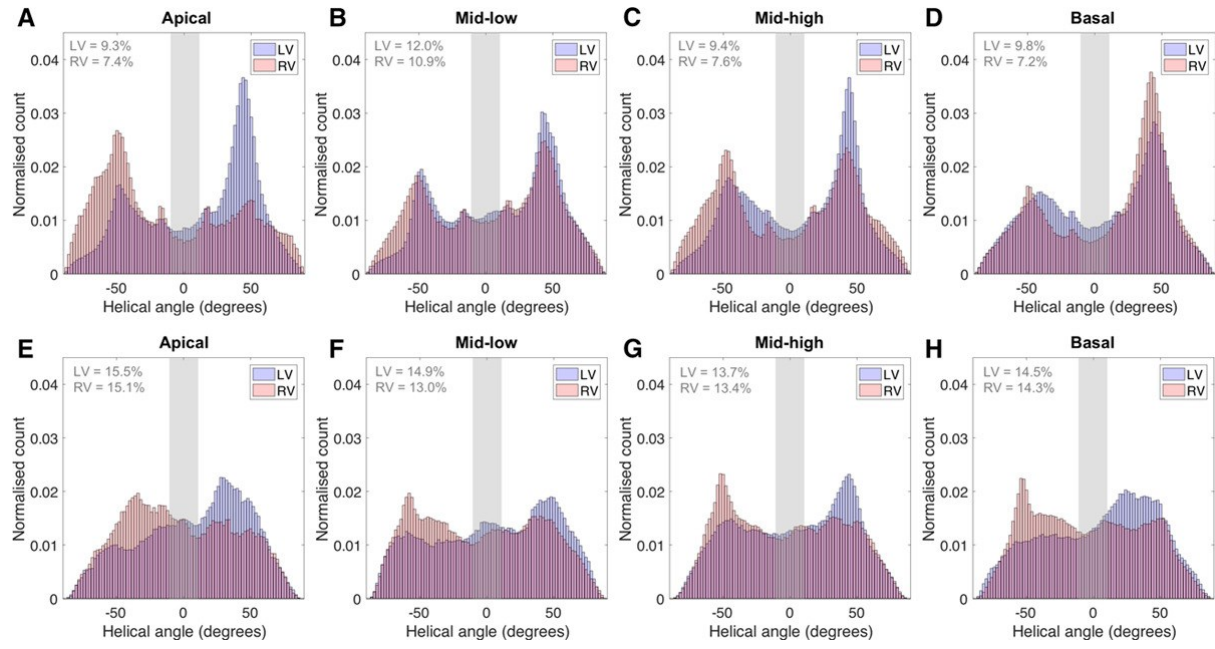


Figure 15: Histograms of the HA in the 4 slices shown in Figure 14. Each histogram shows the distribution of HA in the LV and RV for the normal (A–D) and for the CHD heart (E–H) in respectively the apical, mid-low, mid-high and basal slice. Taken from [47]

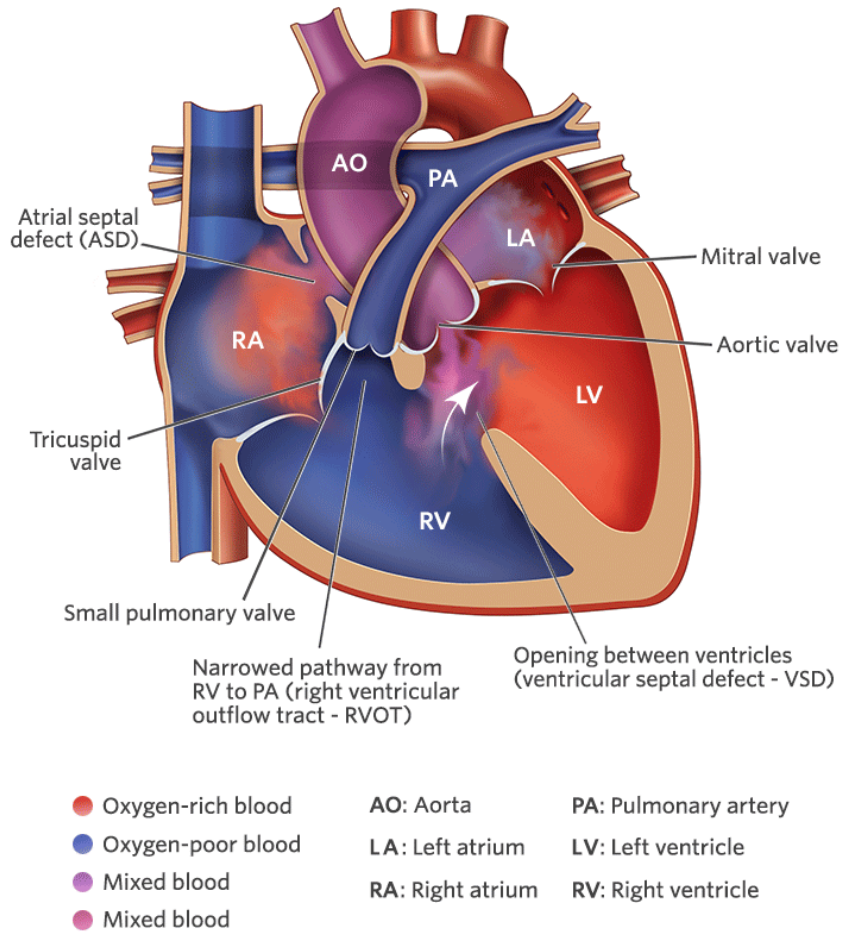
2 Congenital Heart Disease: Tetralogy of Fallot

Congenital heart disease is the most common birth defect, comprising approximately 9.1 per 1,000 live births [52]. While recent advances in medicine have led to a substantial improvement in survival, post-operative CHD patients still require lifelong specialised support by healthcare providers [53]–[55]. One of the most common forms of CHD is Tetralogy of Fallot (TOF), that is encountered in approximately 0.34 out of 1000 live birth [52] and the main clinical interest of this thesis.

2.1 Pathophysiology

What nowadays is known as TOF was named by Maude Abbott in 1924 after the researcher Etienne-Louis Arthur Fallot (1888) and it encompasses the four pathologies shown in Figure 16. Since that time, much research has addressed the understanding and treatment of TOF. As a result, TOF is now regarded as a family of disease rather than one single pathology, with varying pulmonary artery anatomy and other case specific abnormalities [56], [57]. However, the four features that give TOF its name are:

1. **Ventricular Septal Defect (VSD):** A hole between the RV and LV. This defect is normally large in size and results in equal pressures in both ventricles (non-restrictive VSD).
2. **An Overriding of the Aorta:** The misplacement of the aorta towards the right side of the heart. As shown in Figure 16 this places the aortic valve close to the VSD and results in a mixture of oxygenated and deoxygenated blood being pumped through the aorta to the systemic circulation.
3. **Right Ventricular Outflow Obstruction:** Due to a thicker muscle under the pulmonary valve a narrowing of the pulmonary artery occurs. This increases resistance and means that more blood leaves the right heart through the VSD. As a result, the oxygenation of the aortic blood is low and the flow through the pulmonary circulation is reduced.
4. **Right Ventricular Hypertrophy:** The increased resistance in the RV outflow tract and the reduction in pulmonary blood flow, results in an increased mechanical demand on the RV in an attempt to compensate. Over time, this additional demand on the RV results in RV myocardial hypertrophy.



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Figure 16: Schematic of a heart presenting with TOF, with deoxygenated blood shown in blue, oxygenated blood in red and mixed blood in pink. Highlighted by pointers are the mitral, aortic, pulmonary, and tricuspid valves. Further marked are the VSD and narrowing of the RVOT characteristic of TOF. While the third major pathology defining TOF, an overriding aorta, is visible but not explicitly marked. The last major TOF characteristic, RV hypertrophy is not shown. However, an atrial septal defect that can occur in patients but is not necessarily encountered in every TOF patient is included. Taken from [58]

2.2 Microstructure

This section will cover the underlying microstructural changes associated with TOF. These changes can be divided into two categories, cellular hypertrophy, and fibrosis.

2.2.1 Cellular Hypertrophy

Hypertrophy at the cellular level is a significant increase in cell volume, normally originating in an increase in the number of sarcomeres in parallel (concentric) or series (eccentric), accompanied by an increase in the size of the nucleus [1]. This can be accompanied by further changes such as irregular cell shape, enlarged T-tubules, misshaped z-bands, lobulated nuclei and other internal cell irregularities [59].

Histological studies of TOF hearts have identified an increase in cardiomyocyte volume in both the RV and LV as well as the Right Ventricular Outflow Tract (RVOT) [59]–[61]. Chowdhury et al. [59] studied cardiomyocytes from the RVOT in 183 patients (107±79 months old) while undergoing intracardiac repair. 72.1 % of the patient cohort expressed cellular hypertrophy with varying severity and some cases showed additional irregularities such as changes in cell shape, dilated T-tubules, abnormal z-bands and others. Pradegan et al. [60] analysed histological samples from unrepaired TOF, repaired Tetralogy of Fallot (rTOF) and a control cohort. The measurements were taken at 3 different locations (RV anterior wall, RV inferior wall, LV wall) and at all locations in TOF and rTOF specimens there was a significant enlargement in cardiomyocyte volume over the control group.

2.2.2 Fibrosis

Fibrosis in the context of cardiac tissue refers to the process of an increase in the volume fraction of collagen and can be divided into diffuse and focal fibrosis [62], [63]. Focal fibrosis, also often referred to as 'focal scarring', describes the near complete replacement of cardiomyocytes and can be viewed as the end stage of fibrosis. Thus, focal fibrosis is preceded by diffuse fibrosis (often "diffuse scarring"), which is the gradual exchange of myocyte volume with collagen, resulting in increased extracellular space around cardiomyocytes [64]–[66]. The term 'focal scarring' is ubiquitous and may convey different meanings to specialists from different backgrounds ('scar' can refer to a variety of biological processes such as necrosis, apoptosis, and fibrosis, and is present in a range of forms, ischemic or non-ischemic, focal or diffuse). In this thesis the definitions are used from the study of Babu-Narayan et al. [67]: 'focal scarring' (focal fibrosis) refers to the complete replacement with collagen tissue in a local area of the myocardium; while "diffuse scarring" (diffuse fibrosis) depicts various levels of partial replacement with collagen and as such myocardium containing both cardiomyocytes and an increased collagen content [68], [69].

The deposition of scar is driven by the increased synthesis of collagen by myofibroblasts and is, while inherently a physiological aging phenomena, increased in pathologies such as cardiomyopathy [70], hypertension [71], TOF and rTOF [59], [72].

Using histology, Chowdhury et al. [59] found diffuse fibrosis in 65 % of TOF cases and found that older age, systemic arterial desaturation and higher right ventricular end-diastolic pressure played a role in development of the increase in collagen bundles in the pericellular matrix. Notably this work did not find any replacement (focal) fibrosis [59].

Another investigation of fibrosis was conducted by Deanfield et al. [72] in 6 patients that underwent surgical repair of TOF and died suddenly 1-9 years afterwards. The findings of this histological study were various degrees of focal fibrosis throughout the RV. With three patients showing extensive fibrosis at the site of the insertion of the RV, one patient in the septum and one patient in the RV outflow tract. While none of the hearts were found to contain clear areas of focal fibrosis in the LV. Based on their findings and the clinical history of the patients, Deanfield et al. [72] concluded that ventricular arrhythmia was likely to be the cause of the sudden death.

While the detection of fibrosis is clinically relevant as it is linked to abnormal cardiac remodelling, arrhythmias and ventricular systolic and diastolic dysfunction, the detection of diffuse fibrosis is of particular interest as it has been shown to be reversible [73]–[75].

2.3 Outcome

A few studies have investigated the clinical outcome for unoperated TOF patients, generally finding one year survival rates of approximately 60 % and survival past the age of 30 as extremely rare [56], [57], [76]–[78]. Bertranou et al. 1978 [76] studied records from 782 unoperated TOF patients after death. One year survival rate was 66 %, 3 year 49 % and 10 year survival 24 % [76].

2.4 Diagnosis

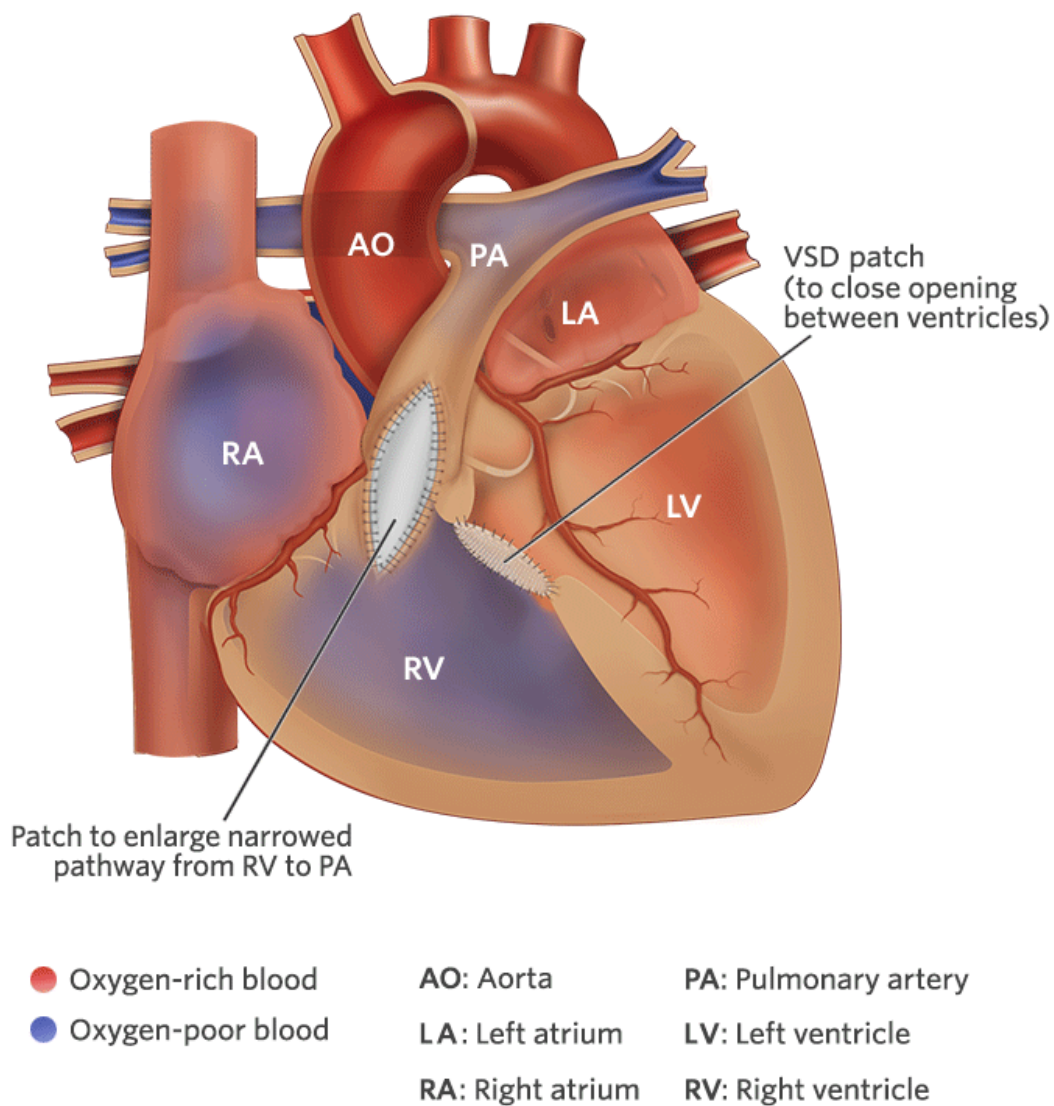
Due to the physiology described above, low oxygen levels are measured in new-borns with TOF. Typically, oximetry would be one of the standard tests after birth, but there are often clear visual signs such as blue lips or nail beds. Additionally, a heart murmur, originating from the narrowing RV outflow tract, heard with a stethoscope is often an indication of the disease. [56], [78]

Those presenting with severe gene mutations such as trisomy 21 and missing chromosome 22 are at higher risk of being born with TOF. Similarly, family history is a risk factor so new-borns with a family history of TOF will be closely monitored. [56]

With any of the above indicators, the suspected infant will be assessed using an echocardiogram to provide a conclusive diagnosis. Prenatal echo can indicate TOF before birth can help, particularly in cases of severely obstructed pulmonary blood flow, by allowing early prostaglandin treatment which can avoid life-threatening cyanosis soon after birth. [57]

2.5 Repaired Tetralogy of Fallot

If TOF is detected, a surgical repair is possible and usually carried out between 3 and 6 months of age. During the open-heart surgery procedure, a heart-lung bypass machine supports circulation [57]. The surgery includes patching the VSD and enlarging the narrowed pulmonary outflow with a Gore-Tex tube (Figure 17). Full recovery in infants is achieved by approximately 4 to 6 weeks and the mortality rate with modern surgical procedures is around 0-2 % [56].



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Figure 17: Diagram displaying the heart after the surgical repair of TOF. Deoxygenated blood shown in blue and oxygenated blood in red. Both the VSD patch as well as the patch for enlargement of the narrow RV-PA transition region is shown. Taken from [58]

2.5.1 Patient Outlook and Long-Term Implications

While long-term survival prospects are promisingly at around 86 % at 20 years after repair [79], patients need special cardiac care for the rest of their lives. Even successful surgery will not result in a completely normal heart and patients are often left with complications, potentially including:

- **Pulmonary Regurgitation (PR):** The surgical procedure necessary for repairing the RV outflow tract obstruction often reduces the integrity of the pulmonary valve and may mean that it cannot completely close. This results in a pulmonary backflow (regurgitation), which in turn results in RV dilation due to the increased load and eventually systolic dysfunction [56], [57]. A valve replacement may be performed, but the repaired pulmonary valve suffers from a limited lifespan and so must be carefully considered [80].
- **Exercise Intolerance:** Exercise intolerance can be a side effect of the surgical repair due to damage to the autonomic nervous system. However, it is predominantly a symptom of the altered hemodynamics related to TOF and the repair, including PR [56].
- **Atrial and ventricular arrhythmias:** A multi-centre study conducted by Gatzoulis et al. [81] followed up 793 patients post repair between 1985 and 1995 and found increased rates of atrial and ventricular anomalies. Of the anomalies, ventricular tachycardia was found to be the most common, with a prevalence of 11.9 % in the mean 21.1 years following repair, followed by arterial flutter with 10.4 % prevalence. In a study by Babu-Narayan et al. [67] these electrical abnormalities were correlated to the development of myocardial fibrosis assessed by Late Gadolinium Enhancement (LGE) MRI (more in Section 3.5.1).
- **Sudden cardiac death:** In the study of Gatzoulis et al. [81], the repair was conducted at a mean age of 8.2 years and they calculated a freedom from sudden cardiac death of 91.7 % over 35 years. This equates to 1516 deaths per 100,000 patient years. In the general population, studies of the rate of sudden cardiac death have found 1.3 per 100,000 patient years [1-22 year age range, Olmsted County Minnesota] [82], 1.9-2.8 per 100,000 patient years [1-35 year age range, Denmark] [83], 1.6 per 100,000 patient years [1-40 year age range, 12 Dutch provinces] [84] and 1.8 per 100,000 patient years [1-34 year age range, England & Wales] [85].

2.5.2 Post-Operative Care

Life-long care is necessary to mitigate some of the risk and allow rTOF patients to live a relatively normal life. Generally, yearly follow ups at a dedicated centre that is capable of handling the complex requirements for these patients are advised [56], [80], [86]. During these follow up visits, a number of diagnostic methods are available to help cardiologists assess the disease status and plan possible further clinical procedures.

One important measure is a marker of cardiac function that can assist in decisions of when to perform a pulmonary valve replacement. As discussed above, premature replacement not only carries the risk associated with additional surgery, but also the long-term viability has to be considered [56]. A measure proposed to assist with the follow up of rTOF patients has been the investigation of the RV structure and in particular the detection of scar tissue using Cardiac Magnetic Resonance (CMR) [67].

ECG and exercise tolerance are relatively easy to obtain and have shown to be early markers for detecting a worsening prognosis [81], [87], particularly if QRS abnormalities are detected. However, given the importance of the clinical implications of diagnostic results in rTOF, modern imaging techniques such as echocardiography and CMR are often used to supplement exercise testing and ECG [88].

Echocardiography (echo) has the advantage of being comparably cheap, portable and cardiologists often have extensive experience using this modality. Furthermore, it provides a superb temporal resolution that particularly benefits the assessment of valves and other dynamic structures [88]. Echo can provide most of the assessments of vessel, RV and LV structures required (Table 1) and is the first line imaging modality in rTOF patients. However, it suffers from limited quantitative capabilities and poses problems if the acoustic window is insufficient. Thus an additional form of imaging (predominantly CMR in the case of rTOF) is often required [88].

CMR is considered the most precise investigation, supporting clinical decisions for this patient group [86][80], [89] and will be covered in the following chapters.

Table 1 Comparison of available imaging modalities for assessment of different conditions

	Echo	CMR	CT	Catheterization
Aortic arch	++	+++	+++	+++
Pulmonary arteries	++	+++	+++	+++
Pulmonary veins	++	+++ Precise anatomical information + flow measurements	++	+++ Wedge pressure
AV valves	+++	+	(+)	+ Pressure gradients
Semilunar valves	+++	++ Quantification of regurgitation	+	+ Pressure gradients
Complex CHD	++	+++ Precise anatomical information + flow measurements	++	++ Pulmonary arterial pressure
Coronary arteries	+ Only proximal segments	++	+++	+++ Gold standard
Tissue characterization (tumours and cardiomyopathies)	+	+++	+	(+)
Ventricular function	++	+++	(+) ECG-gated CT	++
Flow measurements	+	+++	-	-
Shunt quantification	+	+++	-	+++

(+): limited application, major limitations; ++: can be used in the assessment of this lesion, but has some significant limitations and better alternatives are available; +++: useful technique commonly applied in the assessment of the lesion, and it may present some limitation; ++++: technique of choice for the assessment of the lesion; -: cannot be adequately assessed with this modality.

Table 1: The appropriateness of imaging methods available for use in CHDs and their suitability in assessing typical target anatomy and functional parameters. (+) refers to the availability of visualisation with this modality, but with major limitations. (++) commonly used technique for the assessment, however some limitations remain. (+++) technique of choice. (-) not usable for the task at hand. Taken from [90]

3 CMR Imaging Methods in Repaired Tetralogy of Fallot

In the assessment of CHDs such as rTOF, clinicians begin their investigations by determining how anatomical structure and function differ from what is expected in a healthy heart. This is possible with various modalities such as echocardiography, x-ray Computed Tomography (CT), x-ray contrast angiography and CMR, as discussed in the previous chapter and summarised in Table 1. As a clinical technique, CMR has a number of capabilities that make it particularly useful in assessing rTOF patients, including: the ability to acquire images in any plane; 3-dimensional coverage; excellent visualisation of soft tissues; a variety of qualitative and quantitative contrast generating mechanisms; and its non-ionising nature. This is important if considering the number of follow up scans in rTOF. Conservative values of the most benign case can be taken at 10 scans [89] for the first 30 years after repair, given the excellent long term survival prospects [79]. Further assuming an effective dose of 8.2 ± 3.1 mSv [91] for a cardiac CT exam (which can vary between protocols and is reported at to up over 20 mSv [92] in cardiac studies) results in an effective dose of approximate 82 mSv for the first 30 years if using CT alone. For comparison the average dose of atomic bomb survivors is quoted [92] as 200 mSv. While these considerations are important the key advantages that make CMR such a powerful tool in rTOF are the capabilities to quantitatively measure RV and LV anatomy, function and perform tissue characterisation [55], [89], [90].

Structure/ Mechanical Process	Echo		MRI		Details
	Assessed	Quantitative	Assessed	Quantitative	
Residual Shunts	✓	✓	✓	✓	Mostly identified with Echo, but stack of cine SSFP, CEMRA and Flow CMR allow clear visualisation and quantification
Myocardial Viability	✗	✗	✓	✓	Using the various tissue characterisation methods covered in section 3.5
Aortic Regurgitation	✓	✓	✓	✓	Flow CMR as in other quantifications of blood flow considered standard
Tricuspid Valve & Regurgitation	✓	✓	✓	✓	Transoesophageal echocardiography gold standard, but especially stack of bSSFP CINE considered excellent in visualisation. Flow CMR can pose difficulties due to through-plane motion of the Tricuspid valve [90].
Pulmonary Regurgitation	✓ *	✗	✓	✓	Flow CMR standard for assessment
Pulmonary Arteries	✓ *	✓	✓	✓	Stack of bSSFP CINE together with CEMRA allows visualisation of complex anatomic relationships with neighbouring anatomy. The assessment of stenosis and interventional planning are further supported by this [89].
Aortic Arch	✓ *	✗	✓	✗	CMR 3D SSFP and CEMRA allows assessment of arch sidedness and abnormal branching patterns
Aortic Root & Ascending Aorta	✓ *	✓	✓	✓	Stack of bSSFP CINE, 3D SSFP and CEMRA usually considered the best approach
RVOT	✓ *	✓	✓	✓	bSSFP CINE and CEMRA allow detection of aneurysms and highly useful in allowing planning of pulmonary valve replacement procedures [80], [88]
Regional RV Wall Motion & Abnormalities	✗	✗	✓	✗	CINE imaging allows classification of akinetic or dyskinetic wall segments
RV & LV Volumes & Ejection Fraction	✓ *	✓	✓	✓	CMR based assessment of volume and mass considered gold standard.

Table 2: The main elements of an rTOF protocol and the appropriateness of echo and CMR. *Possible, but retrosternal position leads to failure in a considerable number of patients (younger patients are often possible, but adults especially if overweight present considerable challenges). Table compiled from following sources [80], [88]–[90]

Typical CMR assessment of CHD is different from routine imaging of pathologies such as ischemic heart disease. Often specialist training of the technologist is required, with a CHD trained clinician present during imaging to advise on the most suitable CMR methods and imaging planes. This is due to the wide spectrum of anatomies that differ on a case-by-case basis and the complex clinical questions. Under ideal circumstances, every patient would undergo all possible CMR sequences that have been demonstrated to capture clinically relevant data, but time constraints in clinical practice and the endurance of patients lying in a confined space limits what can be achieved. The techniques considered typical elements of a protocol for imaging the “average” rTOF patient are provided in Table 2 [\[80\]](#), [\[89\]](#), [\[90\]](#), [\[93\]](#).

3.1 Basic CMR Sequences

The goal of a basic 2D MR experiment is to fill a two-dimensional Fourier space, also referred to as k-space. k-space data can be converted to an image by applying a 2D Fast Fourier Transform (FFT). While other sequence types exist, the principle of fast 2D image formation, as often used in CMR settings, is described below.

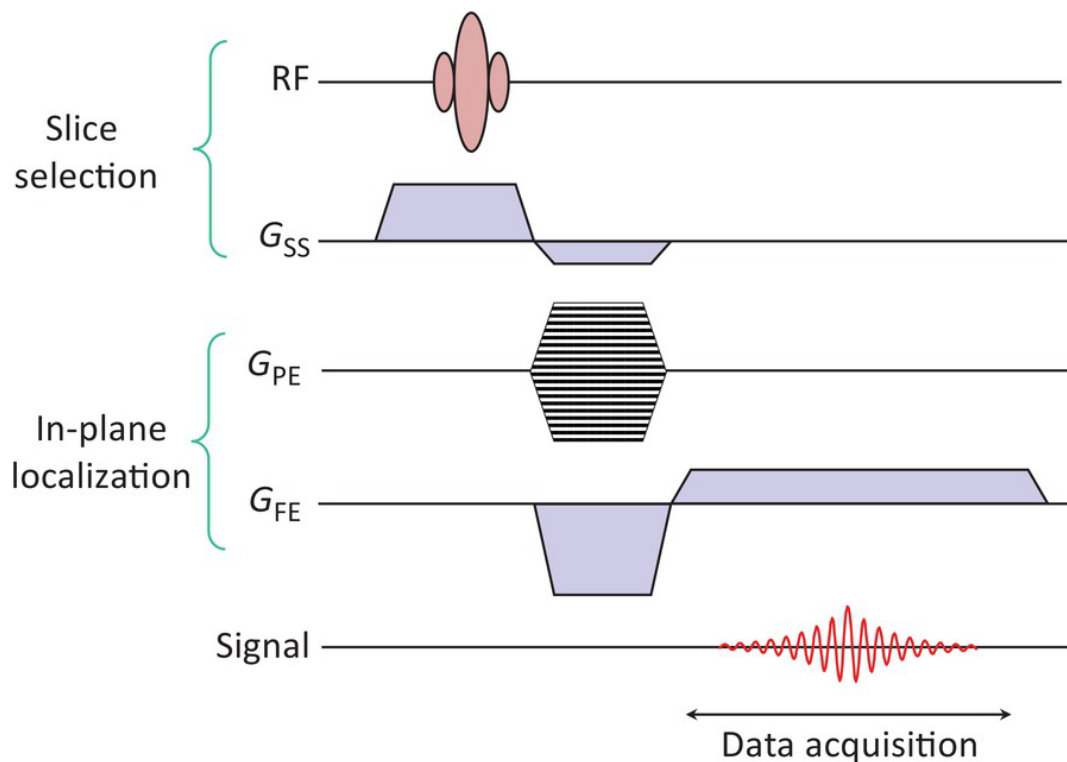


Figure 18: Diagram of a basic gradient echo sequence to sample one line of k-space. The first two rows show the excitation and slice selection using a radiofrequency (RF) pulse together with a slice selection gradient G_{ss} . The RF pulse tips a proportion of the longitudinal magnetisation into the transverse plane, creating a free induction decay signal. G_{ss} is applied during the time that RF excitation is applied and is refocused afterwards to avoid signal loss due to intravoxel phase dispersion. The next line shows the in-plane encoding by a gradient G_{pe} that imparts a spatially dependent phase to the signal or shifting the position along the G_{pe} axis in k-space. Acquisition of the signal during the application of G_{fe} results in a spatially dependent frequency and a whole line of k-space is sampled in the direction of G_{fe} . G_{fe} uses a prephasing gradient before the data acquisition with the opposite sign, to ensure that a gradient echo is sampled, usually placing the acquisition of the central k-space data at the centre of the data acquisition time. Taken from [94]

The most basic of the fast imaging sequences is the Gradient Echo (GRE) pulse sequence, shown in Figure 18 which uses following mechanisms to generate a signal [95].

1. A gradient G_{SS} is played out during the Radio Frequency (RF) excitation pulse with flip angle α . This gradient modulates the resonance frequency along the given axis. The bandwidth of the RF pulse and the gradient strength determines the thickness of the slice of spins that are flipped into the transverse plane and are available for imaging.
2. Since G_{SS} results in an intravoxel phase dispersion, and therefore a signal loss, a rephasing gradient is applied on the same axis after G_{SS} with the opposing sign.
3. In-plane encoding begins with phase encoding. A Phase Encode (PE) gradient G_{PE} is applied, which imparts a spatially dependent phase along the PE axis. This allows one line of k-space to be imaged with the frequency encoding gradient in step 4.
4. On the third orthogonal axis (the frequency encoding axis), a prephasing gradient is applied. This gradient imparts a spatially dependent phase.
5. Finally, the Frequency Encode (FE) gradient G_{FE} , imparts a spatially dependent frequency in the signal along the axis of G_{FE} , which generates a gradient echo and allows the sampling of the Free Induction Decay (FID) signal of the hydrogen spins. This effectively collects data along a line of k-space as the signal is sampled.

This setup allows for a theoretical image acquisition by repeating the process for a number of PE lines, each repetition separated by a Repetition Time (TR). In CMR, TR is typically much shorter than the exponential longitudinal recovery time, T_1 . The residual transverse magnetisation frequently results in artefacts in the signal acquired in the following TR [95].

The most common approach used to allow short TRs using this setup and avoid the implications of an unknown status of the magnetization is to achieve a steady state. This can be done by using a train of excitation pulses, which have a constant α , typically below 90° and a constant TR shorter than the T_2 (transverse) relaxation time [96]. After a few repetitions (TRs) a steady state can be achieved in which both the transverse and longitudinal magnetisation are constant at the time of data sampling [95]. In general, however, one of a number of modified versions of GRE is used for fast imaging.

3.1.1 Spoiled Gradient Echo

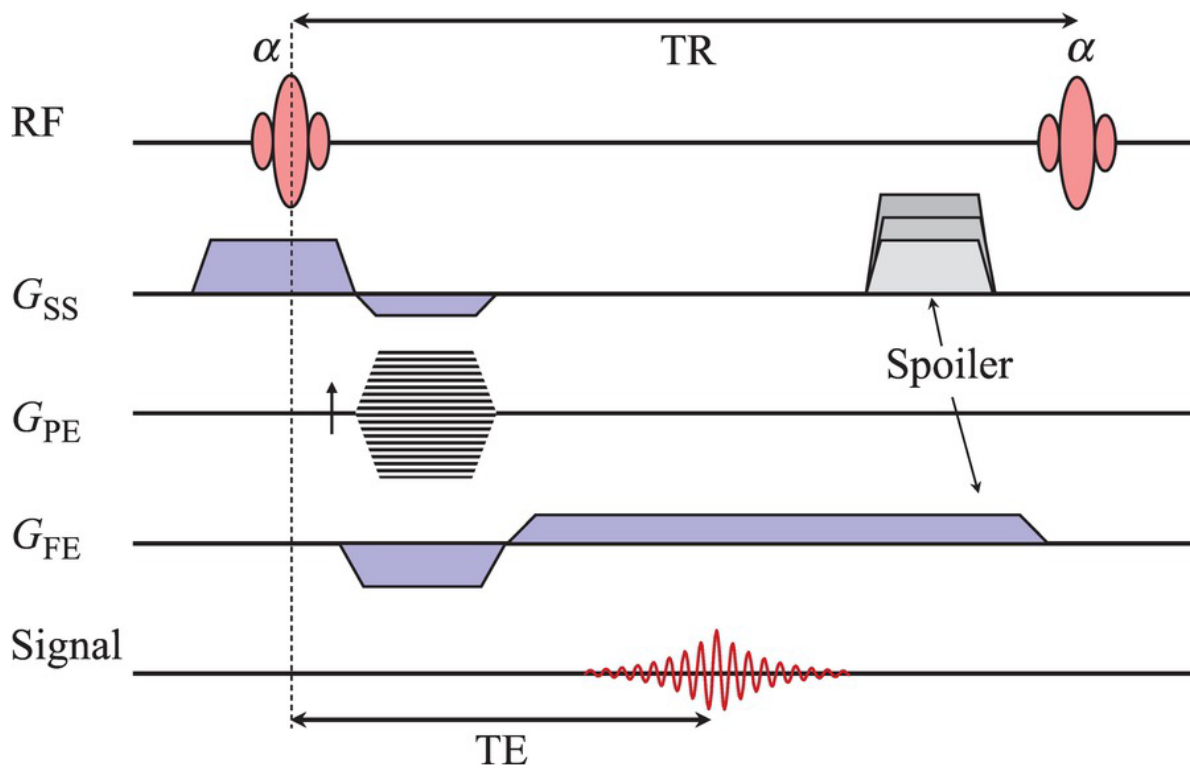


Figure 19: Pulse diagram of a gradient spoiled gradient echo sequence. The notable change from the basic GRE sequence is the addition of a spoiler gradient. Taken from [94]

This sequence can be viewed as the first GRE sequence practically used for fast imaging *in vivo* and was originally developed by Frahm et al. in 1985 [97], before subsequently being adopted by all major vendors. In literature, this technique is often known by other names, since engineers at Siemens, GE and Philips respectively term it FLASH (original name by Frahm), SPGR and T1-FFE respectively.

To produce an image with a FLASH sequence (Figure 19) the most important additions to the basic GRE sequences above are:

- Using the GRE sequence above, the remaining transverse magnetization can result in unwanted signal in the next gradient echo. To avoid this spoiling is used. Spoiling can be performed by using either a gradient at the end of each TR (as shown in Figure 19), that dephases the transverse magnetization or by changing the phase angle of the RF pulse with every consecutive readout [95]. Often both of these methods are applied together [96].
- Image contrast in this setup is predominantly determined by TR, α and the T_1 (longitudinal recovery time) of the tissue. For a given TR and T_1 , the α required to generate maximum signal can be determined. The resulting flip angle is known as the Ernst angle [95]. Flip angles below this Ernst angle will generate a more Proton Density (PD) contrast weighing, while higher angles will result in more T_1 weighted contrast [95].

3.1.2 Balanced Steady State Free Precession

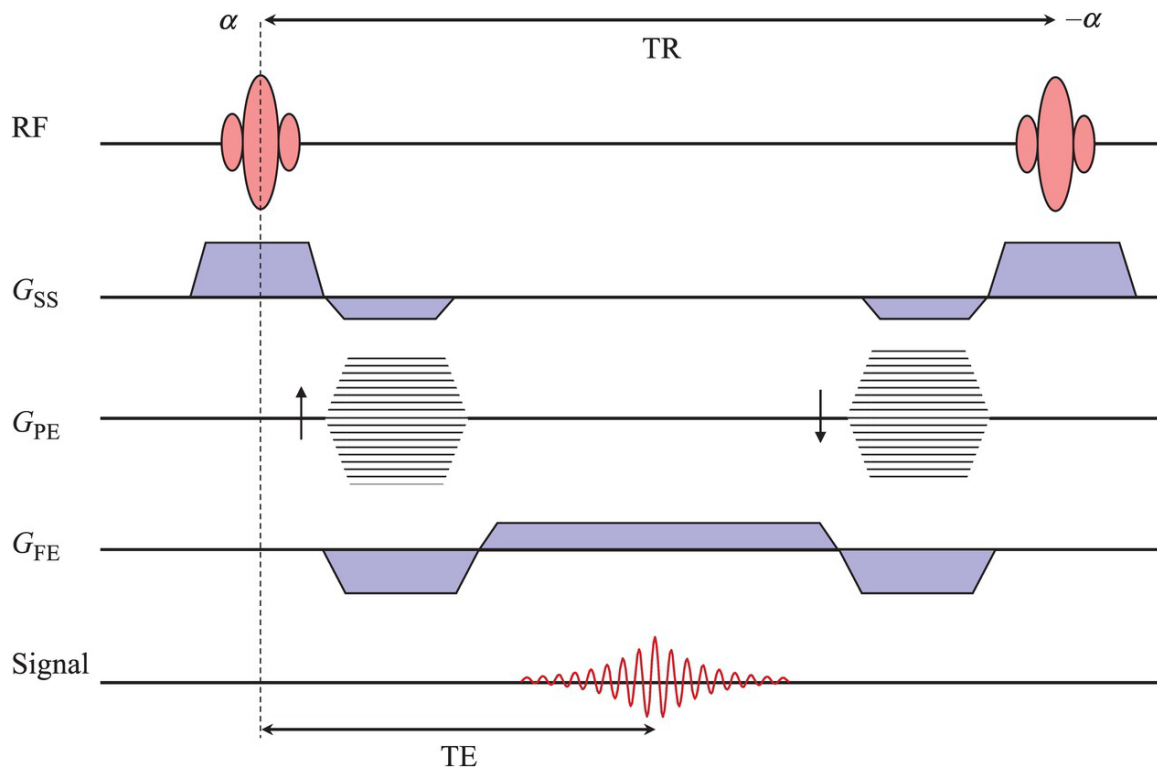


Figure 20: Diagram of a balanced steady state free precession pulse sequence. The notable difference with the spoiled GRE sequence above is that each of the axis is “balanced”, meaning that when summing the integral of the gradients on each individual axis over the course of TR they equal 0. Taken from [94]

Another GRE variant, without spoiling is the balanced Steady State Free Precession (bSSFP) sequence (Figure 20). This sequence differs from the basic GRE sequence above as follows:

- All three gradient axes are rewound to avoid unwanted artefacts. The integral of the gradients on each axis sum to zero within each TR. The resulting pulse sequence diagram is shown in Figure 20.
- In order to obtain a reasonably short TR, high performance gradient systems are required [95].

The main advantage of the bSSFP sequence is the improved Signal Noise Ratio (SNR) over FLASH methods. However, field inhomogeneities in bSSFP acquisitions cause banding artefacts, which appear as dark bands. While this artefact can be compensated for by using careful shimming (subject wise adjustment of the current in gradient coils to minimise local field inhomogeneities) under normal circumstances, metallic implants can cause significant problems [98].

3.2 Coping with Cardiac Motion

The acquisition process described above requires one TR for each PE line sampled. In cardiac imaging the underlying tissue is almost constantly moving due to cardiac and respiratory motion and the location of the tissue may vary between the acquisition of sampled k-space points. As a consequence, CMR scientists have developed techniques to monitor the motion and minimise its effects.

This monitoring is commonly performed using specialised MR safe ECG devices[99], respiratory belts [100], [101] (which are strapped around the chest and can measure the expansion of the chest) or through the MR system itself by acquiring navigators (one dimensional images of a thin strip of tissue through the liver-lung interface) [102]. The resultant signals can then either be used to retrospectively assign the image data to the cardiac or respiratory phase it was acquired at or to trigger/gate the sequence to only acquire imaging data at one phase of the cardiac and respiratory cycles.

While the effects of cardiac motion are almost always minimised by using ECG information, the absence of such a reliable signal for the respiratory cycle and high intrasubject variability in respiratory cycles has led to the majority of acquisitions being performed during a breath hold [103]. By using manual or automated voice commands, the compliant patient is most often instructed to hold their breath after exhaling. This provides a relatively motion free and reproducible respiratory position [104], [105].

3.3 Anatomical Imaging

The requirements for anatomical imaging are twofold: first the cardiac morphology has to be visualised for the clinician to assess the location and connection between the cardiac chambers and great vessels; second, any changes in morphology, such as RV dilation, are quantified in follow-up scans as clinical markers of disease progression [89].

Quantification is achieved using specialised image processing software for segmentation and then the calculation of volumes and derived parameters (see Table 2). This analysis requires considerable expertise and training of clinicians [89]. In the case of rTOF, the pertinent data might typically be collected using the sequences described below.

3.3.1 Cine

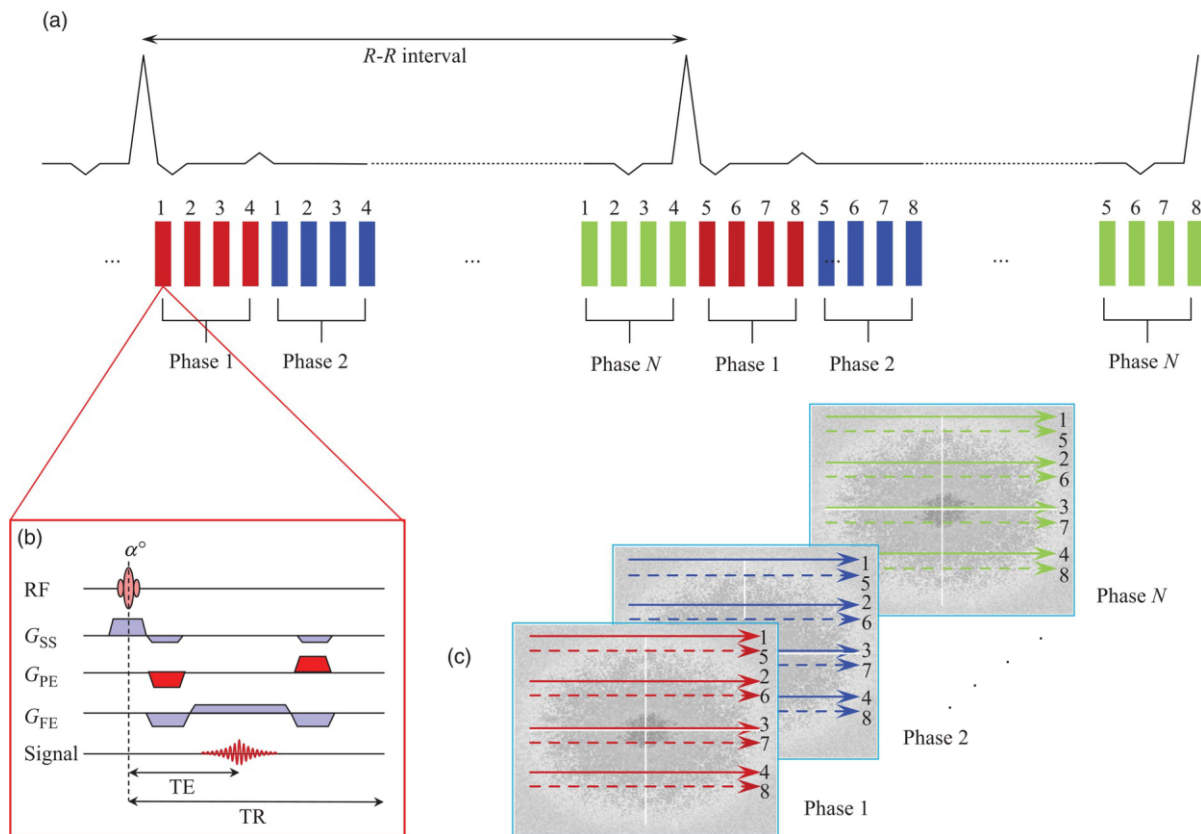


Figure 21: Diagram of a cine acquisition. (a) The colour coded blocks (e.g., 1,2,3,4) represent an individual bSSFP (b) readout. This allows part of k-space (c) to be acquired with each heartbeat for multiple cardiac phases which can then be pieced together to allow reconstruction of a video of the beating heart. Taken from [106]

One of the most important tools of any CMR exam is cine imaging, which involves the acquisition of a number of frames during the cardiac cycle. To achieve this the imaging sequence relies on a breath hold-based acquisition to control the respiratory motion and the use of an ECG to track the cardiac phase. Then instead of sampling one image after the last, a few lines of k-space (a segment) are repeatedly acquired for multiple phases throughout one cardiac cycle, before moving onto another subset of lines in the next cardiac cycle. The segments are later pieced together to complete the required k-space for each cardiac phase before using an FFT to create the frames of a movie of the contracting heart.

Most commonly in CMR and rTOF imaging, a bSSFP (Figure 21) approach will be used as this achieves a superior SNR and a good blood-myocardium-background contrast [12]. However, in the presence of off-resonance effects and flow artifacts caused by metallic implants or field inhomogeneities [90], [107] a spoiled gradient recalled echo (FLASH) sequence may also be used, as banding and flow artifacts can be particularly problematic.

3.3.2 3D Imaging

The acquisitions discussed above are based on a 2D slice and in order to obtain 3D information a stack of 2D slices may be planned along the directions planned to best study the morphology and function of the heart. However, when imaging rTOF patients it can be advantageous to acquire true 3D data, which provides contiguous slices and is more SNR efficient. 3D encoding can be achieved by extending the basic 2D sequences.

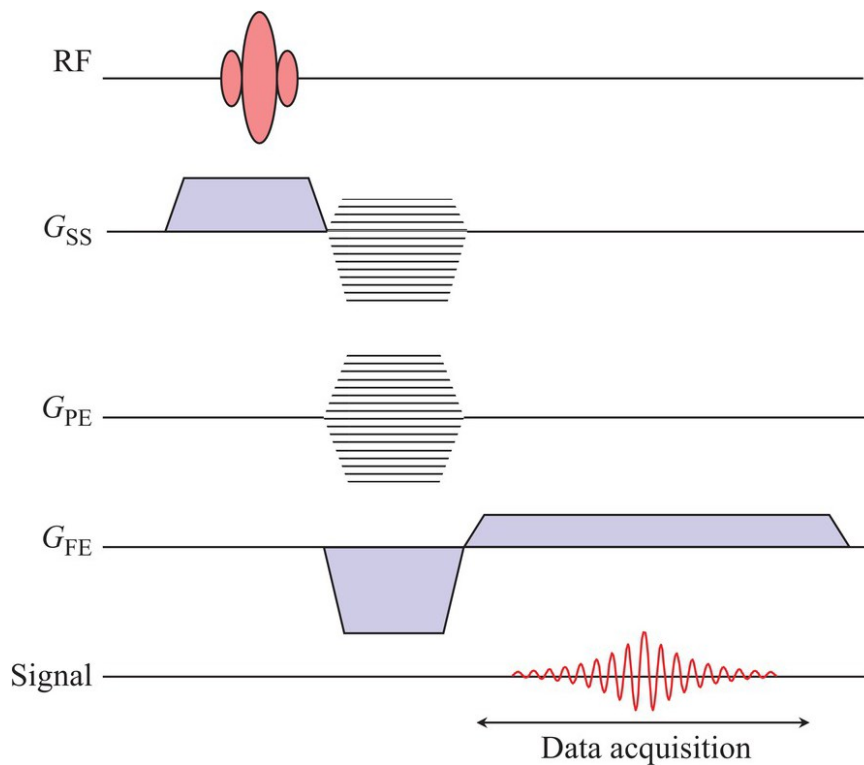


Figure 22: Pulse diagram showing a 3D acquisition. Another phase encoding step is applied along the slice encode direction. Taken from [94]

As shown in Figure 22 3D imaging methods also rely on a slice selection gradient during the RF pulse as in the 2D acquisition (to excite a thick slice or slab [108]), however a second PE gradient is also played out along the slice select axis and each readout during the frequency encode collects a line in a 3D k-space [108]. This second phase encoding direction is often referred to as the partition direction and allows for the samples to be placed into a 3D Fourier space, that can be reconstructed using a FFT [108].

It is not usually possible to acquire all the data for 3D imaging in one breath hold and mis-registration between breath holds in k-space could cause severe artefacts. As a result, 3D sequences are often respiratory gated.

3.3.2.1 CEMRA

A form of imaging that often uses 3D acquisition schemes is Contrast Enhanced Magnetic Resonance Angiography (CEMRA). In this type of imaging a Gadolinium Based Contrast Agent (GBCA) is injected into the bloodstream of the patient to shorten the T_1 of water molecules in close proximity to this compound. Gadolinium itself is toxic. Thus, in order to be safely used in humans, a wrapper molecule, such as meglumine gadoterate is used [109].

This reduction in T_1 caused by a contrast agent, results in a quicker recovery of longitudinal magnetisation and the effect is initially particularly strong in blood (since this is where the highest concentration is immediately after administration) and it allows for very sharp contrast in CEMRA and other applications [110]–[112]. In CEMRA the aim is to capture a 3D volume containing the artery of interest at a timepoint which allows clear delineation from other structures. This is generally when the gadolinium concentration in the artery of interest reaches its first peak during its first transit, since the contrast agents in use are extracellular and penetrate the capillary walls to enter the extracellular space [113], rapidly reducing the vessel-tissue contrast. This requires any CEMRA sequence to have rapid 3D acquisition modes with T_1 weighting and so they often rely on FLASH readouts [113].

3.3.2.2 Clinical Implications

Clinically CEMRA sequences allow visualization of anatomical structures within the heart and its surrounding vessels that, in cine imaging, are difficult to delineate. Studies investigating features such as the aortic root [88], coronary artery anomalies [114], [115] and the aortic arch [90] can profit from these sequences. Other than for these applications, CEMRA is more commonly used for studying vasculature away from the heart and in the peripheries of the body.

3.3.3 Limitations

CEMRA and the subsequent quantitative parameters derived from measuring anatomical structures allow accurate assessment and visualisation of the underlying structures beyond that possible with echo. However, they provide little quantitation of blood flow or assessment of the state of the tissue, e.g., if there is scarred tissue within the myocardium, edema, or disruption of the normal cardiac microstructure; or to assess differences in blood flow from normal. These questions require different types of sequences that are possible with the flexibility of CMR.

3.4 Functional Imaging

3.4.1 Flow Imaging

First shown in cardiac applications by [116]–[118] flow quantification via phase contrast velocity encoded imaging is a widely available sequence on commercial scanners. This sequence is used to measure the velocity and therefore the flow of blood in the heart and blood vessels and has been shown to be useful in a number of clinical problems such as Hypertrophic Cardiomyopathy (HCM) [119], Dilated Cardiomyopathy (DCM) [120] and Myocardial Infarction (MI) [121]. In regard to rTOF the main interest lies in assessing the haemodynamics of the valves and vessels. In particular, regurgitant volumes and regurgitant fraction (defined as the total reverse pulmonary flow as a percentage of the total forward pulmonary flow) were shown to be of value in [80], [89], [122]–[124]. PR volume flow has been measured and used in post-operative follow ups for rTOF as early as 1993 by [122]. More recent studies such as Knauth et al. 2006 [93] have shown that in combination with anatomical measures, flow imaging can be used to predict clinical adverse events and such methods are an important element in any rTOF follow up CMR exam [80], [89], [90].

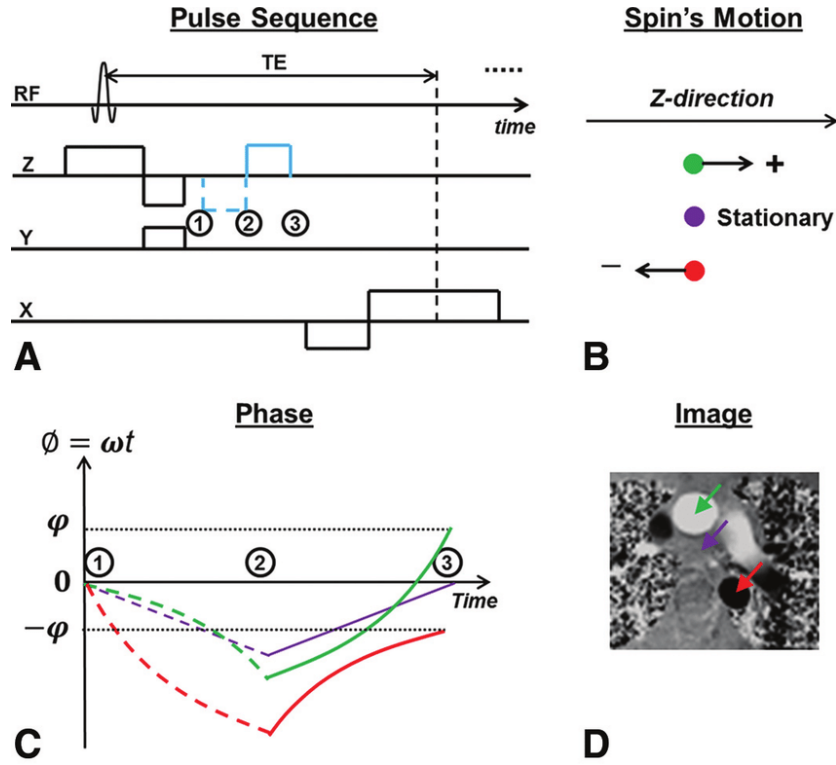


Figure 23: Image generation using a bipolar flow encoding sequence. (A) A pulse sequence with a bipolar flow encoding pulse for flow quantification. Here, the slice select axis is the z direction, the phase encode axis is the y direction and the x axis is the readout/frequency encode axis. Shown in blue here is the bipolar gradient that sensitising the image phase to motion along the z direction. (B) shows three different motion trajectories in the z direction. (C) based on the different states covered in (B) the resulting phase evolution along the timepoints (1,2,3) of the bipolar gradient are plotted. (D) shows through plane velocity encoding in the ascending and descending aorta. The opposite directions of flow in the ascending (green arrow) and descending (red) aorta result in opposite signs in the image phase. Taken from [125]

One of the most commonly used sequence types in CMR is phase velocity mapping, which makes use of bipolar gradients to encode velocity in one particular direction within the image phase. The phase velocity mapping preparation is typically incorporated into a segmented imaging sequence similar to the cine sequences described above [126].

Application of a bipolar velocity encoding gradient G_v results in spins moving in the direction of G_v accumulating a phase ϕ , which is proportional the component of velocity in the direction of G_v . This phase can then be used to calculate the flow velocity v through

$$\phi = \gamma G_v v \delta \Delta \quad 1$$

where γ is the gyromagnetic ratio, δ is the duration that the gradients are applied for and Δ is the time between the gradient lobes. The combined area of the two gradient lobes must sum to o, as otherwise stationary spins would also accumulate a phase (Figure 23).

It is important to note that any phase shift, ϕ , greater than π radians will be wrapped back to $\phi - 2\pi$ due to the circular nature of phase [126]–[130]. Therefore, in phase velocity mapping the maximum encoded velocity without producing wrap (VENC) is:

$$VENC = \frac{\pi}{\gamma \Delta m_{\perp}} \quad 2$$

where γ is the gyromagnetic ratio and $\Delta m_{\perp} = G_v \delta \Delta$ is the gradient first moment of the flow encoding gradients. If the velocity of the imaged spins v_{VOX} in a voxel lays in the range $-VENC < v_{VOX} < VENC$ the phase difference is linear and limited to the range $-\pi < \phi < \pi$ [126].

3.5 Tissue Characterisation

Babu-Narayan et al. [67] were the first to show correlation between scar tissue and adverse clinical markers in rTOF using CMR [67]. Their study found that scar tissue is commonly found after repair of TOF but they also found that the presence of scar is linked to development of ventricular dysfunction, exercise intolerance and other complications such as the development of arrhythmias. The CMR method used for scar detection is late gadolinium enhancement (LGE) and it has become the clinical standard method for investigating focal fibrosis of the myocardium [131]–[133].

3.5.1 Late Gadolinium Enhancement

In LGE imaging a GBCA is injected into the bloodstream of the patient [132], [134]–[139]. By imaging 10–15 minutes after the administration of GBCA, much of the GBCA has washed out of the normal myocardium, but in regions of scar and high proportions of extracellular space, the GBCA washes in and out more slowly. As a result, the T_1 of the scar tissue in this late phase is shorter than that of normal myocardium [138], [139].

This effect can be used with a carefully designed sequence to null the normal myocardium and enhance the focal fibrosis so that it appears bright. Inversion recovery (IR) based methods are usually used in this application.

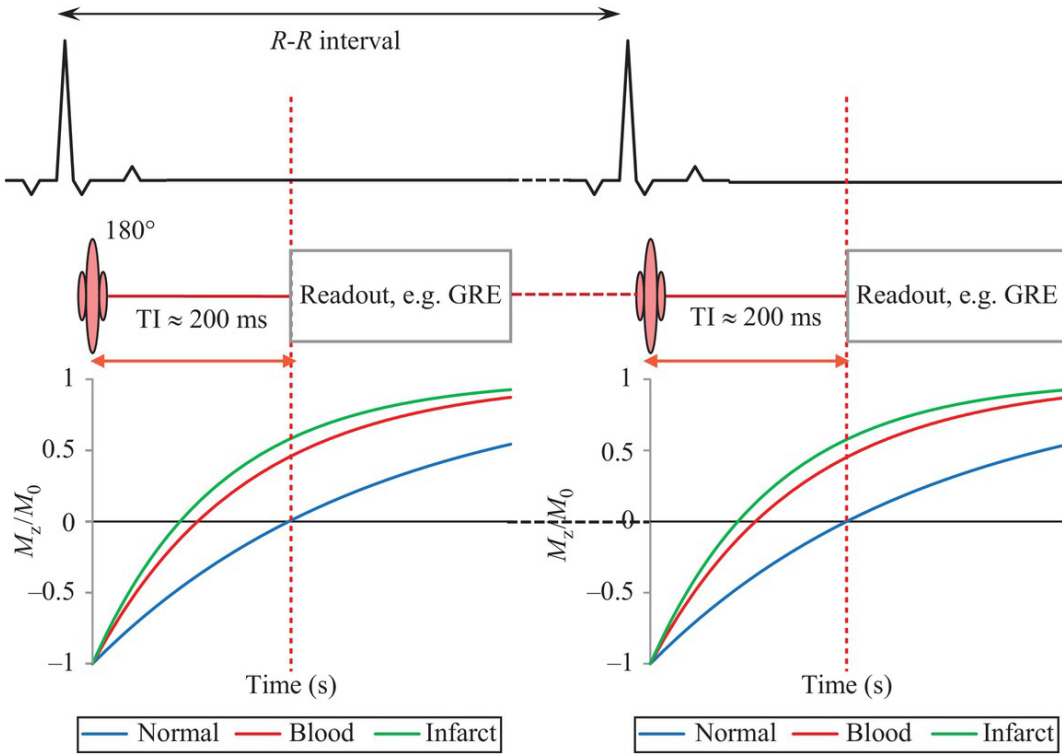


Figure 24: Schematic diagram of an inversion recovery pulse in a cardiac LGE infarct imaging setting. The top row shows the R-R interval, while the next row shows the 180° RF pulse and after a time TI the image acquisition (readout). The last row shows the recovery of the longitudinal magnetisation after the application of the 180° IR pulse. The ideal time TI after the IR pulse, to acquire the image data is the moment in which the recovery curve for normal myocardium passes the zero point, nulling the signal from normal myocardium. Taken from [106]

IR sequences make use of a 180° pulse prior to acquiring the imaging data. The 180° pulse flips the longitudinal magnetisation and it returns to its original state exponentially with a time constant T_1 . As the recovery of longitudinal magnetisation over time is dependent on the T_1 of the imaged tissue, the signal intensity – time course differs between blood, normal and infarcted myocardium [98]. This can be seen in Figure 24 where a clear difference between the blue (normal myocardium) and green (infarcted myocardium) longitudinal magnetisation curves (M_z) is visible. If the image is acquired when the longitudinal magnetisation and, therefore, signal from the normal myocardial tissue crosses zero, the normal appearing myocardium will not contribute signal to the final image, while blood and infarcted myocardium will be visible [98].

Typically, a segmented acquisition is used with either a bSSFP or FLASH readout method. Approaches such as a cine inversion recovery bSSFP sequence, as proposed by Detsky et al. [140], or the spoiled GRE sequence with blood and normal tissue suppression techniques by Cormac et al. [141] are recent developments which may improve the often tricky differentiation of blood from infarcted tissue. Blood signal is often problematic as it has similar T₁ values to the scar tissue at the typical time after contrast administration used for imaging [135].

While a number of sequence improvements have been proposed [137], [142], one widely adopted recent development was by Kellman et al. [135]. This sequence nulls both blood and healthy myocardial tissue simultaneously while combining the required spatial resolution and SNR by using a bSSFP readout with image averaging after non-rigid registration used to correct for intershot respiratory motion.

3.5.1.1 Limitations

While LGE methods have proven immensely useful when investigating focal fibrosis, for example in Babu-Narayan et al. [67], they are not able to adequately assess the presence of diffuse fibrosis. The distribution of the scar tissue over a large proportion of the myocardium means that diffuse fibrosis appears as nearly isointense and can be mistaken for healthy tissue with LGE imaging[134]. In addition to understanding the disease process, providing prognoses, and guiding future treatment options, the identification of diffuse fibrosis and differentiation from focal fibrosis is vital when identifying potential molecular targets for pharmacological substances to bind to. This in turn however greatly depends on the underlying cellular structure which differs between normal myocardium, diffuse fibrosis, and focal fibrosis. Thus, while providing valuable information for focal fibrosis, LGE is not a suitable method for reliable identification and quantification of diffuse fibrosis [69].

3.5.2 T1 Mapping

A technique which may go some way to overcoming the limitations of LGE in identifying diffuse fibrosis is T1 mapping [143]. These methods provide a quantitative measure of T1 on a pixel by pixel basis (a T1 map), [144], [145].

To generate T1 maps, a series of co-registered images are acquired with varying degrees of T1 weighting along a T1 recovery curve. A variety of readout techniques can be used to collect the image data (described later), however all of them aim at rapid coverage so that the data acquisition of a 2D slice can be acquired in a single heart beat and the data required to calculate each T1 map can be acquired within a breath hold [146]. As for the LGE methods described above, T1 mapping requires a magnetisation preparation stage prior to the image data acquisition to enable sampling along the T1 recovery curve. Most commonly this is achieved using either the Modified Look-Locker Imaging (MOLLI) sequence described by Messroghli et al. [147] or the SATuration-recovery Single-sHot Acquisition (SASHA) sequence developed by Chow et al. [148].

3.5.2.1 MOLLI

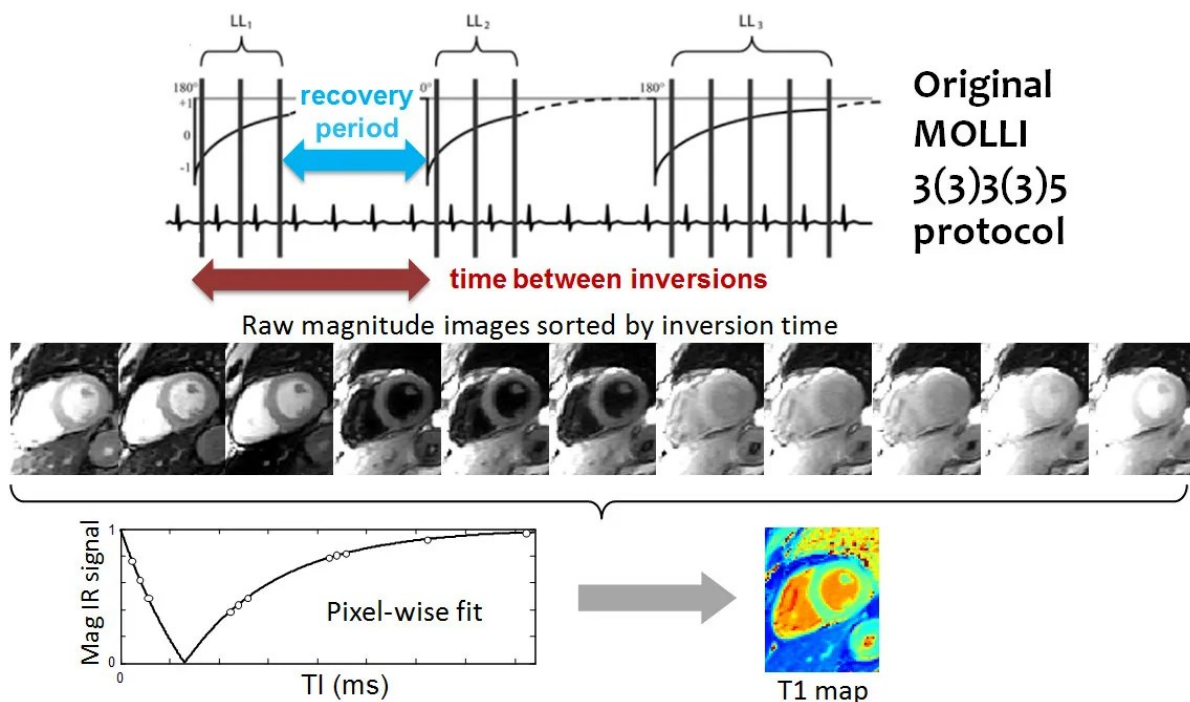


Figure 25: Original MOLLI sequence. The numbering of the protocol in the upper right corner refers to the 3 images acquired after the first inversion pulse, followed by 3-RR interval recovery period (in brackets), 3 more images are acquired after the 2nd of the inversions, followed by 3-RR intervals recovery again and then finally 5 images are acquired after the third inversion pulse. Taken from [146]

MOLLI techniques sample multiple images at different time points during the IR curve, generally in a single breath hold (even if the original MOLLI used several) using single shot 2D acquisitions. In this case, the term single shot may be slightly misleading as it does not refer to a true single shot image as can be acquired with EPI or spiral imaging after a single RF pulse (Chapter 6), but instead typically a bSSFP pulse train samples one image per cardiac cycle. As shown in Figure 25, multiple inversion pulses are used and so the points used to calculate T_1 originate from multiple inversion pulses. To ensure that each IR curve has the same initial magnetisation, recovery periods such as those shown in Figure 25 are used to allow for sufficient recovery between inversions. The timing of the inversion pulses relative to the ECG R-wave is altered between inversions, allowing all images to be acquired at the same time in the cardiac cycle, while also allowing for a range of inversion times. The accuracy and precision of the T_1 maps generated from MOLLI is partly determined by the number and distribution of points on the recovery curve that are sampled. The assumption that the heart is at the same location and so all images show the same tissue is also important for accuracy and precision [146].

In order to calculate T_1 from the IR images, the signal intensity is fitted to the exponential recovery of T_1 . The fitting process is an important factor in accuracy and precision, partly as the readout employed affects the apparent recovery time that is obtained from the fit. This fit produces a time constant T_1^* rather than T_1 as the acquisition of the images perturbs the IR curve. A 3-parameter model for signal recovery is usually employed, described by:

$$S(TI) = A - B * e^{-\frac{TI}{T_1^*}} \quad 3$$

where TI is the inversion time as shown in in Figure 25. If A, B and T_1^* are estimated using a fit, it is possible to use a Look-Locker correction factor, introduced by Deichmann et al. [149], to arrive at the following approximation of T_1 :

$$T_1 \approx T_1^* * \frac{B}{(A - 1)} \quad 4$$

3.5.2.1.1 Limitations

While the original implementation of the MOLLI sequenced suffered from long acquisition times, making single breath hold acquisitions impossible, improvements [150] have mitigated this initial limitation. A bigger problem is that MOLLI sequences systematically underestimate T_1 by 4-10 % in phantoms [147], [150], [151] and have similar or even greater underestimation in tissues with short T_2 [152].

3.5.2.2 SASHA

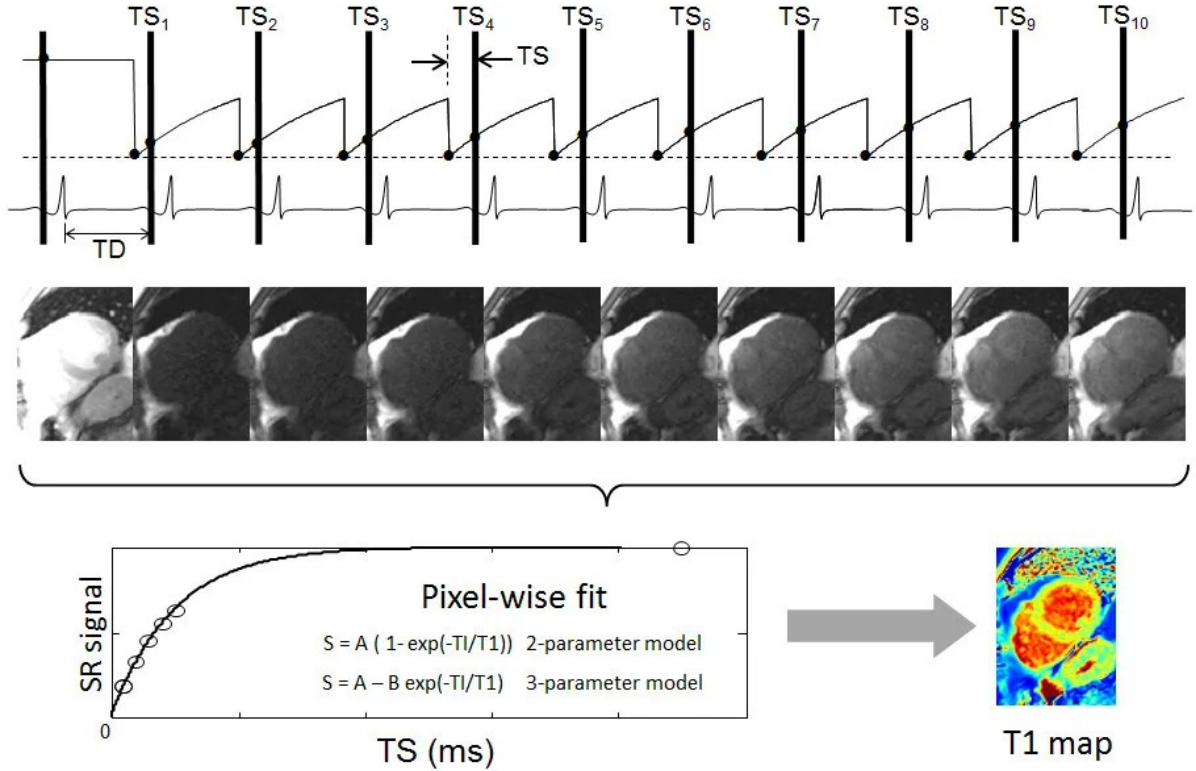


Figure 26: Diagram of the acquisition of a T_1 map using the SASHA sequence. The top row a representation of one breath hold, with the evolution of the longitudinal magnetisation (top, solid line) that is affected through the saturation pulses (at the filled circles) and one image acquisition per saturation pulse, acquired at time TS after the saturation pulse. The first image is acquired before the application of any saturation pulses and acts as a long TS measure. The next row shows the images in the order that they were acquired and shows the signal recovery with TS . An example signal recovery curve is shown below, together with the two commonly used fitting models and the calculated T_1 map. Taken from [146]

As described above, the MOLLI sequence suffers from a systematic underestimation of T_1 and as such a more accurate approach for measuring T_1 is desirable. Higgins et al. [153] have shown that this limited accuracy can at least be partly minimised by replacing the MOLLI IR with a saturation pulse and replacing bSSFP readouts with FLASH. Chow et al. [148] then showed the first sequence that combined the benefits of a high SNR of a bSSFP readout with the accuracy offered by saturation recovery [148].

While SASHA has a smaller dynamic range than MOLLI, the saturation preparation offers the benefit that each image along the curve is independent of the recovery time from prior pulses. As a result, no Look Locker correction is required as the same initial magnetisation is ensured after each saturation pulse, thus resulting in the following 2-parameter model:

$$S(TS) = A * \left(1 - e^{-\frac{TS}{T_1}}\right) \quad 5$$

where TS is the time after the saturation pulse. In Figure 25 the general approach of sampling in one breath hold is shown, after one initial image without saturation (effectively a long TS), multiple images with different saturation delays are acquired, one image per saturation pulse. As for MOLLI, it is important to note that the trigger delay only affects the saturation pulse timing and the image is acquired in the same cardiac phase for each trigger delay, thus reducing misregistration errors.

While the readout in this model might not influence the signal model in this sequence as drastically as the MOLLI approach it can have an impact. This is more problematic with higher readout flip angles, which can be compensated for by using a 3-parameter fit at the expense of precision:

$$S(TS) = A - B * e^{-\frac{TS}{T_1}} \quad 6$$

3.5.2.2.1 Limitations

The main limitations of SASHA are the loss of dynamic range relative to MOLLI (which reduces T_1 precision) and the trade-offs between achieving higher precision or higher accuracy. Higher accuracy can be for example achieved by using the 3-parameter model, however, at a loss in precision due to the extra parameter that needs to be fitted. In general, MOLLI type sequences offer higher precision while SASHA offers higher accuracy with reduced precision [146], [148].

3.5.2.3 ECV

While T_1 mapping of the myocardium without the administration of GBCA (pre-contrast T_1 mapping) has been used to identify diffuse fibrosis [154], [155], an alternative method is available which estimates the proportion of the myocardium occupied by extra cellular space. However this is not possible from one T_1 map alone and estimation of the Extra Cellular Volume Fraction (ECV) requires a more complex approach involving T_1 mapping before and after administration of GBCA [69], [146].

In order to determine ECV experimentally, a native T_1 map (without contrast) is acquired and then T_1 mapping is repeated around 15 minutes after the administration of GBCA. GBCAs in use today are extracellular (they do not cross the cell membrane). The rapid exchange of water molecules between the intra and extracellular space in the blood and myocardium is assumed. The second assumption is that GBCA concentration is equal between the blood plasma and myocardial extracellular space. Using these assumptions the ECV is given by: [69], [146].

$$ECV = (1 - H) \frac{R1_{gad,myocardium} - R1_{native,myocardium}}{R1_{gad,blood} - R1_{native,blood}} \quad 7$$

$$R_1 = \frac{1}{T_1}$$

where H is haematocrit (the fraction of blood occupied by red blood cells), *gad* denotes the measurement is performed after contrast enhancement and *native* before contrast enhancement.

In rTOF ECV has been assessed in a few studies. For example, Chen et al. [156] investigated the clinical use of ECV (in both the RV and LV) as a marker of diffuse fibrosis – which in turn can indicate the extent of hemodynamic load and predict subsequent hypertrophy. They found that LV and RV ECV in patients with rTOF can be correlated to adverse LV-RV interaction and an increase in ECV could be associated with RV volume overload and potential arrhythmias [156]. Another study by Deane et al. [143] found that rTOF children show no elevation in ECV in the LV, but an increase in the RV and the authors suggest that volume loading results in this increased risk of diffuse RV fibrosis. While these initial studies are promising applications of ECV, great care has to be taken when using ECV and T_1 mapping as there are a set of pitfalls that can cause inaccuracy and problematic results particularly in the challenging RV anatomy.

3.5.2.4 Pitfalls

While T_1 mapping has become increasingly popular in recent years, a range of error sources, artifacts and limitations must be considered to ensure accuracy and precision and avoid potentially misguided interpretations of the results [146].

3.5.2.4.1 Off-resonance

Both SASHA and MOLLI frequently employ bSSFP readouts to collect imaging data and are therefore susceptible to banding artifacts (see Section 3.1.2), however an imperfectly shimmed Bo-field can have further implications when measuring T₁ [146], [157].

Kellman et al. [158] assessed the effects of off-resonance on T₁ accuracy in a study investigating MOLLI sequences both at 1.5 T and 3 T. The percentage T₁ error for a range of off-resonance frequencies as a function of T₁ was obtained from phantom measurements with Bloch simulations as validation and the results are shown in Figure 27. In a cohort of 18 subjects they found mean myocardial off-resonance values of 20.3 ± 13.0 Hz, 15.4 ± 29.3 Hz at 1.5 T and 3 T respectively and maximal values of 61.8 ± 15.5 Hz and 125.0 ± 40.6 Hz. With regional off-resonance greater than 80 Hz at 1.5 T in 4 of these subjects a T₁ error of > 3 % is therefore possible in realistic settings.

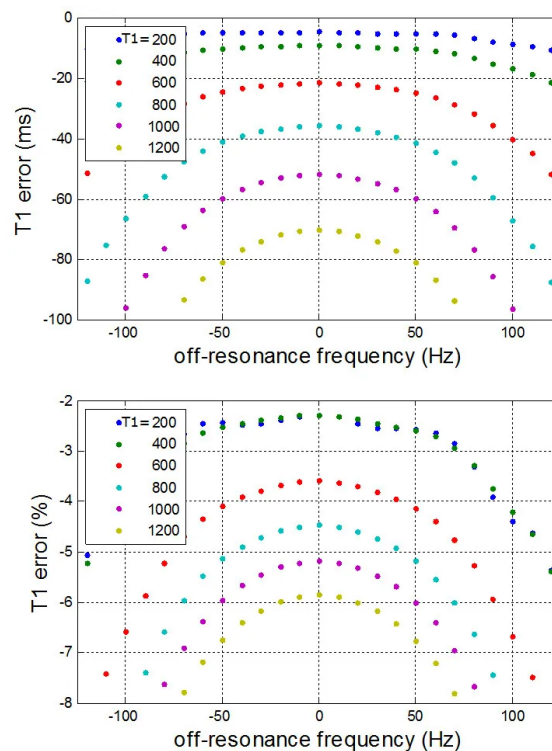


Figure 27: The error in T₁ due to off-resonance when using a MOLLI 5(3)₃ sequence with a 35° flip angle. Evaluation was performed with a range of T₁ values, while the T₂ was constant at 45 ms. The top row shows absolute error (ms), while the bottom row shows percentage error. Taken from [158]

While the SASHA approach is in general less sensitive to off-resonance, the magnitude of the effect in T_1 depends on the fitting model. The 3-parameter model performs better in regards to off-resonance related error than the 2 parameter model [146]. For the 3-parameter model Chow et al. [148] reported T_1 errors below 0.5 % for a range ± 96 Hz of off-resonance and reaching up to 5 % error when off-resonance frequencies are above 143 Hz using Bloch simulations. While Kellman et al. [146] simulated the effect on the 2-parameter model as shown in Figure 28.

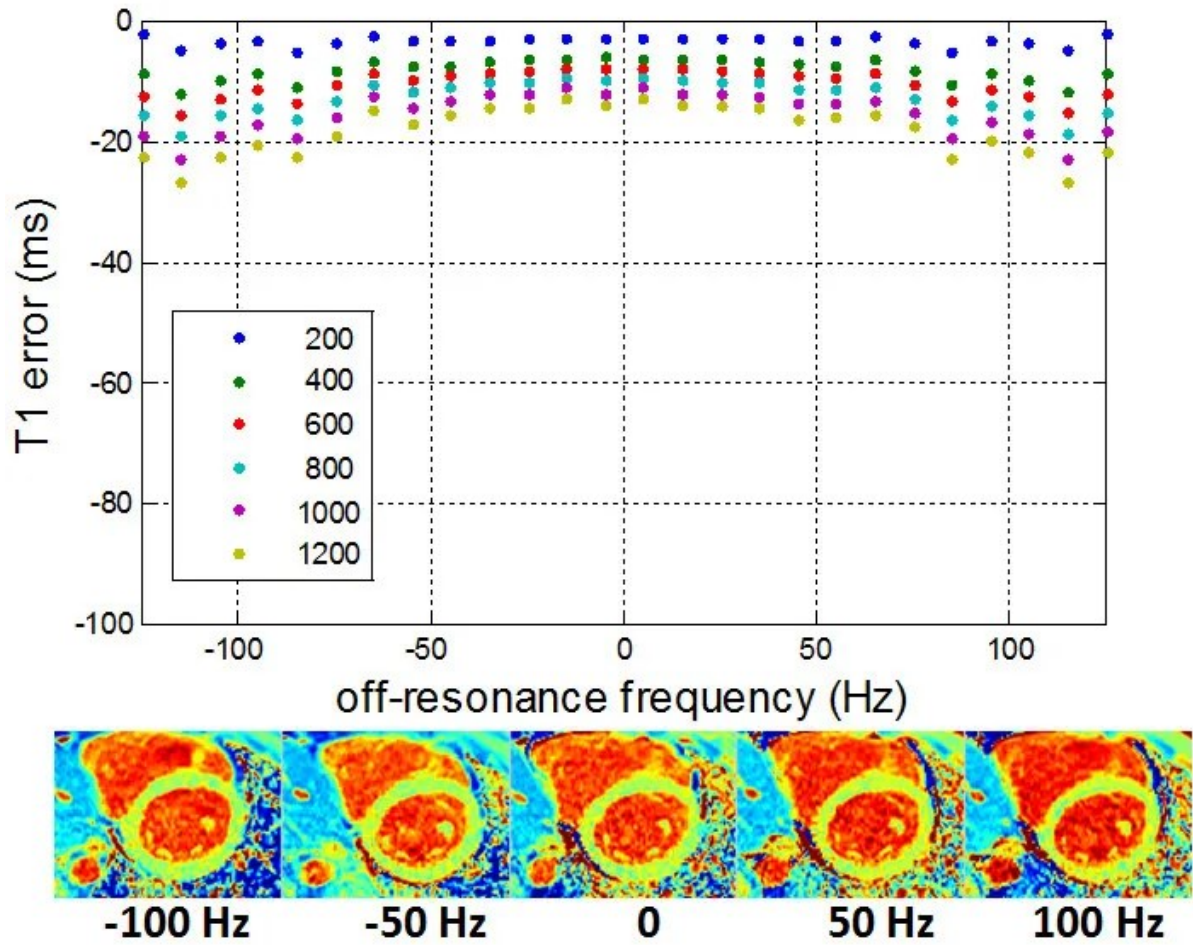


Figure 28: The effect of off-resonance for various values of T_1 and the related error in ms when using a SASHA sequence with the 2-parameter fit. Values for T_2 were set to be 45 ms in this simulation, while a flip angle of 70° , a TR of 2.8 ms and an optimized BIR4-90 saturation pulse were chosen. Taken from [146]

3.5.2.4.2 Spatial Resolution

Spatial resolution in cardiac applications poses a potential problem, as respiratory and cardiac motion means that acquisition windows must be short or complicated navigator and registration algorithms are required. The assumption that the underlying signal for fitting originates in one tissue specimen per pixel can also cause errors in measured T_1 , via partial volume effects. This is especially true in areas where voxels may potentially contain blood and myocardial signal and methods such as eroding the blood-myocardial border [159] [144] are often used before quantification. However, since the spatial resolution is limited and, for example, the eroding method reduces the number of available pixels for quantitation further, it is often not possible to reliably measure T_1 in thin myocardial tissue such as the RV [146].

3.6 Limitations

While CMR offers many important quantitative parameters for the assessment of rTOF patients, and T_1 mapping-based methods may provide some indication of diffuse fibrosis in some conditions, the assessment of diffuse fibrosis in rTOF remains a challenge. This is particularly troubling as it is believed that an accurate assessment of diffuse fibrosis in rTOF patients will allow identification of new targets for drugs and potential treatment strategies that allow reduction of risk factors such as arrhythmias and sudden cardiac death [67]. In the next chapter the basic principles of a novel CMR method that has potential to provide new insights into underlying microstructural changes (including diffuse fibrosis) is introduced.

4 Diffusion Tensor Cardiac Magnetic Resonance

This chapter introduces the basics of Diffusion Weighted Imaging (DWI), Diffusion Tensor Imaging (DTI), the parameters derived from both and the sequences used to apply these methods in the heart.

4.1 Diffusion

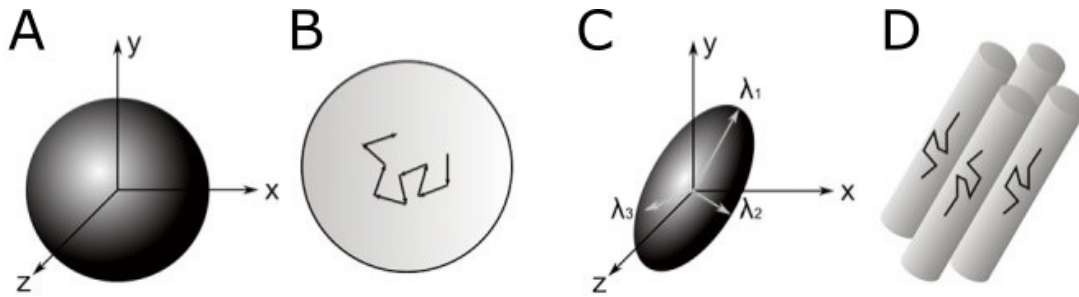


Figure 29: Cartoon of unrestricted diffusion (A, B) and restricted diffusion (C, D). Isotropic “free” diffusion(B), e.g., in a large volume of water is described by a spherical diffusion tensor as the water molecules can diffuse in all directions (A), whereas diffusion within narrow impermeable tubes would be anisotropic and would be represented by a cigar shaped diffusion tensor (C), with the long axis aligned with the orientation of the tubes (D). Taken from [160]

Diffusion is the random movement of particles in a liquid (or gas) due to the thermal energy of the particles. The random nature of the motion is caused by the collision of the moving molecules and is known as Brownian Motion. In a centre of a large volume of an isotropic liquid diffusion from a point is isotropic (Figure 29). While some particles in a given time t travel further and some shorter distances, the root-mean-square displacement r of the particles can be described by:

$$\langle r^2 \rangle = 6Dt \quad 8$$

where D is the diffusivity (or diffusion coefficient) of the fluid which is described by Einstein’s Equation [161]

$$D = \frac{k_B T}{6\pi\mu R} \quad 9$$

where T is absolute temperature, μ the viscosity of the fluid, R the radius of the particles and k_B the Boltzmann constant.

However, this only holds true in an isotropic medium where the diffusion process can be described by a Gaussian probability distribution. In reality, cell membranes, organelles and other structures/processes often restrict or hinder the distances diffused in one or more directions and more complex probability distribution functions are required to accurately describe diffusion [162]. One proposed model, DTI, captures anisotropy while assuming that diffusion is Gaussian. In the DTI model the distances diffused and, therefore, the diffusion coefficient are dependent on the direction interrogated (Figure 29). The diffusion tensor can then be expressed using the mathematical construct of a rank 2 tensor d

$$d = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix} \quad 10$$

that describes an ellipsoid (Figure 29) to represent the magnitude, orientation and anisotropy of diffusion [163]–[165]. While this is an oversimplification it facilitates *in vivo* assessments of microstructure [49].

4.2 Diffusion Weighted Imaging

While Chapter 6 introduces the methods used for sampling the MRI signal to produce an image, this chapter is solely focused on the generation of contrast for diffusion imaging.

The groundwork for measuring diffusion with magnetic resonance was done by Carr and Purcell [166] who demonstrated the signal reduction due to diffusion in an NMR experiment in 1954 and Stejskal and Tanner [167] in 1965 who demonstrated the first Spin Echo (SE) based Nuclear Magnetic Resonance (NMR) sequence to measure diffusion (Figure 30). Originally the translation of this sequence to cardiac imaging was hindered by the motion sensitivity of the SE approach, resulting in drastic signal loss when performed *in vivo* [19]. Several studies [168]–[170] in the 1990s used the Stimulated Echo Acquisition Mode (STEAM) sequence to minimise the effects of cardiac motion in cardiac DWI. Gamper et al. [171] modified the Stejskal Tanner SE type approach in 2008 in an attempt to avoid bulk motion-related signal loss, by, making the diffusion encoded gradients insensitive to constant velocity motion for *in vivo* cardiac imaging. Nielles-Vallespin et al. [49] then demonstrated a reproducible *in vivo* STEAM DTI sequence in 2013, which fuelled the recent interest in cardiac DTI.

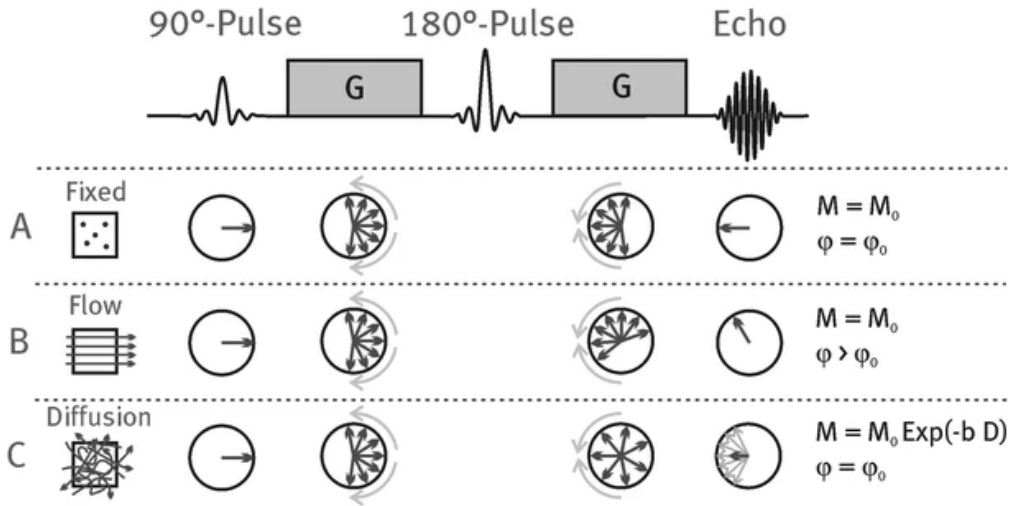


Figure 30: Diagram of a Stejskal-Tanner SE sequence and the evolution of spin phase and magnitude within a voxel during different types of motion. (A) shows the case of stationary spins, and so phase and magnitude are unaffected by the encoding gradients. (B) shows the case for all spins experiencing the same displacement (i.e., constant velocity) and as such only the phase changes. (C) shows the case of random displacements, as encountered in diffusion processes, and while the overall phase is not changed the overall magnitude of the signal is reduced due to the vector combination of the spin vectors with a range of phases. Taken from [172]

The SE sequences differ from the GRE sequences covered in Chapter 3, in that an additional RF pulse is used to form the echo. This second pulse is capable of recovering the spin phase information that typical is lost during the FID due to T_2' (field inhomogeneities) decay [173]. The pulse flips the spins by 180 degrees and so can reverse the phase incoherence that would be encountered due to the static field inhomogeneities during an FID. While this requires more time, it may provide higher SNR.

All sequences with diffusion weighted contrast rely on diffusion-weighting gradients which produce a signal loss which is dependent on the distance diffused [19]. The principle of diffusion encoding has similarities to the approach of flow encoding described in Chapter 3, however while flow imaging encodes bulk motion in the signal phase, diffusion imaging captures random intravoxel motion in the signal intensity as shown in Figure 30 [174]. Diffusion encoding can be considered as an extreme case of phase velocity encoding, where the magnitude of the encoding has been greatly increased to cause sufficient phase changes when water molecules move on the scale of diffusion distances. The randomly orientated displacements of the water molecules result in random signal phases, which, sum over the imaging voxel to less than the sum of the coherent phases in the case of no diffusion.

To achieve this increased sensitivity to motion, diffusion encoding sequences employ a pair of encoding gradients separated by a 180° flip of the magnetisation in the transverse plane. While the bipolar gradient waveforms used in phase velocity mapping could be used with increased gradient strength and duration, the T_2^* signal loss during this increased duration would result in very poor SNR. Applying the first encoding gradient $G(t)$ in the direction $\hat{x}$, the change in the local resonance frequency of the protons results in a spatially dependent phase $\phi(x)$ accumulation according to:

$$\phi(x) = \int_0^t \Delta\omega \, dt = \gamma \int_0^t G(t) x(t) \, dt \quad 11$$

where $\Delta\omega$ is the difference in the resonance frequency, t is the time, γ the gyromagnetic ratio and $x(t)$ is the displacement along $\hat{x}$. If the magnetisation is now flipped by 180° in the transverse plane and the same gradient $G(t)$ is applied again, the phase accumulation is reversed for static spins. However, this is only true if the protons had the same location during both encoding gradients; motion during or between the diffusion gradients will result in spins experiencing a different magnetic field and subsequently a net phase accumulation [174]. As discussed in Chapter 3.4.1, this phase is linearly related to the distance displaced along the axis of encoding, which is also apparent from Equation 11. As a result, in the case of bulk motion (flow, tissue motion due to the respiratory or cardiac cycle) the protons within a voxel experience the same phase accumulation. While the random motion on a smaller scale caused by diffusion within each voxel will lead to intravoxel dephasing and can be described by:

$$S_1 = S_0 \cdot e^{-\langle\phi^2\rangle} = S_0 \cdot e^{-d \cdot b} \quad 12$$

Where S_0 is the signal without the application of diffusion gradients, S_1 the signal with diffusion encoding gradients, d a scalar diffusion coefficient and b a diffusion weighting factor, referred to as the b-value in literature. The b-value describes the magnitude of the diffusion encoding. Assuming monopolar diffusion encoding with rectangular shaped gradients (infinite slew rates), b can be calculated as follows:

$$b = (\gamma G \delta)^2 \left(\Delta - \frac{\delta}{3} \right) \quad 13$$

where Δ is the time between the start of the two encoding gradients, δ is the duration of each of the diffusion gradients and G is the gradient amplitude. Consequentially there is a limit to the maximum b-values possible since the gradient hardware (maximum gradient strength) is limited. The time available to run the gradient (Δ and δ) without the MR signal decaying too much with T_2 and resulting in insufficient SNR is also limited.

While the b-value describes the overall sensitisation to diffusion there is another important property of the gradients to consider: the direction on which to play out these diffusion encoding gradients. Using a combination of gradients along all three scanner axes means that the direction that diffusion is encoded in can be chosen freely.

An important consideration for the use of DWI and DT-CMR was recently described in a letter from Stoeck et al. [175]. It was pointed out that the self-diffusivity of free water at 37° C which is $2.92 \times 10^{-3} \text{ mm}^2/\text{s}$ should provide an upper limit to the measured diffusivity in in vivo DWI and DT-CMR. Any values exceeding this are artefactual and likely to originate from bulk cardiac motion, which is roughly four orders of magnitudes larger than typical distances diffused in the heart [19]. As such it is pertinent that methods are applied to address this bulk motion, as otherwise results from DT-CMR cannot be reliably interpreted.

4.2.1 Effects of Microvascular Perfusion

One important addition to the model of DWI is the influence of microvascular perfusion. The pseudo-random arrangement of the capillaries means that the perfusing blood may show a similarly intravoxel incoherent motion to diffusion processes [176]. As such a biexponential signal model can be introduced:

$$S_1 = S_0 \left(A e^{-D_1 b} + (1 - A) e^{-D_2 b} \right) \quad 14$$

where A and 1-A are the relative contributions of each process and D_1 and D_2 the apparent diffusion coefficients of each process [177]. It was shown by Bihan et al. [176], [178] that due to the velocity of the underlying perfusing water molecules, the signal from the perfusing water decays more rapidly than the signal from the diffusing water as b-value is increased. This leads to the typical assumption that above a certain b-value threshold the term containing D_2 (relating to perfusion) is sufficiently small that monoexponential decay with b-value can be assumed and D_1 is entirely due to self-diffusion [179].

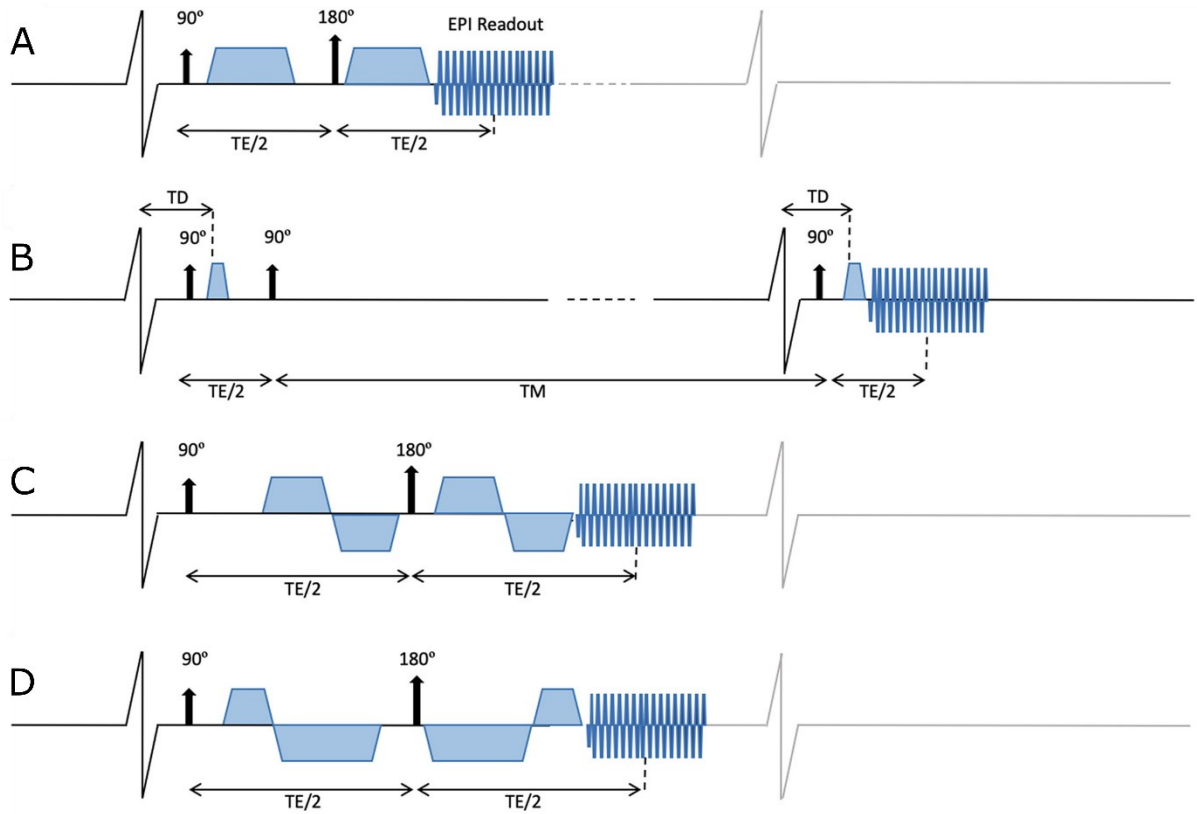


Figure 31: Diffusion sequences used in DT-CMR. (A) Stejskal-Tanner type SE approach with the time $TE/2$ denoting the time between the 90° and the 180° pulse. The same time is required for the echo to form after the 180° refocussing pulse. This sequence is not suitable for in vivo DT-CMR use due to the sensitivity to cardiac motion during the encoding. (B) Monopolar STEAM approach with $TE/2$ denoting the time between the first two 90° pulses, before the transverse magnetisation is stored along M_z . Thus, the stimulated echo forms $TE/2$ after the third 90° pulse. The time TM refers to the mixing time between the second and third RF pulses, while TD denotes the time between the ECG R-wave and the start of the diffusion encoding. The monopolar diffusion encoding gradients in STEAM require the same TD to ensure that the pairs of diffusion encoding gradients are applied when the heart is in the same cardiac phase. (C) First-order motion compensated SE approach with a longer $TE/2$ due to the requirements of the bipolar diffusion gradients, which null the first gradient moment and avoid motion related signal loss when tissue moves with constant velocity. (D) Second-order motion compensated SE approach, with the $TE/2$ longer than in (C) due to the more complex second order nulling gradients required to avoid motion related signal loss from constant acceleration and velocity motion. Modified from [19]

4.2.2 Motion Compensated Spin Echo (MCSE)

SE diffusion encoding sequences have been used throughout the body [176], [178], [180]. However, their application to *in vivo* cardiac diffusion imaging is a recent development. The reason for this is that diffusion sequences require sufficiently large b-values to produce a measurable signal loss (e.g. $\sim 1/D$ [181]). Based on Equation 13 this means that G or ∂ need to be sufficiently large as Δ is minimised to reduce T2-related signal loss. While there is a limit to G due to hardware and nerve stimulation limitations, increasing ∂ will result in (see Equation 13 and Figure 30) a heightened sensitivity to bulk motion and, therefore, in cardiac acquisitions result in drastic signal loss [182] (also Section 6.1).

The effect of bulk motion on the phase ϕ in the presence of gradient $\vec{G}$ is approximated using the following Taylor expansion:

$$\begin{aligned}\phi &= \gamma \int_0^t \vec{G}(\tau) \vec{x}(\tau) d\tau \\ &\approx \gamma \int_0^t \vec{G}(\tau) \vec{x}(t_0) d\tau + \gamma \int_0^t \vec{G}(\tau) \vec{v}(t_0) t d\tau + \frac{1}{2} \gamma \int_0^t \vec{G}(\tau) \vec{a}(t_0) t^2 d\tau + \dots\end{aligned}\tag{15}$$

where $\vec{x}(\tau)$ is the spin displacement, $\vec{x}(t_0)$, $\vec{v}(t_0)$ and $\vec{a}(t_0)$ respectively the position, velocity and acceleration at t_0 , which denotes the start timepoint. As a result, equation 15 can be written as:

$$\phi = \gamma \left(m_0 + m_1 \vec{v}(t_0) + \frac{1}{2} m_2 \vec{a}(t_0) + \dots \right)\tag{16}$$

with:

$$m_n = \int_0^t \vec{G}(\tau) t^n d\tau\tag{17}$$

where m_n is the n^{th} gradient moment.

Designing gradients where the n^{th} moment is zero ensures that spins which have a trajectory during the gradients with a constant n^{th} time derivative do not result in phase change and, therefore, signal loss. Gamper et al. [171] proposed using a pair of bipolar gradients to null the first order moments to compensate for constant velocity motion in *in vivo* cardiac imaging. This technique was then advanced by Welsh et al. [183], who designed gradient waveforms with the first and second moments zeroed and also with the first 3 moments zeroed, to avoid the effects of constant acceleration and jerk to image rat hearts *in vivo*. In Figure 31, the first

order and second order moment nulled waveforms are displayed and demonstrate the expected increase in TE. There is, therefore, a trade-off between motion robustness and T₂-related signal loss as TE increases.

Further investigation of these methods [48], [184]–[189] and studies from Stoeck et al. [48], [187] suggest that the second order motion correction yields the best balance in terms of motion compensation vs TE elongation *in vivo*, in humans [187], rats [183] and pigs [48]. In the porcine study [48] the hearts were arrested after the *in vivo* scan and rescanned using an *ex vivo* protocol, showing good agreement with *in vivo* results for the second order compensated waveforms [48].

4.2.3 STEAM

A stimulated echo requires three rather than the two RF pulses used in SE and the STEAM sequence splits the acquisition over two consecutive cardiac cycles [190]. In the first cardiac cycle, the first RF pulse tips magnetisation into the transverse plane and the first diffusion encoding gradient is run at a time, T_D (Figure 31) after the R-wave. The second RF pulse rotates the magnetisation by 90° and the resulting longitudinal magnetisation is then stored (decaying with T₁ from this point). In the second cardiac cycle, the third 90° pulse tips the remaining stored magnetisation into the transverse plane and is timed to allow the second diffusion gradient to be run at the same delay from the R-wave in the second cardiac cycle (T_D) (Figure 31). It is apparent from Equation 13 that separating the diffusion encoding by 1 cardiac cycle ($\Delta \sim 1s$) means that diffusion encoding gradients can be shorter (reduced ∂) and lower amplitude than in SE (G). These shorter and smaller gradients are less susceptible to bulk motion artefacts due to motion during the gradients. STEAM allows acquisition of much higher b-values with little increase in ∂ and short TE [19].

Separating the diffusion encoding gradients by one cardiac cycle means that the actual b-value for STEAM depends on the heart rate of the subject and as such can vary between and during an acquisition. This heart rate dependence can be accounted for in the calculation of the diffusion tensor and is covered in Chapter 4.3.

Another benefit of STEAM is that via the three 90° pulses and slice selection gradients it is possible to reduce the Field Of View (FOV) contributing to the stimulated echo [49], [191]. This can be done in either of the in-plane directions, by making the slice selection gradients of the first two 90° pulses perpendicular to the third, or in both in-plane directions by making all three slice select gradients orthogonal. This can be particularly beneficial for spiral acquisitions as discussed in Section 6.3.

The heart must be in the same position when both diffusion encoding gradients are run and, as a result, STEAM is mostly used in combination with breath holding. In addition to the phase based considerations described above, cardiac or respiratory motion during Δ can mean that the slice excited in the first cardiac cycle is not imaged in the second cardiac cycle resulting in complete signal loss [19]. Navigator based approaches have been used [49] but require longer scan durations (approximately 20 %) and there is some residual bulk motion artefact.

4.2.3.1 Strain

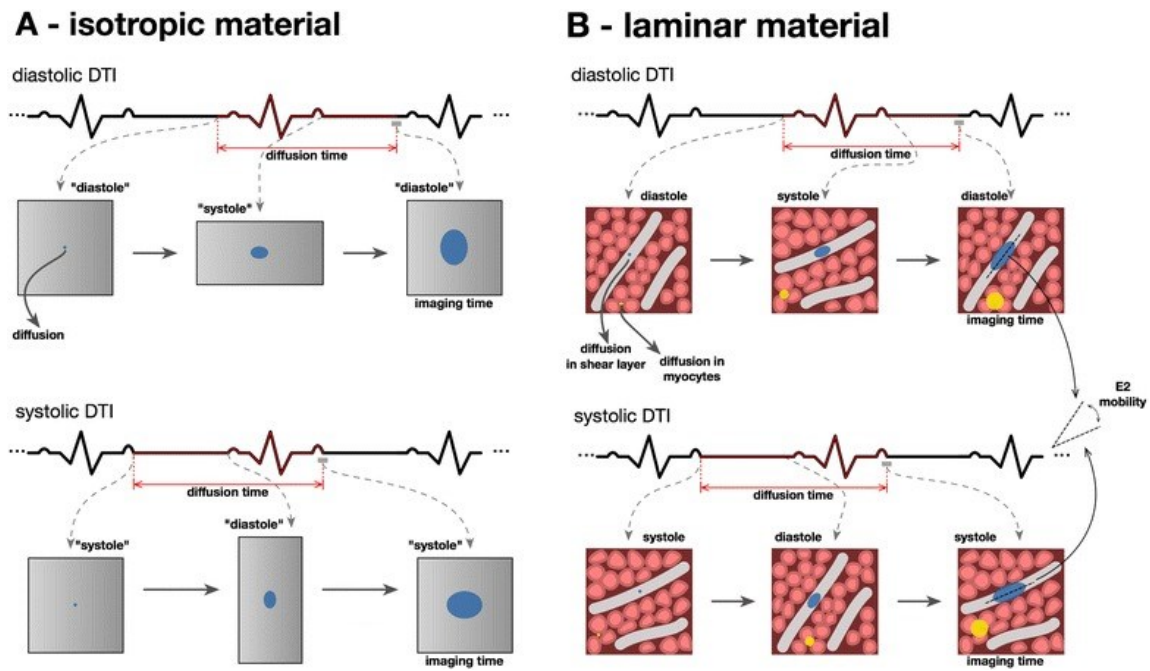


Figure 32: The influence of strain on diffusion, both when the tissue is stretched or compressed (systolic and diastolic trigger times). Strain has a different effect on diffusion in a gel-like material (A) compared to a material where diffusion is restricted by shear layers in a laminar material (B). Taken from [50].

Another complication of the dual cardiac cycle acquisition in STEAM is the contraction of the heart itself. As described in Chapter 1, the microstructure changes during the cardiac cycle and while the diffusion signal in STEAM is encoded at the same position in two consecutive cardiac cycles, the tissue deformation during Δ introduces a possible error into the diffusion measurement (Figure 32).

The first description and correction for this effect was proposed by Reese et al. in 1996 [168]. Through investigation of the strain effects experienced by a gel phantom (Figure 32A), the influence of the deformation on the tensor was modelled mathematically resulting in a proposed correction method and this was validated in the phantom experiments. Tseng et al. [192] suggested that strain correction methods can be avoided by limiting the measurement of diffusion to the so called “sweet-spot”. The sweet spots are the times in the cardiac phase in which the stretching and compression effects of strain on the measured diffusion cancel each other out and the measured tensor is equal to the tensor measured in a static material [192]. Stoeck et al. [185] demonstrated strain corrected diastolic and systolic STEAM data and in one example dataset acquired at the sweet spot.

Ferreira et al. [193] corrected for strain by using the Reese model in 11 porcine hearts imaged *in vivo* and then compared to an *ex vivo* DTI protocol. The data corrected based on the gel-like material provided comparable results to the *ex vivo* data when assessing the primary eigenvector (via the HA), but the secondary eigenvector (that coincides with the orientation of the sheetlets and shear layers) showed a significant overcorrection, when compared to *ex vivo* data. While the Reese model assumes a gel-like material the myocardium has a complex multiscale microstructure that varies through the cardiac cycle and cannot be adequately described by a model this simple. This is visualised in Figure 32, where on the left side the isotropic case is shown and on the right a laminar material is shown, demonstrating the additional complexity [193].

4.2.4 STEAM vs. MCSE

Second order MCSE and STEAM are the two most common approaches to *in vivo* DT-CMR currently in use. While STEAM is a more established technique, MCSE has grown in popularity since its inception.

One of the main differences between STEAM and MCSE is the SNR. While there are potentially many methods of measuring SNR, here we will focus on theoretical SNR efficiency. This has the advantage of not only accounting for the factors that determine the STEAM and MCSE SNR, but also considers how long each image takes to acquire. For MCSE using flip angles of 90° and 180° SNR per unit time squared is:

$$SNR_{efficiency,MCSE} \propto \left(1 - e^{-\frac{TR_{MCSE}}{T_1}}\right) e^{-\frac{TE_{MCSE}}{T_2}} \Delta V e^{-bD} \quad 18$$

where TR_{MCSE} is the inter-shot recovery time for the MCSE sequence, TE_{MCSE} is the echo time as defined in Figure 31, ΔV the voxel volume.

While for STEAM under the similar assumption of three 90° flip angles the SNR efficiency per unit time squared is given by:

$$SNR_{efficiency,STEAM} \propto \frac{1}{2} \frac{1}{2} \left(1 - e^{-\frac{TR_{STEAM}}{T_1}} \right) e^{-\frac{TM}{T_1}} e^{-\frac{TE_{STEAM}}{T_2}} \Delta V e^{-bD} \quad 19$$

where TR_{STEAM} is the inter-shot recovery time for the STEAM sequence (not equal to true TR), TE_{STEAM} is the echo time as defined in Figure 31 c and TM is the time from the second to the third 90° pulse and so denoting the time along which the transverse magnetization is stored along M_z .

The first observation regarding these equations are the two factors of $\frac{1}{2}$ in the STEAM approach. They originate in the 50 % inherent signal loss in stimulated echo echoes and the reduction in efficiency due to the two cardiac cycles required for each image in STEAM.

The factor of $e^{-\frac{TM}{T_1}}$ means that the SNR efficiency is more dependent on changes in the RR interval for STEAM than MCSE (factor does not exist in MCSE). In Figure 33 this relationship between heart rate and the ratio between SNR_{SE} and SNR_{STEAM} is plotted. In contrast, for STEAM sequences the TE is considerably shorter than in the MCSE sequences (Figure 31), which results in less T2 related decay and which is important in cardiac applications where average T2 values are only approximately 45 ms (at 3 T) [146].

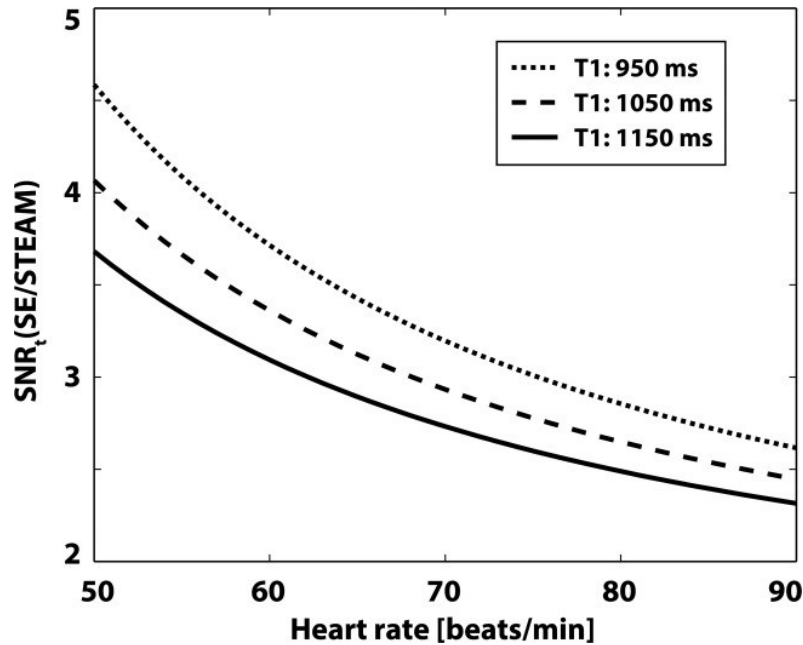


Figure 33: Plot of the dependence of the ratio between SNR_{SE} and SNR_{STEAM} with heart rate for 3 different T_1 values. Taken from [184]

As a result of the above, the SNR efficiency in MCSE approaches is theoretically much higher, as noted by [19], [184], [186]. This difference in SNR has been investigated in studies at 3 T [186] and 1.5 T [184]. Von Deuster et al. [184] found the SNR efficiency of the MCSE to be higher than the STEAM sequence, while Scott et al. [186] found the MCSE approach less reliable in diastolic imaging. This reduction in reliability of MCSE in diastole may be linked to the more complex trajectory of motion despite the lower amplitude of motion in late diastole. Aliotta et al. [194] found a reduced precision of MCSE in diastole compared to a mid-systolic acquisition.

As described in Section 4.2, the SE techniques rely on using sufficient maximal gradient amplitude and/or duration, but the STEAM sequence takes advantage of a very long Δ to achieve sufficient b-values for diffusion imaging. While for MCSE sequences, the achievable b-values are not as high as in STEAM, the Δ itself has fundamental implications on the origin of the diffusion signal [186]. This is demonstrated by Equation 8, which illustrates how far the water molecules have displaced on average over the time Δ . The impact of microscopic structures on the underlying diffusion signal can therefore be very different as shown in Figure 34 [186]. This difference means that the two sequences have different sensitivities to structures on different scales and both have particular advantages/disadvantages so should be viewed as complementary tools [186].

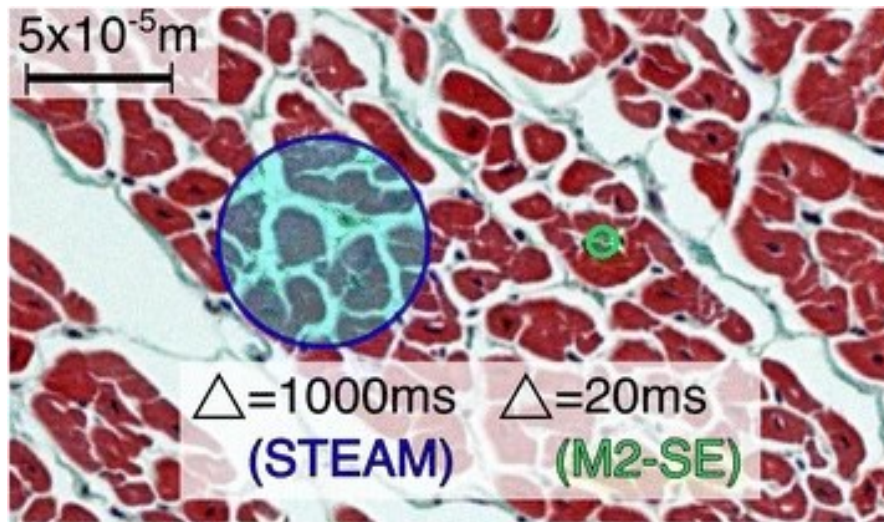


Figure 34: Histology from a pig heart showing cardiomyocytes. The slice was taken perpendicular to the myocyte long axis and overlaid with the typical root mean square (RMS) distance diffused during the time Δ for STEAM and MCSE. Diffusivity is assumed to be that of free water at 37° C at $3 \times 10^{-3} \text{ mm}^2/\text{s}$. The radius of the blue circle is approximately 75 μm and for the green circle it is approximately 10 μm . Taken from [186]

4.3 Diffusion Tensor Imaging

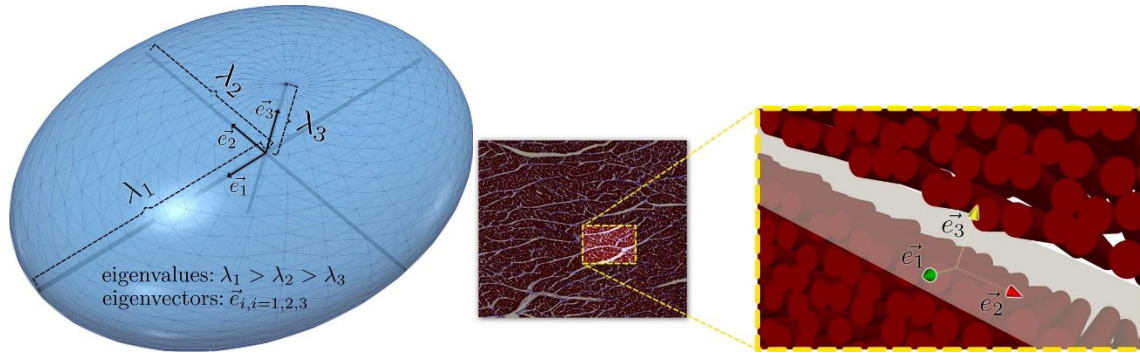


Figure 35: Ellipsoid and eigensystem that describe the anisotropic diffusion within tissue. On the left, the three eigenvectors ($\hat{e}_1$, $\hat{e}_2$, $\hat{e}_3$) and the corresponding eigenvalues (λ_1 , λ_2 , λ_3). In the centre, a histology image of myocardial tissue, cut perpendicular to the cardiomyocyte long axis. The right-hand image shows a cartoon representation of the sheetlets and the eigenvectors in this setting, showing how the diffusion tensor eigenvectors are assumed to be aligned within this geometry. Taken from [19]

In Section 4.1 the concept of the diffusion tensor was introduced to enable modelling of anisotropic diffusion. The aim of this chapter is to explain how to get from a single diffusion weighted image to calculating the diffusion tensor for each individual pixel. For simplicity all of the tensor formulae are only provided for a single pixel but can be applied to all pixels in an image.

Equation 10 describes the desired end result of the tensor calculation: a diffusion tensor with 6 independent tensor elements (D_{ij}) that are used to represent the self-diffusion of water molecules within the imaged voxel. For calculation of this tensor, images with at least 6 independent diffusion encoding directions and a reference image with reduced diffusion weighting must be acquired. While this is the minimal amount of data required, often the number of measurements is higher to provide an overdetermined system of equations that allows for better fitting in the presence of noise [165], [179], [195].

Using the general signal Equation 12 above, the diffusion weighting factor b can be replaced by the matrix B :

$$B = \begin{bmatrix} -b_{xx1} & -b_{yy1} & -b_{zz1} & -2b_{xy1} & -2b_{xz1} & -2b_{yz1} & 1 \\ -b_{xx2} & -b_{yy2} & -b_{zz2} & -2b_{xy2} & -2b_{xz2} & -2b_{yz2} & 1 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ -b_{xxN} & -b_{yyN} & -b_{zzN} & -2b_{xyN} & -2b_{xzN} & -2b_{yzN} & 1 \end{bmatrix} \quad 20$$

where b_{ij} are the b-values of the different directions. Thus, when redefining the scalar diffusion coefficient $\mathbb{D}$ as column vector of the unique Tensor elements D_{ij} :

$$\mathbb{D} = \begin{bmatrix} D_{xx} \\ D_{yy} \\ D_{zz} \\ D_{xy} \\ D_{xz} \\ D_{yz} \end{bmatrix} \quad 21$$

the following equation system can be created:

$$S = \begin{bmatrix} \ln(S_1) \\ \ln(S_2) \\ \vdots \\ \ln(S_N) \end{bmatrix} = B\mathbb{D} \quad 22$$

where S_i are the signals from each of the N measurements. However, this is a simplification as in reality S will be compromised by noise and so the equation has to be extended to include the noise vector η , resulting in:

$$S = B\mathbb{D} + \eta \quad 23$$

In the case of the minimal 6 directions and reference data the matrix B is quadratic and as such an analytical solution is possible. Assuming that noise effects are negligible $\mathbb{D}$ can be calculated as:

$$\mathbb{D} = B^{-1}S \quad 24$$

However, in real applications noise cannot be assumed negligible and in particular DT-CMR applications often require multiple averages to achieve acceptable SNR. While it is possible to average the magnitude data before the tensor calculation, it is favourable to include the individual measurements in the fitting process. This is because the mean background signal increases if the magnitude data is simply averaged [196].

Another consideration towards the fitting process is the variability of b-values based on heart rate. By including the individual images this allows for correction of potential errors arising from intra-scan heart rate variation [196].

Another consideration are microvascular perfusion effects. In Section 4.2.1 it was described how, with increasing b-value the perfusion component of the signal decays faster than the diffusion component. Scott et al. [179] suggested that using multiple reference images with b-values of 150 s/mm² and main data with 750 s/mm² are optimal for STEAM DT-CMR.

When including additional measurements, the B matrix described in Equation 20 becomes rectangular and as such does not have an inverse that could be used in the analytical approach. Instead, an unweighted linear least square method based on the pseudoinverse B^ψ is used:

$$\mathbb{D} = B^\psi S = (B^T B)^{-1} B^T S \quad 25$$

and can take advantage of the extra measurements acquired [165].

4.4 Diffusion Parameters

The tensor itself contains all the information available from DTI, but it is not very intuitive as a 3×3 matrix at each pixel. A number of approaches are available to visualise the tensor, including displaying the eigenvectors as arrows in a single slice, or viewing the tensor as either an ellipsoid or superquadric glyphs. The latter being preferable to ellipsoids as the apparent shape of an ellipsoid may vary from different viewpoints [197], this is shown in Figure 36. Alternatively, the primary eigenvector can be traced as streamlines between slices to form tractograms (Figure 37).

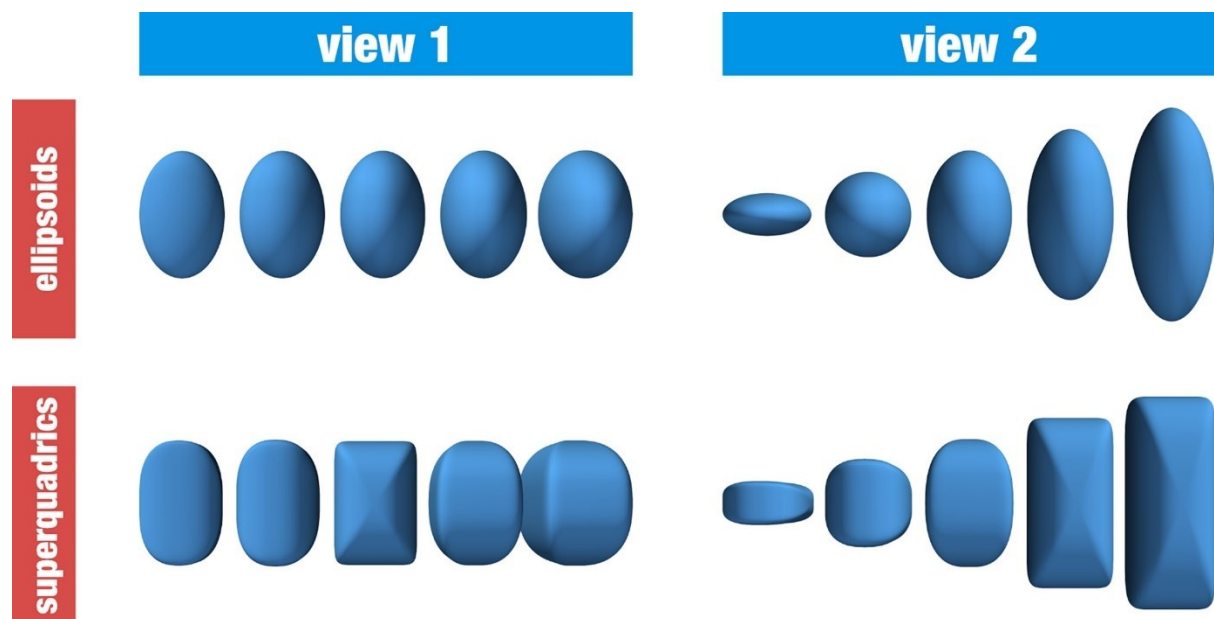


Figure 36: Display of a tensor glyphs from different viewpoints. The ellipsoids are difficult to distinguish in the view on the left, while the superquadratic glyphs enable different shapes to be resolved the different views. Taken from [19]

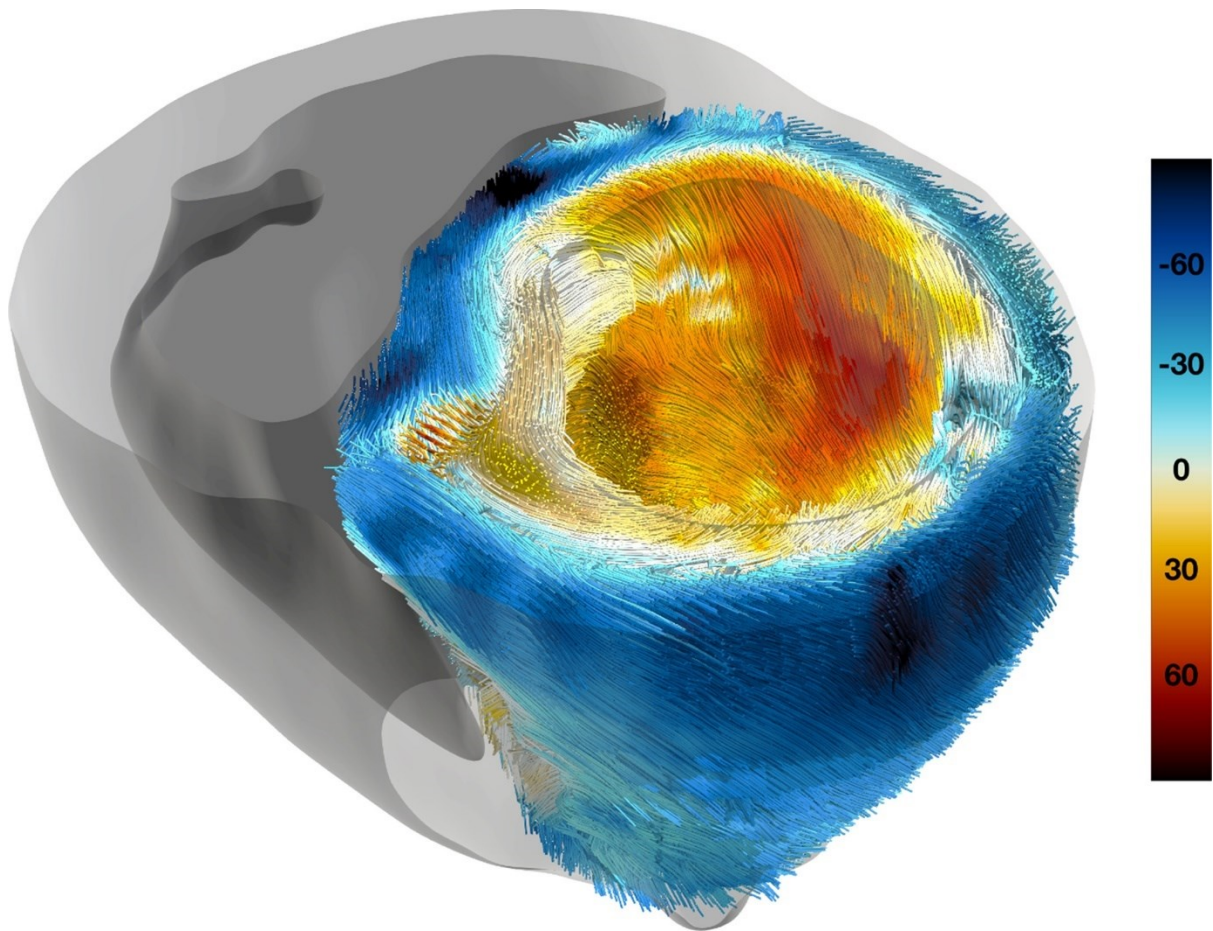


Figure 37: A tractogram from an ex vivo pig LV. Tracks are formed by creating streamlines that follow the primary eigenvector orientation. Tracks are coloured by the helix angle in this figure (colour bar in $^{\circ}$). While the tractogram allows the display of the overall trends in orientation of the cardiomyocytes it does not suggest the existence of myocardial “fibres”. Instead, a tractogram shows general trends from apex to base, as well as from endo to epicardium. Taken from [19]

While these visualisations based on D can be beneficial in some circumstances, calculation of the eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) and eigenvectors ($\hat{e}_1, \hat{e}_2, \hat{e}_3$) may be of more interest.

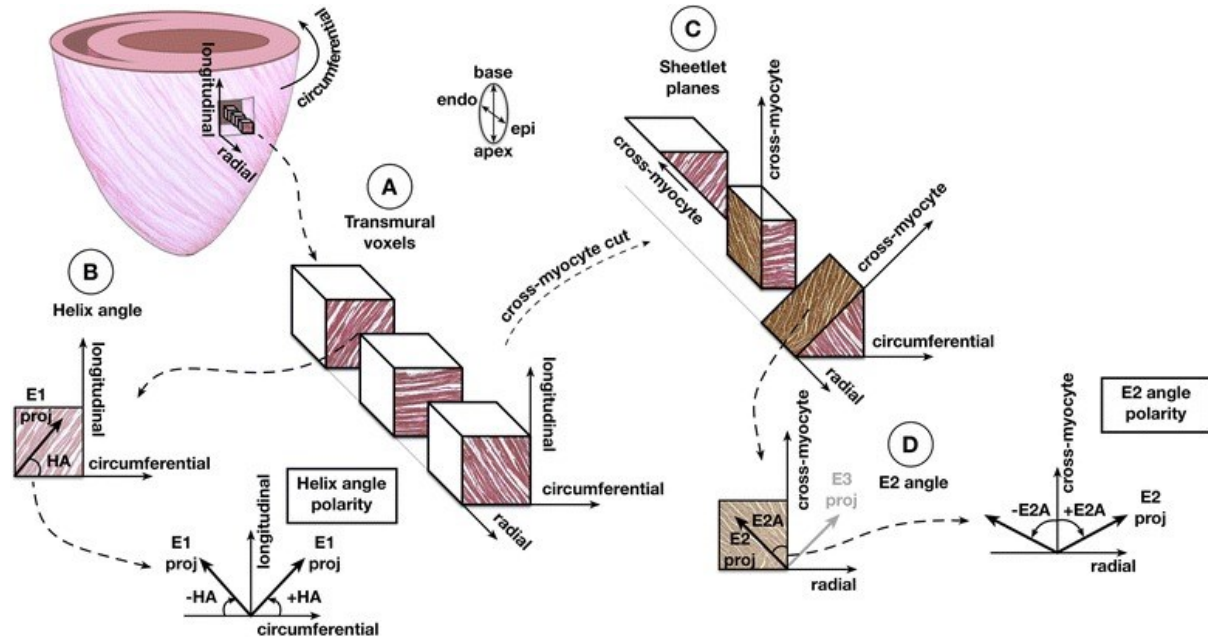


Figure 38: The definition of some frequently used angles in DT-CMR. (A) Transmural voxels and overlaid example histology representing the primary cardiomyocyte direction in the plane parallel to the local wall tangent plane. (B) Definition of the HA when $\hat{e}_1$ is projected into the local wall tangent plane, defined by the longitudinal and circumferential directions. (C) Cross-myocyte cut of the voxel to showing the sheetlets. (D) Definition of E2A based on projecting $\hat{e}_2$ into the cross-myocyte (perpendicular to $\hat{e}_1$ and the radial direction) – radial plane and then calculating the angle of this projection with the cross-myocyte vector. Taken from [50]

4.4.1 Eigensystem

4.4.1.1 $\hat{e}_1$

The first eigenvector describes the direction in which diffusion is the least restricted and in the case of cardiomyocytes, this is the long axis of the cells, along which the cellular contraction occurs (see Chapter 1.2). While it is possible to display this information in relation to a global coordinate system, the approach often taken in literature is to project this vector into the local wall tangent plane in the coordinate system described by Figure 38 and calculate the angle of this projection with the short-axis plane. As validated in a number of studies [19], [24], [48]–[50], [179], this angle depicts the same helical structure as described in Chapter 1.2.2 and, in the light of this, is referred to as the HA. Instead of quoting the HA, the Helix Angle Gradient (HAG) is often measured due to the transmural variation in HA. This measure is described by the change of HA in degrees per percent of transmural depth [186].

4.4.1.2 $\hat{e}_2$

The second eigenvector has been shown [50] to lie within the mean intravoxel sheetlet plane (as described in Chapter 1.2.3), perpendicular to $\hat{e}_1$ (by definition). Similar to HA, EzA is frequently described by projecting it into a local coordinate system, in order to calculate a single angle per voxel. This can be seen in Figure 38. Perpendicular to both $\hat{e}_1$ and the radial axis, a cross-myocyte vector is defined. $\hat{e}_2$ is projected into the radial/cross-myocyte plane and the angle between the projection of $\hat{e}_2$ and the cross-myocyte vector is referred to as secondary eigenvector angulation or EzA [50]. While the sign of this value may provide interesting information on sheetlet planes (Figure 38) in future, it is usually quoted as an absolute value in most studies [50]. When calculated as the difference in absolute EzA between cardiac phases, this provides an indication of sheetlet mobility, measuring the relative change of angulation of the sheetlets relative to the local wall tangent plane as the heart contracts [50].

4.4.1.3 $\hat{e}_3$

The third eigenvector is defined as the cross product of the first two can be depicted as done in Figure 38. As such it allows assessment of the sheetlet planes similar to $\hat{e}_2$ by investigating the sheetlet-normal direction. Similar to the $\hat{e}_1$ and $\hat{e}_2$ it can be projected on a voxel wise basis and has been used in the literature [51], [198] and was used in Section 1.2.5. However, due to the fact that $\hat{e}_3$ has the smallest corresponding eigenvalue (the direction with the most restrictions) and assuming that noise induced variability is approximately the same between the eigenvalues, it will be the eigenvector most affected by noise.

4.4.2 Rotational Invariant Measures

In addition to the angular measures described above, it can be beneficial to calculate rotational invariant parameters from the eigensystem.

4.4.2.1 Mean Diffusivity & Apparent Diffusion Coefficient

Both Mean Diffusivity (MD) [19] and Apparent Diffusion Coefficient (ADC) [199] aim to parameterise the root-mean-square distance diffused during Δ , as introduced in Figure 29, obtained with either DTI or DWI respectively.

ADC is the only quantitative parameter directly available from DWI and it is obtained from at least two images with different diffusion weightings $b_{1,2}$. The definition is:

$$ADC = \frac{\log\left(\frac{S(b_1)}{S(b_2)}\right)}{b_2 - b_1} \quad 26$$

where $S_{1,2}$ is the signal obtained at the two diffusion weightings. While in the case of isotropic diffusion this concept can fully describe diffusion, it cannot account for anisotropy. The ADC obtained from two DWI captures the diffusivity in the direction of the diffusion encoding applied. While more representative ADC measures can be obtained by acquiring images with diffusion encoded along three orthogonal axes, a different metric is required to give a more complete picture.

MD provides a similar measure to ADC from a full DTI dataset. The advantage of the higher dimensionality is that even in the case of anisotropic diffusion, the following equation provides a metric less prone to bias [19].

$$MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \quad 27$$

4.4.2.2 Fractional Anisotropy

Fractional Anisotropy (FA) is a measure of the anisotropy of diffusion within the voxel. FA is defined as:

$$FA = \sqrt{\frac{3}{2}} * \frac{\sqrt{(\lambda_1 - \lambda_M)^2 + (\lambda_2 - \lambda_M)^2 + (\lambda_3 - \lambda_M)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \quad 28$$

$$\lambda_M = \lambda_1^2 + \lambda_2^2 + \lambda_3^2$$

FA varies between 0 and 1, where 0 describes a completely isotropic case (spherical tensor) and 1 is the most anisotropic case where diffusion is limited to a line [200]. An increase in cardiomyocyte size, an increase in extracellular volume fraction or a loss of local coherence in the cardiomyocyte arrangement, is expected to result in a reduction in FA, as visualized in Figure 39.

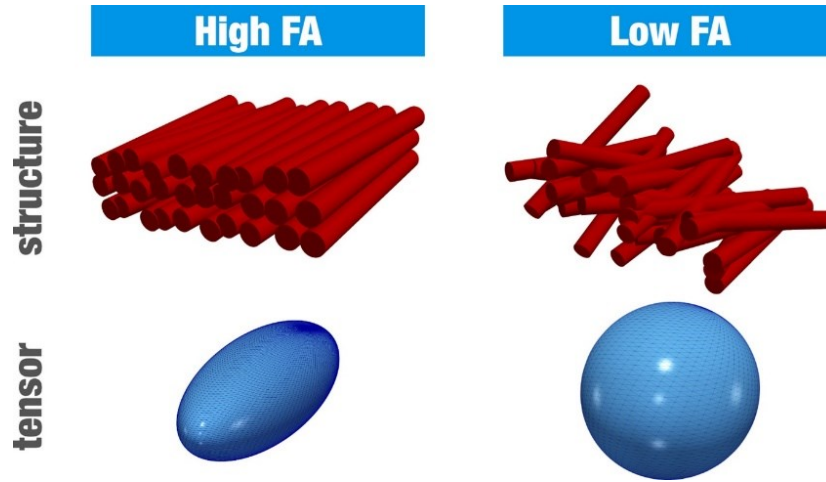


Figure 39: The diffusion tensor and cartoon representations of cardiomyocytes (red rods) at a low(right) and high(left) FA. The high FA here shows an ordered group of cardiomyocytes, whereas the low FA example includes more disorder. Taken from [19].

4.5 General Limitations

One underlying assumption of DT-CMR is that changes in the microstructure will be detectable when averaged over a voxel. However, this potentially introduces bias if, for example, small heterogeneous areas occur in a largely homogeneous voxel. While a number of techniques have been proposed to model the sub-voxel changes in structure [201] few have been applied in the heart and issues such as potential multiple shear layer populations or the contribution of non-uniform cardiomyocyte size distributions to the measured signal are largely poorly understood. One method that may prove useful is investigation using histology based computational modelling as done by Rose et al. [162].

A potential approach that addresses at least some of the simplifications of the DTI model is Diffusion Spectrum Imaging (DSI) [202]. Here, data are acquired in many directions and with many b-values and as such allow the reconstruction of a diffusion spectra. This avoids the assumption of DTI that diffusion can be described by three scalar diffusion coefficients (eigenvalues) and three perpendicular orientations. Thus, DSI may differentiate between multiple groups of microstructural information within one voxel. While there has been and is ongoing research in the use on *ex vivo* hearts such as shown by Sosnovik et al. [203], the application to *in vivo* imaging of the heart is very difficult due to the long scan times and very high b-values required.

5 DT-CMR Findings

While some of the findings of DT-CMR studies were included in Section 1.2 in the context of describing the cardiac microstructure, this chapter reviews the literature describing DT-CMR in health and disease.

5.1 The LV

5.1.1 Healthy Volunteers

MD and FA are often quoted to describe the shape of diffusion tensor [24], [48], [50], [184], [186], [204]–[206]. These parameters vary depending on b-value and cardiac phase, but also depend on the sequence type due to the differences in diffusion time between STEAM and MCSE. Therefore, the results reported in Table 3 are grouped according to these parameters. The results shown are global values and most studies acquired data in one or more mid-ventricular slices. McGill et al. [205] investigated regional differences in the microstructure of the healthy heart, reporting that:

- The mesocardium is the most anisotropic with $FA=0.46\pm0.04$ (MD of $0.89\pm0.07\times10^{-3}$ mm²/s).
- The endocardium is less anisotropic than the mesocardium with $FA=0.40\pm0.04$ and $MD=0.91\pm0.08\times10^{-3}$ mm²/s.
- The epicardium has similar FA values to the endocardium at $FA=0.39\pm0.004$ with $MD=0.87\pm0.07\times10^{-3}$ mm²/s.

The peak in FA that occurs in the mesocardium is believed to be caused by a reduction in the variation of circumferentially oriented mesocardiac cardiomyocytes within one voxel. FA contains both a microscopic FA component and a component due to the variation in microscopic orientations across the voxel. The increased coherence of orientations in these mesocardial voxels result in a higher measured anisotropy [205]. The reason for the transmural change of MD is believed to be the result of an increasing density of shear layers from epicardium to endocardium [205]. It is notable that the follow up study by McGill et al. [207] showed a further dependence of FA and MD on demographic variables such as age, sex etc.

Author, Year	Sequence	b value [s/mm ²]	Timing	Mean Diffusivity [10 ⁻³ mm ² /s]	Fractional Anisotropy
Reese, 1995	STEAM	300	-	0.87 ± 0.13	
Nielles-Vallespin, 2013	STEAM	350	Systole	0.8 ± 0.2	0.6 ± 0.2
Stoeck, 2014	STEAM	500	Diastole	0.87 ± 0.11	0.61 ± 0.04
			Systole	1.1 ± 0.18	0.6 ± 0.03
Tunnickliffe, 2014	STEAM	350	Diastole	1.20 ± 0.09	0.54 ± 0.03
			Systole	1.10 ± 0.06	0.41 ± 0.04
Lau, 2015	STEAM	350	Systole	1.19 ± 0.16	0.48 ± 0.08
Moulin, 2015	SE	350	Diastole	1.72 ± 0.09	0.36 ± 0.02
Scott, 2015	STEAM	750	Systole	0.87 ± 0.06	0.41 ± 0.04
Nguyen, 2016	SE	350	“most quiescent cardiac phase”	1.86 ± 0.3	0.24 ± 0.04
McGill, 2016	STEAM	350	Systole	0.93 ± 0.14	0.47 ± 0.05
			Diastole	1.11 ± 0.13	0.56 ± 0.04
Scott, 2016	STEAM	500	Systole	1.07 ± 0.06	0.41 ± 0.03
Von Deuster, 2016	STEAM	450	Sweet Spot	1.05 ± 0.08	0.59 ± 0.03
	SE	450	Systole	1.43 ± 0.06	0.38 ± 0.02
Scott, 2018	STEAM	450	Diastole	1.13 ± 0.08	0.61 ± 0.04
			Systole	1.02 ± 0.14	0.47 ± 0.03
	SE	450	Diastole	1.78 ± 0.34	0.41 ± 0.07
			Systole	1.46 ± 0.43	0.40 ± 0.09

Table 3: FA and MD values reported in DT-CMR studies of healthy subjects. (1)Reese, 1995 [208] (2) Nielles-Vallespin, 2013 [49], (3) Stoeck, 2014 (4)Tunnickliffe, 2014 [204] (5) Lau, 2015 [209] (6) Moulin, 2015 [210] (7) Scott, 2015 [179] (8) Nguyen, 2016 (9) McGill, 2016 [207] (10) Scott, 2016 [196] (11) von Deuster, 2016 [184] (12) Aliotta, 2017 [194](13) Scott, 2018 [186]. Modified from [34]

The primary eigenvector ($\hat{e}_1$) is believed to align with the cardiomyocyte long axis (as discussed in Chapter 4.4.1), and a number of studies have validated this via comparison with histological (or other) measures of cardiomyocyte orientation (Table 4). A recent study by Nielles-Vallespin et al. [24] used *in vivo*, *in situ* after induced arrest and *ex vivo* DT-CMR with subsequent histology of pig hearts arrested in either peak systole or end diastole to validate the DT-CMR measures of cardiomyocyte and sheetlet orientation. The median E1A (HA in this study) range was shown to increase from a median 90° (IQR: 86° to 94°) in diastole to 96° (IQR: 89° to 101°) in systole *in vivo*. By administering potassium chloride (KCl) or barium chloride (BaCl_2) *in situ* imaging after cardiac arrest demonstrated an E1A range changing from a median 75° (IQR: 60° to 81°) in (KCl induced arrest, resulting in diastolic-like configuration) to 118° (IQR: 117° to 119°) (BaCl_2 induced arrest, resulting in a systolic-like configuration). These results were similar in the following *ex vivo* scans with the median E1A range changing from median 89° (IQR: 85° to 92°) (KCl arrest) to 109° (IQR: 107° to 113°) (BaCl_2 arrest). When including the histological analysis of the median HA range which increased from 72° (IQR: 50° to 75°) (KCl arrest) to 73° (IQR: 60° to 84°) (BaCl_2 arrest) this study validates that *in vivo* E1A values provides a measurement of the mean intravoxel HA. In a human *in vivo* study by Scott et al. [186] this relates to the previous described measure of helix angle gradient (HAG) of $-0.8^\circ/\%$, $-0.73^\circ/\%$ in systole respectively for a MCSE and STEAM approach and lower values of $-0.49^\circ/\%$ and $-0.52^\circ/\%$ in diastole.

Author, Year	Sequence	State	Species	Phase	Parameters	Findings
Hsu, 1998	SE	ex vivo	Dog	-	DT-CMR: HA (α_{HA}) Histology: Fibre angle (α_{HA})	Excellent correlation between α_{HA} and α_{HA} . Average difference of $-2.36^\circ \pm 0.98$ on a point basis, and correlation coefficient of 0.942 ± 0.008 for transmural rotation of HA.
Scollan, 1998	SE	ex vivo	Rabbit	-	DT-CMR: HA α (inclination angle), Transverse angle ϕ Histology: Fibre inclination angle	α is similar by DT-CMR and histology; correlation coefficient of 0.92 ± 0.15 and transmural variation consistent with previous reports. Average difference between histology and DT-CMR of 4.9° . Transverse angle of 7.9° , consistent with previous reports.
Holmes, 2000	SE	ex vivo	Rabbit	-	DT-CMR: HA α (inclination angle) Histology: Fibre inclination angle	Good agreement between α from histology and DT-CMR with average difference of -3.7° and correlation coefficient of 0.979
Scollan, 2000	SE	ex vivo	Rabbit	-	DT-CMR: HA α (inclination angle) Histology: Fibre inclination angle	Expected transmural gradient of α . Root mean-squared error of $5.3^\circ \pm 5.1^\circ$ between DT-CMR and histology. Qualitative agreement between E_2 and E_3 with sheet and sheet normal.
Tseng, 2003	STEAM	ex vivo	Cow	-	DT-CMR: E_1, E_2, E_3 Ink print/ histology: fibre direction, sheet direction, sheet-normal direction	Root mean-squared angular disparity between DT-CMR findings and inked print of myocardium (approximates to $\alpha \times$ magnification) 11° for E_1 and fibre direction, 14° for E_2 and E_3 with the sheet and sheet-normal directions.
Chen, 2005	SE	ex vivo	Rat	Potassium arrested (end-diastole) PA Barium contracted with volume (early systole) BV+, Barium contracted without volume (end systole) BV-.	DT-CMR: HA (α_0), transverse angle (α_t) and sheet angle via the secondary eigenvector (β_2) Histology: Sheet cleavage angle (β_1) (between the cleavage plane and direction normal to the epicardium)	$\Delta\alpha_0$ (endo-epi) increased from diastole to systole, ($105^\circ \pm 6^\circ$ in PA, $110^\circ \pm 8^\circ$ in BV+, and $134^\circ \pm 4^\circ$ BV-), due to more longitudinally oriented epi- and endocardial fibres in systole. Sheets more wall-perpendicular in systole: absolute β_1 decreased from diastole by 2.5% and 4.4% in BV+ and BV- respectively. Histology supported this finding with similar changes in absolute β_1 ($34^\circ \pm 4^\circ$ to $82^\circ \pm 7^\circ$). α_t was between -20° and $+20^\circ$ in all states.
King, 2011	SE	ex vivo	Sheep	-	DT-CMR: Myofiber angle α_{DT} , sheet angle of β_{DT} from E_2 and β_{DT} from E_3 Histology: Myofiber angle α_H , sheet angle β_H and β_H	α_{DT} and α_H : mean difference of $1^\circ \pm 16^\circ$ Sub-populations of sheets, defined by E_2 and E_3 projections on the Overall mean difference of $8^\circ \pm 27^\circ$ between (β_{DT} and β_H) and (β_H and β_H)
Nielsen-Vallespin, 2017	STEAM	in vivo in situ ex vivo	Pig	Potassium arrested (end-diastole) Barium arrested (end-systole)	DT-CMR: Helix angle (EA) and EA (sheetlet angle) Histology: HA and sheetlet angle (SA)	HA has lower magnitude of changes from diastole to systole. EA range correlates well with HA range ($r=0.92$, $p<0.0001$) <i>in vivo</i> : $90^\circ \rightarrow 96^\circ$, <i>in situ</i> arrested: $75^\circ \rightarrow 118^\circ$ <i>ex vivo</i> : $86^\circ \rightarrow 109^\circ$, histology HA: $72^\circ \rightarrow 73^\circ$ EA increases from diastole to systole <i>in vivo</i> : $13^\circ \rightarrow 59^\circ$, <i>in situ</i> arrested: $15^\circ \rightarrow 59^\circ$ <i>ex vivo</i> : $18^\circ \rightarrow 62^\circ$, Histology SA: $30^\circ \rightarrow 75^\circ$

Table 4: A summary of the results of various studies performed to validate DT-CMR using histology. (1) Hsu, 1998 [211] (2) Scollan, 1998 [40] (3) Holmes, 2000 [40] (4) Scollan, 2000 [198] (5) Tseng, 2003 [212] (6) Chen, 2005 [213] (7) Kung, 2011 [36] (8) Nielsen-Vallespin, 2017 [24]. Taken from [34]

In contrast to $\hat{e}_1$, the orientation of the secondary eigenvector $\hat{e}_2$, which is linked to sheetlet orientation, has been shown to vary significantly throughout the cardiac cycle [24], [50]. This is shown in Figure 40, and corresponds to an increase of E2A from diastole to systole of [24]:

- 13° to 59° *in vivo*
- 15° to 59° *in situ* arrested
- 18° to 62° *ex vivo*
- 30° to 75° histologically (sheetlet angle)

The corresponding median $\pm$ IQR values of an *in vivo* human study by Scott et al. [186] are an absolute E2A of $37\pm 9^\circ$, $55\pm 10^\circ$ for systole respectively for MCSE and STEAM and $26\pm 5^\circ$, $15\pm 4^\circ$ for diastole.

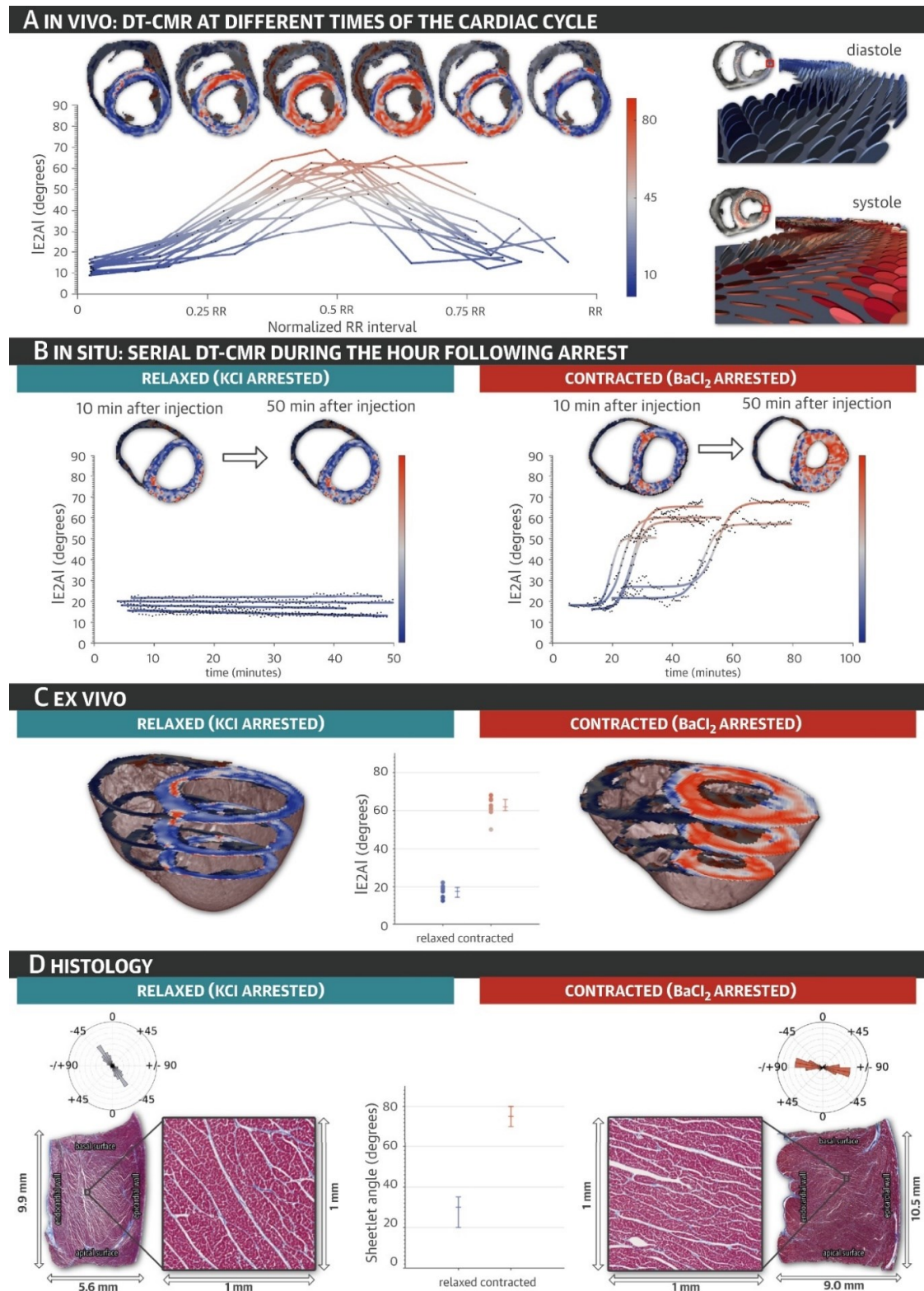


Figure 40: The validation of the evolution of E2A throughout the cardiac cycle from in vivo, in situ arrested (potassium chloride (KCl)-diastole-like configuration or barium chloride (BaCl₂) – systolic-like configuration), ex vivo DT-CMR and histology. (A) In vivo E2A plotted over the cardiac cycle. (B) In situ E2A plots along time after injection of KCl or BaCl₂. (C) 3 ex vivo slices of E2A maps of the arrested heart. (D) Histological validation of the underlying structures described by the sheetlet angle. Taken from [34]

5.1.2 In Disease

5.1.2.1 *Cardiomyopathy*

Two of the most common types of cardiomyopathy are HCM and DCM [214]. HCM involves an abnormally thick LV wall that shows reduced contractility and a reduction in the blood volume pumped per cycle. DCM on the other hand also shows a reduced contractility and a reduction in the blood volume pumped, but the LV cavity is enlarged, and varying levels of wall thickness may be present.

Due to histological evidence [214], [215] of cardiomyocyte disarray in HCM patients there has been great interest in attempting to use DT-CMR for detecting this microstructural abnormality [216], [217]. As would be expected in myocardial disarray, a recent study found a decrease in FA compared to healthy volunteers. While, this findings shows potential to be used to identify adverse events such as arrhythmias or sudden cardiac death[218], no histological validation has been carried out to date. Nguyen et al. [199] investigated diffuse fibrosis in a HCM cohort using the DWI parameter ADC and ECV maps. Their results showed that ADC can identify diffuse myocardial fibrosis and so may provide valuable clinical information without the need of a contrast agent.

DCM has been investigated using DT-CMR in an *ex vivo* study of Syrian hamsters [219] and human *in vivo* studies [24], [220], [221]. FA in the DCM cohort was found to decrease when compared to the control group [219], [220]. Studies of sheetlet mobility (ΔE_2A) have been conducted in both HCM and DCM cohorts, by Ferreira et al. [50] for HCM and both Khalique et al.[221] and von Deuster et al. [220] in DCM, while Nielles-Vallespin et al. [24] compared the two cohorts to each other and healthy volunteers. Both cohorts showed a reduction of this parameter relative to controls, however, the underlying mechanisms differ. In HCM the sheetlets are in a systolic-like conformation throughout the cardiac cycle, different to DCM where a more diastolic-like state is retained throughout.

5.1.2.2 *Cardiac Amyloidosis*

Cardiac Amyloidosis (CA) is the subcategory of a multi-system disease in which proteins enter the so called amyloid-state, described by unstable protein forming elongated fibers [222]. This leads to a subsequent loss of normal tissue function. Different types of CA exist but Light Chain Amyloidosis (AL) and Transthyretin Amyloid Amyloidosis (ATTR) are of particular importance and linked to myocardial thickening and diastolic dysfunction that can result in heart failure [223].

LGE sequences have been a valuable asset for diagnosis of CA in a clinical setting[224], while recent studies by Gotschy et al. [225] and Khalique et al. [226] utilised DT-CMR to investigate the microstructural changes introduced by the amyloid state. The findings included significant differences in MD (increased) and FA (decreased) compared to the control cohort, while HA showed a more circumferential orientation in CA subjects [225], [226]. This change of the primary eigenvector direction was accompanied by a higher absolute diastolic E2A sheet angle [225], [226]. DT-CMR results were correlated to other quantitative CMR measures and while MD and FA showed correlations with native T₁ and ECV measures, the HA changes were associated with strain measures [225].

5.1.2.3 Myocardial Infarction

MI is defined by tissue death in the myocardium caused by ischaemia. This process results in structural changes of the myocardium such as fibrosis in the area of the MI, as well as remote changes such as myocyte hypertrophy and apoptosis, myocyte disarray, angiogenesis, and increased interstitial collagen [19], [227]. MI has been shown to be causative for a large percentage of heart failure and ventricular tachyarrhythmia [227], [228] and as such has been one of the main focuses of diffusion imaging in the heart so far [27], [211], [229]–[234].

While a few studies [25], [27], [230] have found an increase of MD/ADC in MI, it is interesting to note that Hsu et al. [211] found an initial decrease in the first hours after infarct in the affected region. After this initial period the diffusivity begins to increase [229] to the higher value quoted in other studies. Most studies [25], [27], [230] have shown a reduction in FA due to MI, while one study by Kung et al. [232] found an increase. Another important consideration is the evolution of HA in the affected areas of the heart. Here a study by Wu et al. [235] showed an increase in the proportion of left-handed helical structures and decrease of the right-handed helical structures in the infarcted area 26 days post-MI. In the follow up study [236], at a median of 165 days after the initial scan, an increase of right-handed helical structures in the remote area together with an increase in wall thickness was observed.

5.2 RV Findings

5.2.1 Healthy

The more challenging geometry of the RV compared to the LV and the relatively recent development of DT-CMR methods, mean that much less is known about the RV microstructure, even in healthy subjects. While methods are constantly improved the current findings in healthy subjects are limited to a *ex vivo* studies (in part animal work), some of which have been touched upon in Chapter 1.2.5.

A study by Kakaletsis et al. [237] studied microstructural properties in both RV and LV myocardium. An *ex vivo* ovine model was used in which a tissue samples of both RV and LV myocardium underwent a mechanical testing protocol consisting of different shear and compression models. The resulting histological microstructural analysis showed that the RV myocardium compared to the LV is less stiff along the cardiomyocyte long axis [237].

Another *ex vivo* animal study (porcine, n=14) was conducted by Omann et al. [238] with the hearts either arrested in contracted or relaxed states. DTI was performed on a 9.4 T system using a SE diffusion sequence with 30 diffusion directions and b values of (low=0 s/mm², high=1000 s/mm²). In terms of HA and TA no significant difference between diastasis and systole could be detected in the RV.

5.2.2 Congenital Heart Disease

Very few studies have investigated CHD using DT-CMR. To the best of the authors knowledge the only published human *in vivo* DT-CMR work in CHD was by Khalique et al. [206] investigating Situs Inversus Totalis (SIT) and Harmer et al. [239] presented a case study of DT-CMR in the systemic RV. The latter study found a predominance of longitudinal and oblique orientated cardiomyocytes and explained these findings using a hypothesis of adaptation of the RV to systemic pressure and load, but it was a single case report. The study by Khalique et al. [206] compared the SIT RV to the normal LV and found HA to be more heterogeneous in SIT patients than controls, with a general pattern of the inversion of cardiomyocyte orientation at the base transitioning towards normal in the apex. This change in cardiomyocyte arrangement was accompanied with a reduction in systolic E2A which results in a reduction in sheetlet mobility in SIT patients. However, the RV of SIT patients is the systemic ventricle and, therefore bears more resemblance to the LV of a normal heart.

An *ex vivo* study of 24 human hearts (n=10 TOF, n=8 dextro-transposition of great arteries (D-TGA), n = 4 systemic RV, n=1 SIT, n=1 levo-TGA) using a monopolar SE (with 32 diffusion directions and a b value of 853 s/mm²) sequence was conducted by Tous et. al [240]. In the results of this study, TOF hearts showed a reduced HAG with circumferential myocytes across the myocardial wall dominant and further showed opposing sheetlet angles in the septum when compared to those of the left ventricular (LV) free wall [240].

Further *ex vivo* work was conducted by Campanale et al. [241], who investigated 3 explanted hearts from young patients with a systemic RV and a single explanted control heart with postnatally acquired RV hypertrophy. Diffusion images were acquired with a SE single shot EPI diffusion sequence using a multi shell (4 b=0 images and 3 shells at b= 1000, 1500, 2000 s/mm² of 30 diffusion encoding directions each) scheme. The cardiomyocyte orientation in the systemic RV appears disorganised when compared to the control.

6 Data Acquisition In DT-CMR

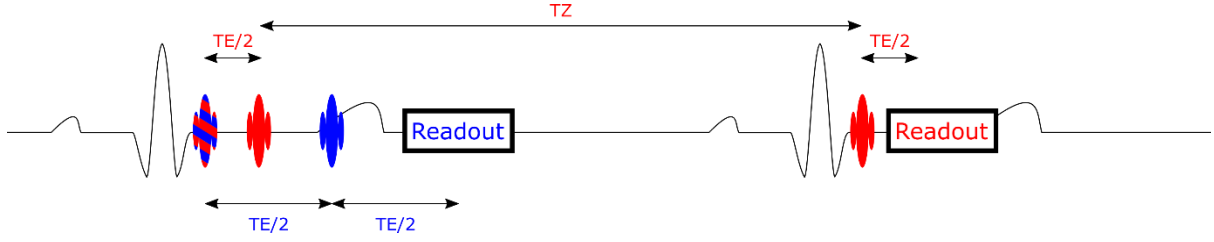


Figure 41: A schematic of the contrast generation (STEAM in red, MCSE in blue) module and the time when the readout module is executed. TZ denotes the time the transverse magnetisation is stored along M_z in STEAM, while TE denotes the time before the echo occurs. The readout in both applications is independent of the image generation, apart for considerations regarding the TE .

In Figure 41 a schematic diagram of frequently used DT-CMR sequences is shown and demonstrates the separation between the contrast generating part and the image acquisition part in both sequences. While both STEAM and MCSE have different diffusion times and considerations regarding SNR efficiency they face similar challenges regarding motion induced phase (covered below) if segmented acquisition schemes are used. Most approaches found in the literature have consequently adopted breath-hold single-shot techniques that are able to sample k-space completely after each excitation. The most popular approach is the Echo Planar Imaging (EPI) method [48]–[50], [171], [186], [242] originally developed by Mansfield in 1977 [243], while recent developments have shown the application of fast spiral methods in combination with the STEAM DT-CMR sequence [244], [245].

6.1 Motion-Induced Phase in Diffusion Imaging

As described in Section 4.2, bulk motion of the myocardium during diffusion encoding poses a considerable challenge to *in vivo* DT-CMR applications. Rigid body translational motion without rotation during monopolar diffusion gradient encoding, gives rise to a constant phase shift of the signal from the object [19]. Stretching or rotating a pixel results in a phase dispersion across this pixel if the motion has a component in the direction of the diffusion encoding and this may lead to complete signal loss with sufficient motion [182].

Potential sequences to allow successful imaging *in vivo* by implementing correction and coping strategies have been covered in Chapter 4, but both MCSE and STEAM remain somewhat susceptible to the influences of motion. This is of particular concern when choosing the readout strategy, as the phase changes associated with motion [246] pose difficulties for segmented readouts. Any difference in motion of the heart between the time at which readouts acquired for the same final image, would result in a difference in phase between the data from the readouts. If combined without correction, the changes in phase often result in the individual signals cancelling each other out and cause a near complete signal void in some areas [182], [244], [246], [247].

While it is possible to avoid these artefacts by using single shot methods, it is still possible to successfully carry out segmented imaging using methods known as phase-navigators [247], [248]. Such techniques require the acquisition of a representation of the central k-space data with each segmented readout. This is important as it is assumed that the motion induced phase is of low spatial resolution and as such is contained in this central k-space. Thus, the phase navigator data can be used to match the phase information between interleaves and allow subsequent combination without signal cancellation. This has been shown in approaches such as Periodically Rotated Overlapping Parallel Lines with Enhanced Reconstruction (PROPELLER) [248], Self-Navigated Interleaved Spirals (SNAILS) [247] and most recently in DT-CMR using a similar approach to SNAILS by Gorodezky et al. [244]. It should be noted that while these techniques allow segmentation and the associated benefits such as higher resolution associated with it, they require longer scan times than single-shot methods and the sampling schemes are somewhat inefficient due to the data redundancy or the repeatedly acquired central k-space data.

6.2 Cartesian Sampling

6.2.1 Echo Planar Imaging

Following the signal and contrast generation part of an imaging sequence, EPI methods use an alternating gradient along the readout/frequency encoding direction to measure one line of k-space per readout gradient lobe (Figure 42) and so k-space can be rapidly traversed after a single excitation/contrast forming module.

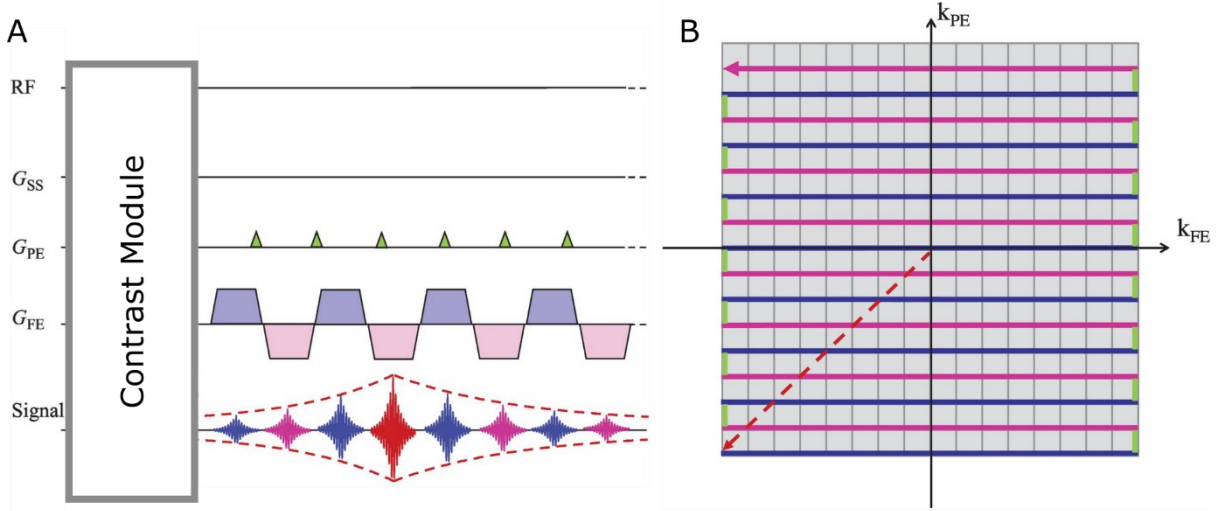


Figure 42: Pulse sequence diagram of an EPI readout. (A) shows the signal generation by a contrast module and then the readout through a bipolar trapezoidal gradient train. It should be noted that during the contrast module a pre phaser should be applied along FE and PE direction to move the start of the sampling into one of the k-space corners. This is shown in (B) as a red dotted line. Using the gradients shown in (A) it is possible to traverse k-space as shown in (B), here the colours match the corresponding movement along k-space. Green denoting the movement in PE, while blue and pink show the movement back and forth in FE. Modified from [95].

An individual gradient lobe is shown in Figure 43 and shows that while during the ramp up/down the speed that k-space is traversed is non-linear, during the flattop the relationship is linear. In most applications data is only acquired during this linear region of the flattop as this eradicates the need for an additional operation to account for the varying sampling density when sampling during ramp up/down [249]. However, it is possible to take advantage of the ramp up/down times if efficiency of the readout is crucial, such as in DT-CMR. Sampling the ramp up and ramp down times will allow for a shorter echo spacing, which effectively increases the phase encode bandwidth and reduces off-resonance artefacts. Additionally, it allows for shortening of the echo trains which reduces sensitivity to effects such as off-resonance, T_2^* related signal decay and motion sensitivity.

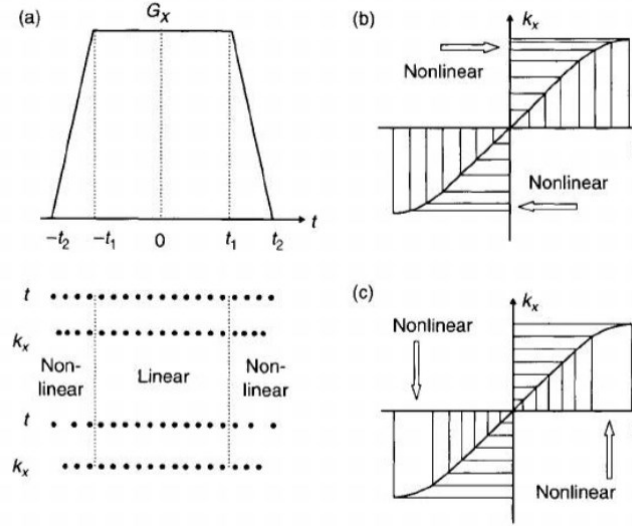


Figure 43: The trapezoidal gradient lobe used in EPI for readout and the associated sampling behaviour. (a) shows the gradient lobe itself with $-t_1$ to t_1 denoting the flattop time and $-t_2$ to $-t_1$ and t_1 to t_2 showing the ramp up and down times in the top panel. In the bottom panel the impact of sampling during the ramp times on the k -space sample spacing is shown. In the time from $-t_2$ to $-t_1$ and from t_1 to t_2 , equispaced sampling in time, results in non-equispaced k -spaced samples, while during the flattop a linear relationship between t and k_x is observed. This can be further seen in the diagram k_x plotted with time in (b). To allow for an equidistant sampling behaviour during the ramp times the dwell time in this region can be adjusted which would result in the sampling shown in (c) or the bottom row shown in (a). Taken from [249].

The concatenation of gradient lobes together with a sign change allows for sampling from $-/+ k_{FE\ max}/2$ to $+/- k_{FE\ max}/2$ along frequency encode axis and so requires an initial prephasing gradient to offset the start position by $k_{FE\ max}/2$ from the centre of k -space.

In Figure 42 the typical pulse diagram for an EPI readout, including the phase encode gradients (green) is shown. Similar to the frequency encode axis of an EPI readout, the first gradient played out in the phase encode direction is a prephasing gradient to move the start position readout to $k_{PE\ max}/2$. While different approaches have been proposed to traverse k -space in the phase encode direction, such as using a constant gradient, which results in a zig-zagging trajectory through k -space [249], so called blip gradients are most commonly used [249]. These short, often triangular gradients allow for the k -space trajectory to be incrementally nudged along to the next point on the phase encode axis, while the bipolar EPI readout gradients ramp down and up.

The last important consideration covered in this section is the influence of the sign change in the bipolar gradients on the signal received. This rapid change in gradient amplitude causes eddy currents which result in rephasing–dephasing imperfections, leading to a misalignment of the alternating readout lines [250]. This is visualised in Figure 44 and can result in $N/2$ ghosts if not corrected. These artefacts appear as ghosts of the original image located half the FOV away from the original image [249]. The corrections developed to cope with this artefact are covered in the reconstruction section.

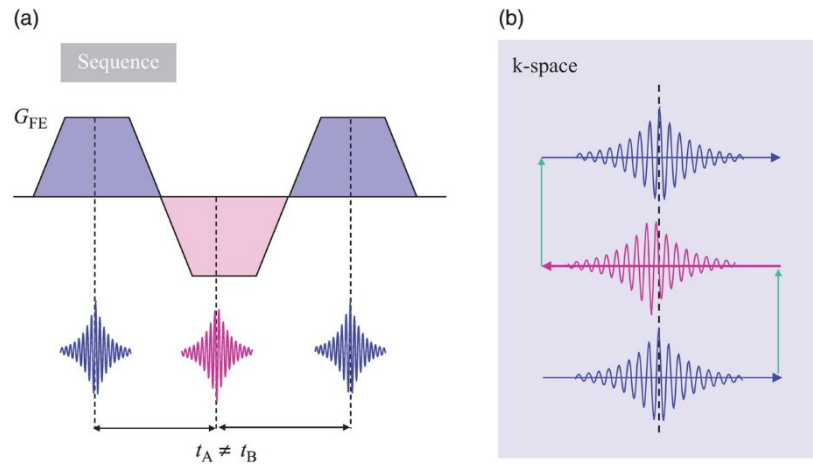


Figure 44: Influence of change in sampling direction on the sampled echo. (a) showing three gradient lobes where the second one has a negative sign. Dotted lines show the centre of the echo and note that the time $t_A \neq t_B$. In (b) this is further visualised in terms of the three respective echoes in k-space and the difference in the location of the gradient echo centre, relative to the acquisition of the central k-space data. Taken from [94]

6.2.1.1 Limitations

Common problems, considerations and limitations when using EPI are:

- **Image distortion.** Off-resonance due to factors such as field inhomogeneities and eddy currents can lead to substantial artefacts [249]. Commonly these artefacts appear as a compression or stretch of the imaged object along the phase encode direction [249].
- **T₂* decay.** The duration of an EPI echo train is in the range of 23 ms for DT-CMR. Considering that the average T₂* value in the myocardium is around 20.5 ms [251] this will lead to a reduction in signal intensity throughout the EPI readout [249]. In case of an echo forming sequence such as SE or STEAM where the echo is at the center of k-space this reduction will be located towards the edges of k-space and so result in subsequent image blurring.
- **Chemical shift artefacts.** Due to the typically high readout bandwidth in the frequency encode direction, chemical shift artifacts are suppressed along this axis. In the case of the phase encode direction, however, the relatively low bandwidth can result in substantial artefacts, especially if lipids are present in the imaged slice [249]. Thus, EPI sequences are often accompanied by fat saturation pulses [249].

6.2.2 Reduced Sampling Schemes

The T₂* envelope and off-resonance effects limit how many k-space lines can be acquired in a single EPI readout and much effort has therefore been spent in developing techniques that increase the overall amount of k-space that can be reconstructed from the available data.

6.2.2.1 Keyhole Imaging

Jones et al. [252] and Van Vaals et al. [253] are attributed with inventing the keyhole method, which was originally developed for increasing the spatial resolution of dynamic scans, evaluating the wash-in and wash-out of gadolinium based contrast agent. This is achieved by initially (or at a subset of timepoints) acquiring one complete high-resolution reference image and then for other timepoints only sampling the centre of k-space, allowing for the high spatial frequency data be copied from the reference scan.

The keyhole approach is often affected by artefacts due to intershot differences between the fully sampled scan and the subsequent dynamic updates, creating inconsistencies in k-space. Such alterations include differences in phase slopes across the image and a relative change of signal intensity that must to be accounted for [254].

The main problem of keyhole imaging however is the assumption that the dynamic changes in the imaged object over time are low spatial resolution. This was pointed out by Hu in [255] who concluded that while this method provides no benefits in terms of resolution, it does allow for studies that require temporal static anatomical references in addition to high temporal resolution to gain this references in a more effective way.

Keyhole approaches have been applied to DTI by assuming that the signal loss occurring due to diffusion encoding can be fully contained within low spatial resolution data. As such the higher spatial frequencies between different diffusion encoding directions should be similar and can be shared with each other. Sun et al. [256] imaged rat brains with a DTI protocol (1 b-value=0 s/mm², 6 b-value=850 s/mm²) while sampling all k-space lines. From this initial dataset simulations were performed using different data sharing strategies. Here the b-value=0 s/mm² was always fully sampled, while one of the 6 b-value=850 s/mm² DWI was selected as a diffusion weighted reference. The peripheral k-space from this diffusion weighted reference was then copied into the 5 other DWI images to create an effective simulation of the keyhole approach. The results showed a substantial underestimation of FA, while simultaneously either over or underestimating MD values. Wedeen et al. [182] also describe a potential problem, caused by certain movements such as shear, which result in a shift of the central region of k-space. If the shift is great enough, then the central k-space data may be shifted outside the sampled region, resulting in catastrophic signal loss. Reducing the extent of the sampled k-space data increases the likelihood that this effect will be seen and along with the inconsistencies in DTI parameters shown in studies, means that keyhole EPI is yet to show potential for cardiac DTI applications.

6.2.2.2 *Partial Fourier*

Another approach to accelerating image acquisition is partial Fourier imaging, which covers k-space asymmetrically, as shown in Figure 45. The underlying assumption of partial Fourier methods is that if an image object is represented by real numbers, then the Fourier transformation will be a symmetrical (also referred to as Hermitian) matrix. Therefore, if only the real part of an object is sought, acquiring half of k-space would be sufficient to allow the reconstruction of the object [257].

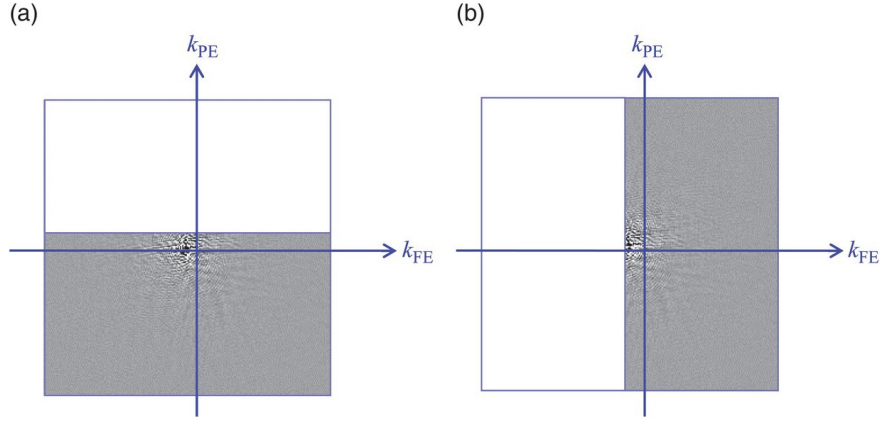


Figure 45: Two examples of partial Fourier acquisition. (a) shows a case in which only slightly more than half the lines of k-space are sampled in the PE direction, while in (b) partial Fourier was applied in the FE direction which is also referred to as partial echo acquisition. Taken from [94]

In real applications however, the image of the object will never be purely real, as eddy currents, off-resonance, and other effects cause phase shifts in the data. Thus, k-space will not be a true Hermitian matrix, as the imaginary part will result in an antisymmetric pattern around the centre of k-space. The common solution is to sample more than 50 % (but less than 100 % of k-space) and use one of a number of methods to correct for the possible phase errors. Typical sampling schemes acquire between 55 % and 75 % and, therefore, still allow for a shorter EPI readout or increased spatial resolution, although the SNR in the spatial frequencies that are not sampled symmetrically is reduced [257].

This technique has been extensively used in neuro DTI applications such as [258]–[260]. While applications to cardiac DTI have been made [209], [242], the sampling factor has to be chosen carefully. This is due to the implications of bulk motion on the signal phase, as described above [182], that can result in a shift of the central region of k-space and a potential catastrophic signal loss.

6.2.2.3 Segmented Acquisition

Other techniques that can help to avoid long readouts and enable higher spatial resolution EPI acquisitions include segmented acquisition schemes. Such methods split the acquisition between two or more excitations (e.g., spin or stimulated echoes). While there are potentially many sampling schemes that can be used to split the acquisition, data is usually acquired either (Figure 46) by acquiring every n th phase encode line or as blocks of k -space.

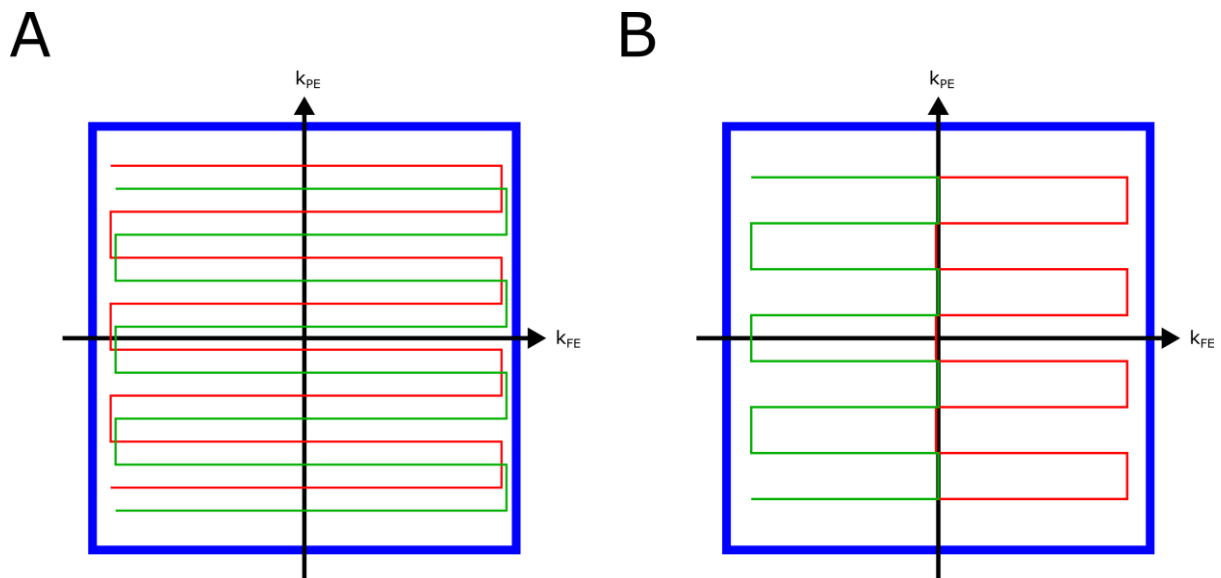


Figure 46: Examples of multishot segmented EPI trajectories. Each of the individual acquisitions shown in red and green are acquired after a separate excitation/contrast module and combined retrospectively to form one fully sampled k -space.

While in many cardiac applications segmented acquisition of images over multiple cardiac cycles is standard practice, diffusion encoding makes this more difficult for DT-CMR. Thus, while it has been shown to be an adequate technique in neuro DTI [260]–[262] an application to cardiac diffusion using the phase navigators described in Section 6.1 has yet to be shown.

6.3 Spiral

Similar to EPI, spiral trajectories can be used to acquire the full extent of k-space after a single excitation/contrast forming module. K-space is covered along a spiral path by continuously sampling the signal while a set of increasing amplitude sinusoid-like gradients is played out to traverse k-space. However, the gradients should use the available gradient hardware more efficiently than EPI methods. The resulting coverage of k-space is shown in Figure 47. As the sampled k-space points do not naturally fall onto a Cartesian grid, specific reconstruction methods are necessary as described in Chapter 7.2.1. The advantages spirals offer include the flexible possibilities for varying the sampling density with k-space radius (covered below), the sampling efficiency gained by not sampling k-space corners and the natural gradient moment nulling (sinusoidal gradients that start from 0) that reduce signal loss from intravoxel dephasing caused by motion during the gradients.

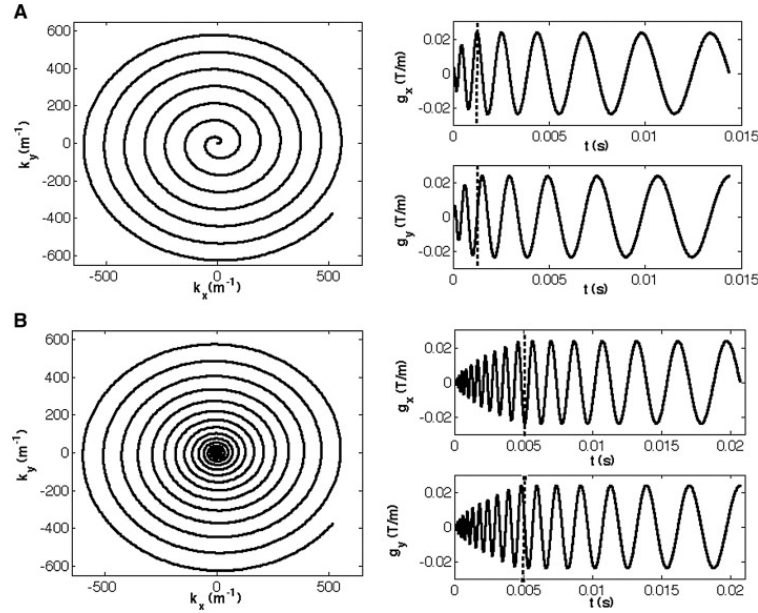


Figure 47: An Archimedean spiral (A) and a variable density spiral (B). On the left the trajectory in k-space is shown, while on the right both x and y gradient waveforms can be seen. The dotted vertical line in the gradient waveforms denotes the change from slew rate limited mode to amplitude limited mode. Taken from [263]

A basic, uniform density spiral trajectory k , can be described via [264]:

$$k(t) = \lambda \tau e^{j\tau} \quad 29$$

where t is time, τ is a function of time, j notes complex notation, and the real and imaginary components represent the x and y data. Furthermore

$$\lambda = \frac{1}{2FOV} = \frac{\Delta k_{max}}{2\pi} \quad 30$$

Δk_{max} refers to the maximal distance between samples to fulfill the Nyquist criteria for the desired FOV. This term denoting the complex location in k-space can be used to calculate the required gradient amplitude $G(t)$ and gradient slew rate $S(t)$ using [264]

$$G(t) = \frac{2\pi\lambda}{\gamma} e^{j\tau} [\dot{\tau} + j \tau \dot{\tau}] \quad 31$$

where γ is the gyromagnetic ratio and $\dot{\tau}$ is the first derivative of τ

$$S(t) = \frac{2\pi\lambda}{\gamma} e^{j\tau} [\ddot{\tau} - \dot{\tau}^2 + (2 \dot{\tau}^2 + \tau \dot{\tau})j] \quad 32$$

where $\ddot{\tau}$ is the second derivative of τ .

This framework allows for a variety of approaches to design spirals, while restrictions on maximal slew rate and amplitude will be determined by available gradient hardware. Limitations on gradient hardware performance lead to two operational modes: slew rate limited, and amplitude limited. At the beginning of a spiral the gradient amplitude is 0 and due to the limited gradient slew rate, the gradient amplitude cannot be increased infinitely. Then after a time of slew rate limited operation the maximal amplitude of the gradient hardware is reached, and the gradient amplitude limited phase starts. This change of mode is shown by the dotted vertical line in Figure 47 [263].

Using the model above, the spiral sampling scheme is mainly controlled by τ . Early work by Ahn et al. [265] used a Archimedean approach in which τ was designed so that the spiral traverses k-space at a constant angular velocity. This allows for a relatively simple trajectory where the maximum gradient is reached at the very end of the spiral. An extension to this approach is shown in Figure 47.A where now the velocity is selected to be linear. While not apparent from the spacing of the spiral arms of both of these approaches, k-space is sampled more densely at the center, as the slew rate limit never allows for a completely homogeneously sampled spiral. This waveform design was then extended by various studies [266]–[268] to provide variable density spirals which allow variable sampling densities as the data collection spirals outwards. As the sampling density determines the FOV, variable density spirals effectively have a FOV that varies between spatial frequencies.

An important consideration that this trajectory design brings in combination with the STEAM sequence covered in Chapter 4.2.3 is the potential reduced FOV. STEAM allows for the excited region to be reduced in both in plane encoding directions. Considering the square nature of spirals (both axis of k-space are sampled simultaneously) this allows for a very efficient readout strategies.

6.3.1 Interleaved Spiral Acquisition

Similar to the segmented acquisition in EPI, spiral acquisitions can be split over more than one excitation if required by resolution or SNR constraints. In order to split a spiral trajectory over multiple shots, the parameter λ from above is redefined as:

$$\lambda = \frac{N_{Interleaves}}{2FOV} = \frac{N_{Interleaves} \Delta k_{max}}{2\pi} \quad 33$$

where $N_{Interleaves}$ is the number of interleaves and can be increased to create an under sampled spiral trajectory, with an increased spacing between each spiral arm. For each interleave this spiral can then be rotated by

$$\frac{2\pi}{N_{Interleaves}} \text{ radians} \quad 34$$

to result in a fully sampled image when the data from the multiple spirals is combined (Figure 48).

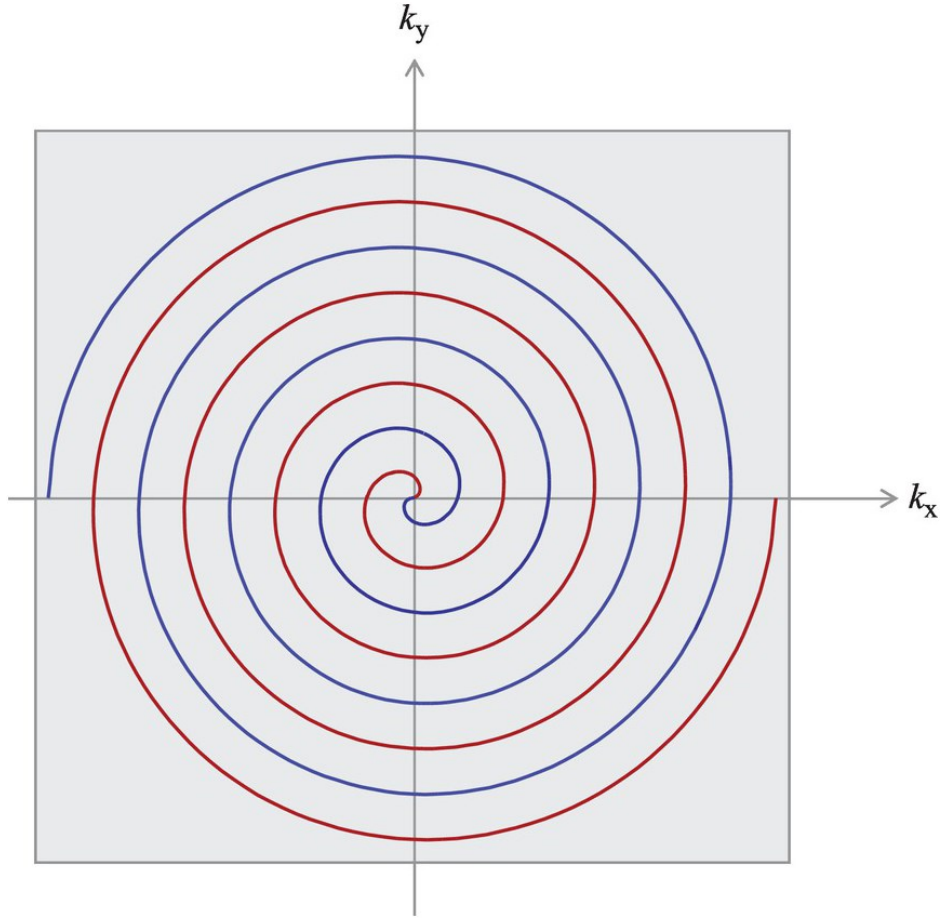


Figure 48: Schematic diagram of an interleaved spiral trajectory. Each individual spiral arm (red, blue) is a spiral under sampled by the factor of two and will be acquired individually after a contrast generation module. By combining the data from interleaves retrospectively it is possible to arrive at a fully sampled k-space and either achieve higher SNR or higher resolution. Taken from [269]

While the Nyquist criteria are satisfied by the combination of interleaved spirals, spirals offer considerable flexibility in the sampling density, which can be varied with k-space radius. While variable density approaches are possible with other readout forms such as EPI and unavoidable with radial imaging, spiral imaging offers a straightforward way of fully sampling the centre of k-space in 2 dimensions in each individual readout and flexibly sampling the rest of k-space. Thus, particularly in sensitive applications such as DT-CMR [182] spirals can be designed to incorporate variable density approaches for higher resolution imaging as has been shown by Gorodezky et al. [244]. In this thesis, the variable density spiral described by

$$k(t) = \lambda \tau^\alpha e^{j\tau^\alpha} \quad 35$$

where α is the variable density parameter was used. The resulting sampling strategy that fully captures the central region, can be used in other applications as calibration data for parallel imaging or for motion correction [263]. In the context of DT-CMR application however this

allows the use of motion induced phase correction to combine multiple diffusion weighted interleaves.

6.3.2 Limitations

As discussed, spiral images are more SNR efficient than their Cartesian counterparts and have improved motion resistance due to native gradient moment nulling. However, they also often suffer from a number of artefacts, caused by:

- **T₂^{*} decay:** Similar to Cartesian acquisitions, such as EPI, long readouts in spiral acquisitions lead to a reduction in signal intensity due to T₂^{*} decay during the readout. Assuming a center-out spiral, the outer k-space samples show a lower signal intensity and this slope in k-space intensity leads to image blurring [174], [249].
- **Off-resonance effects:** Spatial variation in the local Larmor frequency affects Cartesian readouts such as EPI and spiral trajectories. These changes in resonant frequency can be caused by the shielding effect of the molecule surrounding the hydrogen nucleus (e.g. fat vs. water) or changes in magnetic susceptibility (e.g. at a tissue-air interface) [270]. Difference in resonant frequency cause a difference in the phase evolution throughout the readout. In Cartesian acquisitions only one gradient is varied at a time and so the resulting dephasing effects of field inhomogeneities only affect a single direction, thus, resulting in a shift of the signal in one direction. In spiral readouts however the two in-plane gradients are varied continuously and so the off-resonant signal is shifted in both directions leading to image blurring [263].
- **Concomitant fields:** These spatially-varying fields are caused through imaging gradients according to Maxwell's equations and cause a phase accumulation during the readout. This dephasing effect is another source of image blurring. While present in all readout types, the presence of the two orthogonal gradients running simultaneously in spiral readouts make spiral images particular prone to the resulting artefact [263].
- **Trajectory imperfections:** While the trajectories provided to the scanner are calculated from the equations above in the pulse sequence code, the k-space trajectories actually achieved vary slightly and introduce blurring. Trajectory variations are caused by imperfect eddy current correction, gradient delays and hardware designs that are optimized for Cartesian imaging [263].

7 Image Reconstruction

In its most basic form, the reconstruction of MRI data acquired using a Cartesian sampling pattern can consist of a basic 2D FFT after frequency demodulation. However, there are number of methods used to either reduce artefacts in the final images or allow more rapid acquisitions. More complex k-space paths also require an associated increase in the reconstruction complexity.

7.1 Cartesian

7.1.1 EPI

A number of EPI specific steps are required before the image can be produced using the standard FFT approach.

EPI samples even and odd lines in opposite directions (Figure 44). To correct for this, the first step is to row flip either the even or the odd lines. Then the $N/2$ ghosts described in Section 6.2.1 have to be corrected for. There have been numerous publications on how to correct for these artefacts [271]–[275], but the most common approach in DT-CMR is the acquisition of a reference scan at the beginning of each breath hold [49]. This reference scan is a short EPI readout where no phase encoding gradients are applied. An FFT is applied to each of the acquired reference lines. The phase difference between the even and odd lines are compared and a correction is determined. One common approach is to assume that the artefacts can be adequately modelled by a constant + linear phase slope in image space, which can be straightforwardly applied to either the odd or even lines in the imaging data [49]. More advanced methods, however, do exist, as described by Ahn et al. [275] and in [273].

Other considerations in EPI include:

- Image distortion due to off-resonance, which is amplified by the low bandwidth in the phase encode direction, although corrections exist, such as that suggested by [276].
- T_2^* decay results in blurring of the image. Correction techniques such as those described in Section 7.2.4 could be applied.

7.1.2 Parallel Imaging

Parallel imaging techniques originated from the observation that phased array coils, used to improve SNR [277] also provide information on the location of the signal through their individual spatially-varying signal sensitivity profile that could be used to resolve artefacts in under sampled (sub-Nyquist) data.

The typical under sampling pattern used for parallel imaging is derived from the properties of k-space displayed in Figure 49. A reduction in the overall extent of k-space covered (reduce $k_{\max}$) but maintaining the sampling density (maintain Δk) results in a low-resolution image. Maintaining the same extent of k-space sampled as in the fully sampled image (maintain $k_{\max}$), but reducing the sampling rate (increased Δk) results in the same spatial resolution but a smaller sampled FOV and therefore, Nyquist ghosting (aliasing or wrap artefact) occurs [278].

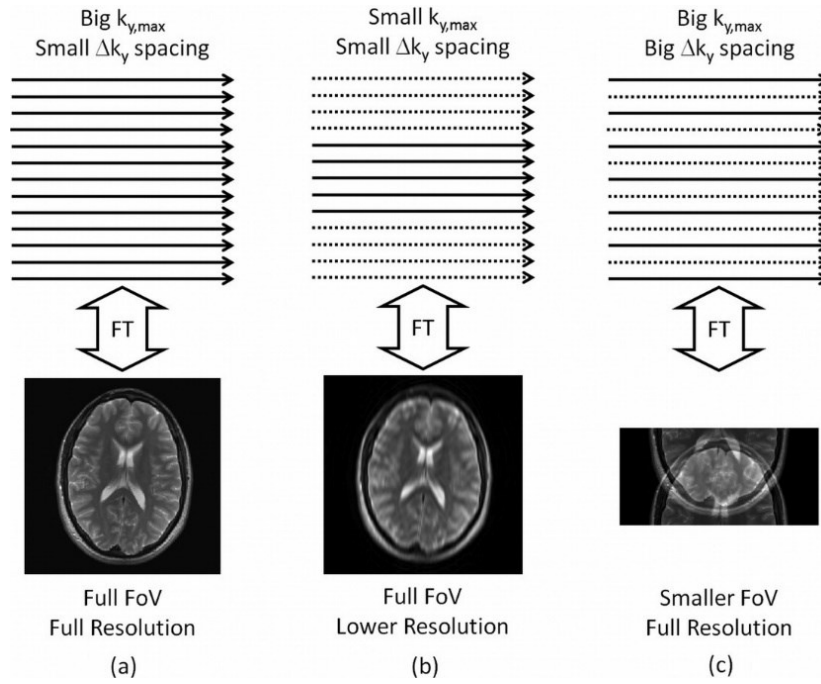


Figure 49: The effect of different under sampling strategies on an image. (a) A fully sampled image with dense sampling along both axes. (b) shows an image that was sampled with fewer k-space lines, but the same sampling density, thereby reducing the extent of k-space sampled and resulting in a full FOV, but lower spatial resolution. (c) shows an image with a similar number of k-space lines to (a) but omitting every odd k-space line, thus reducing the sampling density and resulting in full spatial resolution, but a reduced FOV which causes aliasing or wrap artefact as the Nyquist criteria has been violated. Taken from [278].

Figure 50 demonstrates the application of the Nyquist theorem to MRI sampling. The objects can be thought of as two pixels in the imaged object. In the case that the signal is sampled at a sufficiently small sampling dwell time η , the Nyquist criterion:

$$\frac{1}{\eta} > 2 \frac{1}{B} \quad 36$$

where $1/B$ is the highest to sample frequency, is fulfilled and the spatial locations of the signals are resolved correctly. In the case of a sampling rate that does not fulfil the Nyquist criterion however the separate signals can overlap and become indistinguishable. However, parallel imaging algorithms use data sampled at sub-Nyquist rates from multiple receive coils. The spatial variation in sensitivity of the receive coils means that the Nyquist theorem is not truly violated as long as the number of receive channels is at least equal to the under-sampling factor.

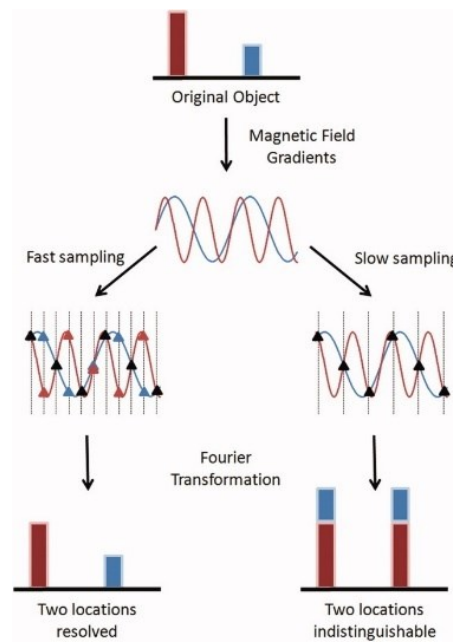


Figure 50: The effect of different sampling rates on a signal from two spatially separated objects. On the left-hand side, the sampling rate is just sufficient (Nyquist sampling) to resolve the two signals correctly. The right-hand side shows a sampling rate slower than the Nyquist limit and so an overlay of the signals occurs. Taken from [278]

In EPI, typically only the phase encode direction is under sampled. While it is also possible to under sample in the readout direction, this would not result in a substantial increase in efficiency.

The two most popular parallel imaging algorithms are known as Sensitivity Encoding (SENSE) and Generalised Auto Calibrating Partial Parallel Acquisition (GRAPPA) and are covered below.

7.1.2.1 SENSE

SENSE was first introduced in 1999 by Pruessmann et al. [279] and since then has been extended and applied to nearly every field within MRI [278], [280]. SENSE is an image-based method and the underlying formalism is independent of many of the readout considerations specific to raw data and k-space. The main requirement of SENSE is the generation of a Coil Sensitivity (CS) (or B₁-) map for each receiver coil.

There have been multiple proposals on how to obtain this CS map. While they can be predicted using the Bio-Savart law, coil geometry and coil placement within the scanner, it would be cumbersome to measure the exact location and geometry of the coils and it does not consider differences due to effects such as patient loading[257]. The most common approach is to obtain CS maps from a fully sampled low resolution reference scan of the region that is to be imaged[279]. This is possible by either fully sampling the centre of k-space and only under sampling the outer part of k-space (the central k-space data can be used as a low-resolution image for the CS maps) during imaging, or by acquiring a fully sampled reference scan in a separate acquisition (possibly at the beginning of each breath hold).

If this CS map is known, then the SENSE algorithm can be used to reconstruct the full FOV image without aliasing. First, each of the j receive channels are individually reconstructed to complex image space, resulting in $I_j(x, y)$ images containing wrap artefact. In the case of an acceleration factor of 2 this would result in the superposition of the signal from two positions at each pixel (Figure 51) and can be expressed as:

$$I_j(x, y) = C_j(x, y)p(x, y) + C_j\left(x, y + \frac{FOV}{2}\right)p\left(x, y + \frac{FOV}{2}\right) \quad 37$$

where $p(x, y)$ is the unwrapped image at pixel location (x, y) and C_j is the relevant Coil Sensitivity Map (CSM). While here the case of a $\frac{FOV}{2}$ fold image wrap is shown, higher acceleration factors add wrap from more positions at each pixel. Assuming that the number of distinct receive channels is not bigger than the under-sampling factor, then the original image can be reconstructed by solving Equation 37. This however comes with an associated loss of SNR_{SENSE} compared to a fully sampled reconstruction (SNR_{normal}) which is described by:

$$SNR_{SENSE} = \frac{SNR_{normal}}{g\sqrt{R}} \quad 38$$

Where R is the acceleration factor and g is the so-called geometry factor described by Pruessmann et al. [279] which further reduces the SNR, depending on receive coil geometry and performance.

$$\begin{aligned}
 S_1(x, y) &= C_1(x, y) \rho(x, y) + C_1\left(x, y + \frac{FOV}{2}\right) \rho\left(x, y + \frac{FOV}{2}\right) \\
 S_2(x, y) &= C_2(x, y) \rho(x, y) + C_2\left(x, y + \frac{FOV}{2}\right) \rho\left(x, y + \frac{FOV}{2}\right)
 \end{aligned}$$

Figure 51: A visual example of SENSE reconstruction. S_i is the image from receive channel i . C_i is the corresponding coil sensitivity map and ρ is the unwrapped image. x, y denote individual image locations and the wrap occurs at $FOV/2$ due to using an acceleration factor of 2. Taken from [280]

7.1.2.2 GRAPPA

In contrast to the SENSE algorithm GRAPPA is a k-space based method (Figure 52). Instead of unwrapping the aliasing that occurs after the FFT, the missing data is synthesised in k-space. To achieve this GRAPPA also requires a reference acquisition. However, instead of calculating the coil sensitivity directly, as discussed above, this method uses the fully sampled data to generate a set of weighting factors, which can be used to infer the data in one pixel from both the data in surrounding pixels and the other receive coils. These factors can then be used to synthesise the missing data in under sampled acquisitions from the surrounding data [281] .

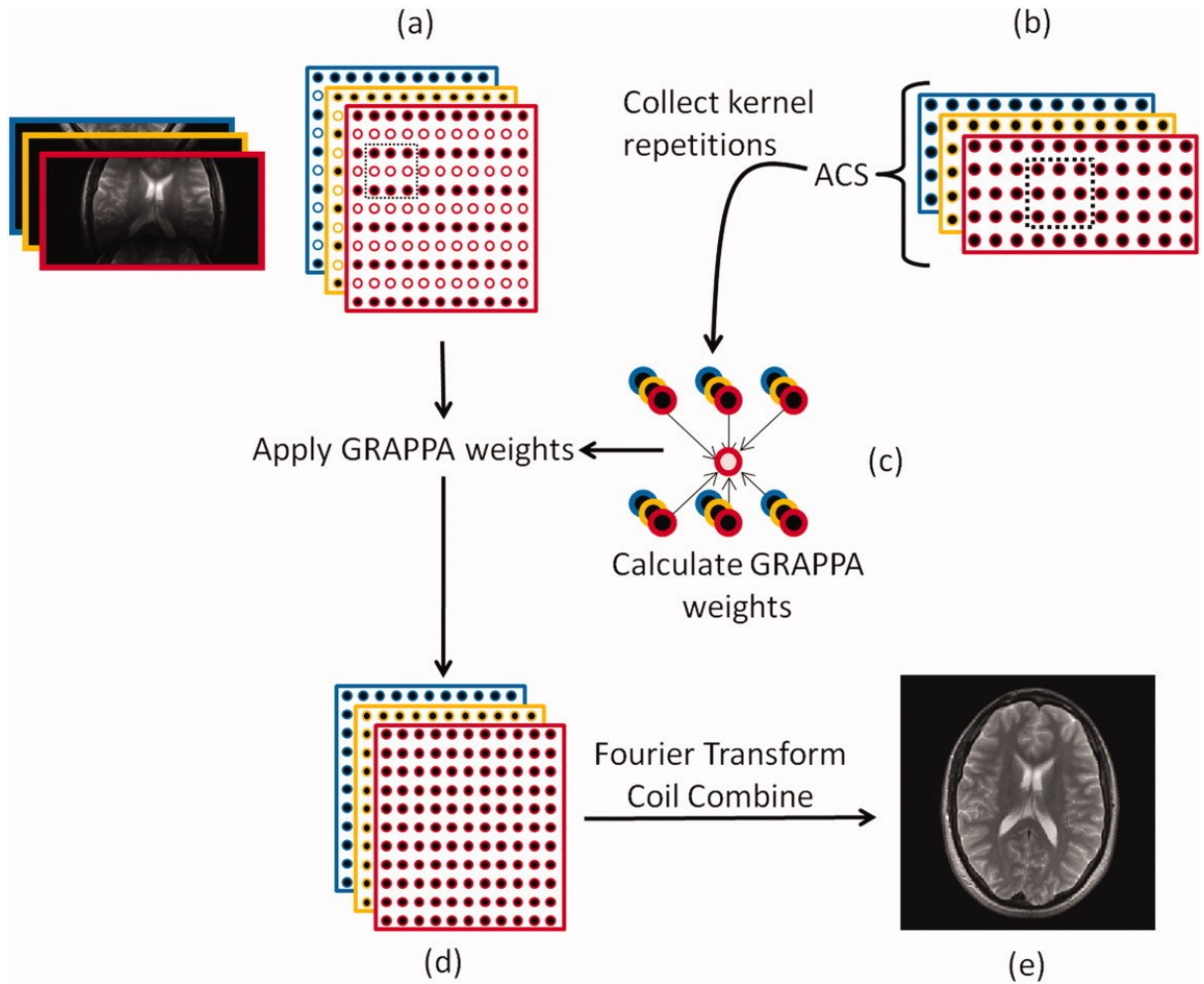


Figure 52: Diagram of the GRAPPA algorithm. (a) shows the sub-sampled k-space data for each receive coil channel. (b) the fully sampled reference data (also termed auto-calibration signal[ACS]) is used to calculate the GRAPPA weights shown in (c). By convolving the undersampled data with these weights it is possible to synthesise a fully sampled matrix (d). FFT and combination of the individual coil images is then used to generate the final image (e). Taken from [278]

7.1.3 Zero Filling

Zero Filling is a method often used to increase the apparent spatial resolution in MRI. Zeros are appended to the outer k-space matrix of the original data. As the spatial resolution of an image is determined by the extent of sampling in k-space, padding the k-space array with zeroes, produces a smaller effective pixel in the reconstructed image. This reduces the blocky appearance of images without increasing the spatial resolution. The extension of k-space with zeros (most commonly by a factor of 2) has a similar effect to SINC interpolation in image space and so mitigates some of the partial volume effects in the displayed image [257]. This is accompanied by an increase in Gibbs ringing, due to the resultant sharp edge in k-space between the sampled and unsampled regions and should be viewed as a technique for improved display and not a technique to increase resolution [257].

In terms of DTI, this technique was investigated by Sun et al. [256] and is used throughout the field [50], [193]. Sun found that zero filling can have an influence on DTI data, presented by an increase in FA and a decrease in ADC.

7.2 Spiral

7.2.1 Gridding

In spiral imaging, data is not sampled on an equally spaced matrix and so cannot undergo a standard FFT reconstruction approach. Typically, non-Cartesian points are interpolated onto a Cartesian matrix using a convolution-based approach known as gridding (Figure 53). An infinite SINC function is considered to be the optimal convolution kernel for use in this operation to avoid aliasing artefacts [282]. However convolution with an infinite function requires a calculation at each sampled spiral point of the whole final matrix and this approach is rarely used due computational inefficiency [174]. Instead the Kaiser-Bessel function is often used as a convolution kernel [283]. A number of additional steps must also be performed to adequately reconstruct images [263]:

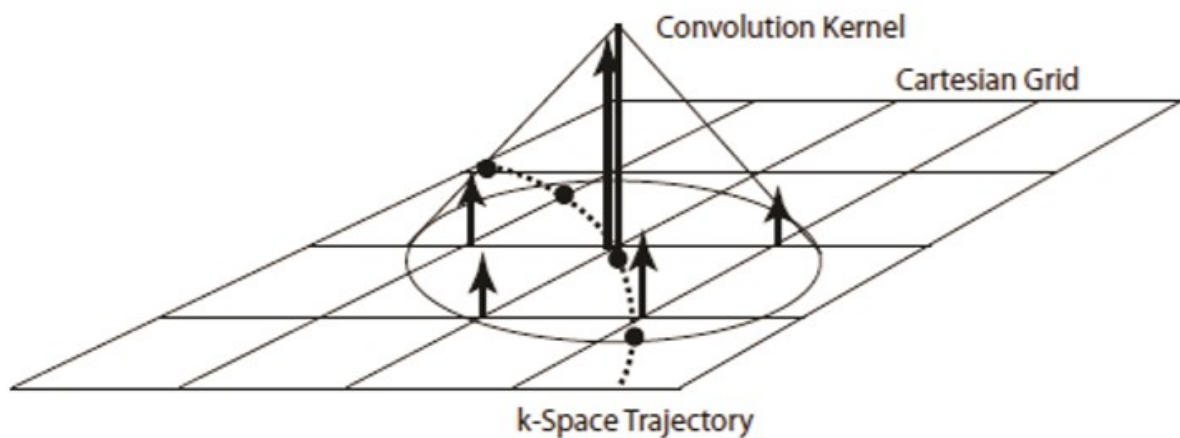


Figure 53: The process of gridding. A data sample along the non Cartesian k -space trajectory is interpolated using a convolution kernel onto pixels in a Cartesian grid, allowing subsequent image calculation using an FFT. Taken from [284]

- **The matrix size:** It is common to initially grid onto a matrix corresponding to a larger FOV than the sampled image and later crop the image space data to the desired matrix size [282]. While this results in losing some computational efficiency in handling a larger matrix, this approach allows for single lobed gridding kernels such as the Kaiser-Bessel function to be used with minimal aliasing. This is shown in Figure 54, where it is clear that the assumption of periodicity in the FFT results in the Kaiser-Bessel kernel causing wrap artefact if the data is not gridded onto a matrix larger than the imaged FOV [282].
- **Density compensation:** Figure 55 shows an Archimedean spiral trajectory and its corresponding Voronoi diagram. Even without the presence of a variable density spiral approach it is apparent that the centre of k-space is more densely sampled than the outside, since the respective area per sample in the Voronoi is small at the inside compared to the outside. By introducing a density compensation factor before gridding the image blurring caused by the higher sampling density at the centre of k-space is avoided [263]. While there are many possible approaches to calculating the density compensation function, a common method is to use the areas of the Voronoi diagram itself [284].
- **The size of the kernel:** By increasing the size over which the Kaiser-Bessel function spreads it is possible to achieve a closer result to infinite kernels such as the SINC approach discussed above [257], at the expense of higher computational cost.
- **Kernel Roll-Off Correction:** When choosing a finite gridding kernel such as the Kaiser-Bessel function the roll off to the outer area of the convolution will result in an intensity distortion in image space. An easy way to correct for this is to divide the final image by the FFT of the kernel and is known as described by Jackson et al. [283] as roll-off correction.

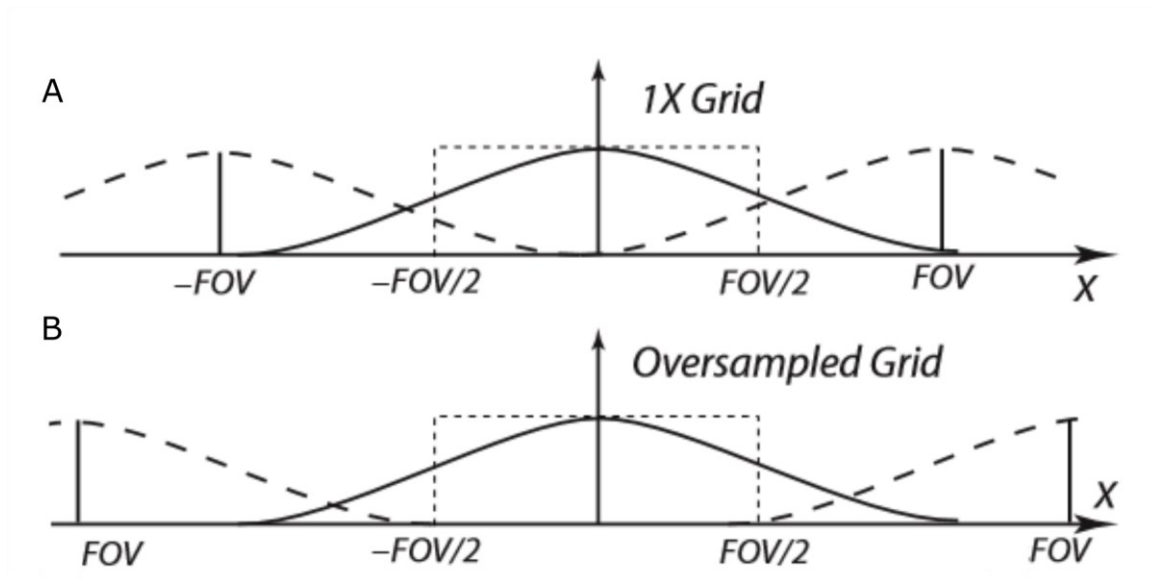


Figure 54: Showing the influence of a normal grid (A) and an oversampled grid (B) on the gridding process of a Kaiser-Bessel function and the potential for aliasing. The dotted lines to the left and right are here the replicas of the convolution of the closest data samples. Through finer sampling as shown in (B) it is possible to reduce the potential aliasing of these. Taken from [284]

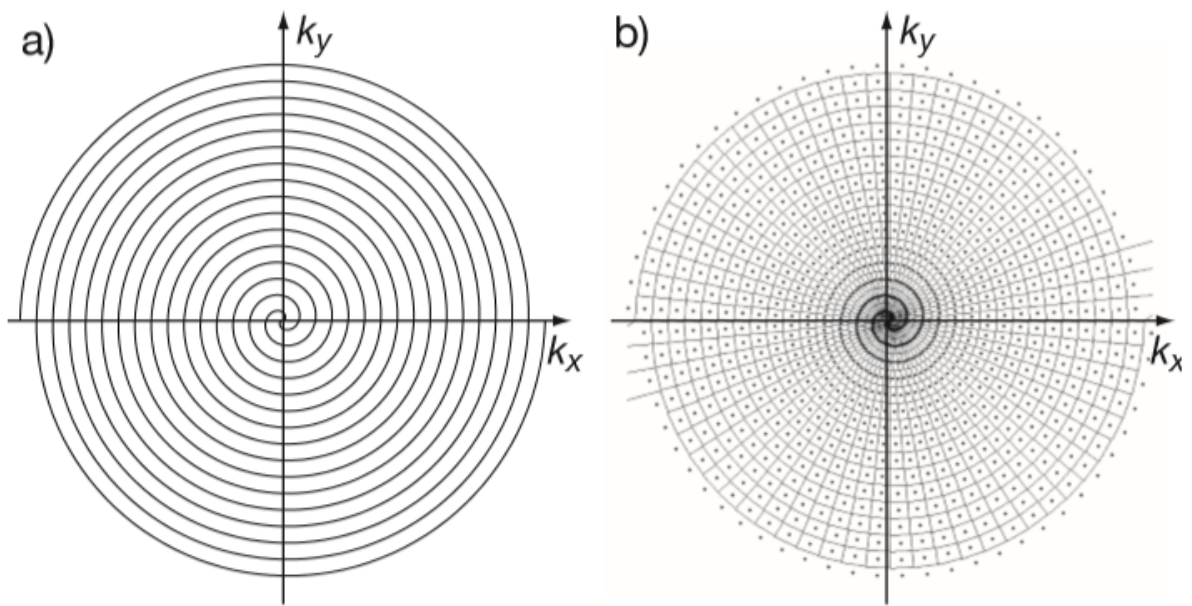


Figure 55: Archimedean spiral shown in (a) and the accompanying Voronoi diagram in (b). the sampling density is higher near the centre of k -space, which is reflected in the smaller area around each sampling point in the Voronoi diagram. Taken from [284]

7.2.2 Motion-Induced Phase Correction in Interleaved Spiral Imaging

The influence of bulk motion on segmented acquisition schemes in diffusion imaging was described in Chapter 4.2. In spiral imaging the signal loss that would be encountered due to phase cancellation errors in segmented diffusion weighted images can be mitigated for by using a approach known as SNAILS [247].

The motion induced phase is assumed to be contained within the lowest spatial frequencies and therefore can be estimated from the fully sampled part of a variable density spiral trajectory. After gridding, a copy of each interleave is made and a window function is applied to the copy to extract the low-resolution data. An FFT is applied to both the full interleave data and the low-resolution copy, after which it is possible to multiply the conjugate phase of the low-resolution data with the original data. After this phase correction motion induced phase cancelation should be avoided when multiple interleaves are combined in complex space (Figure 56) [247].

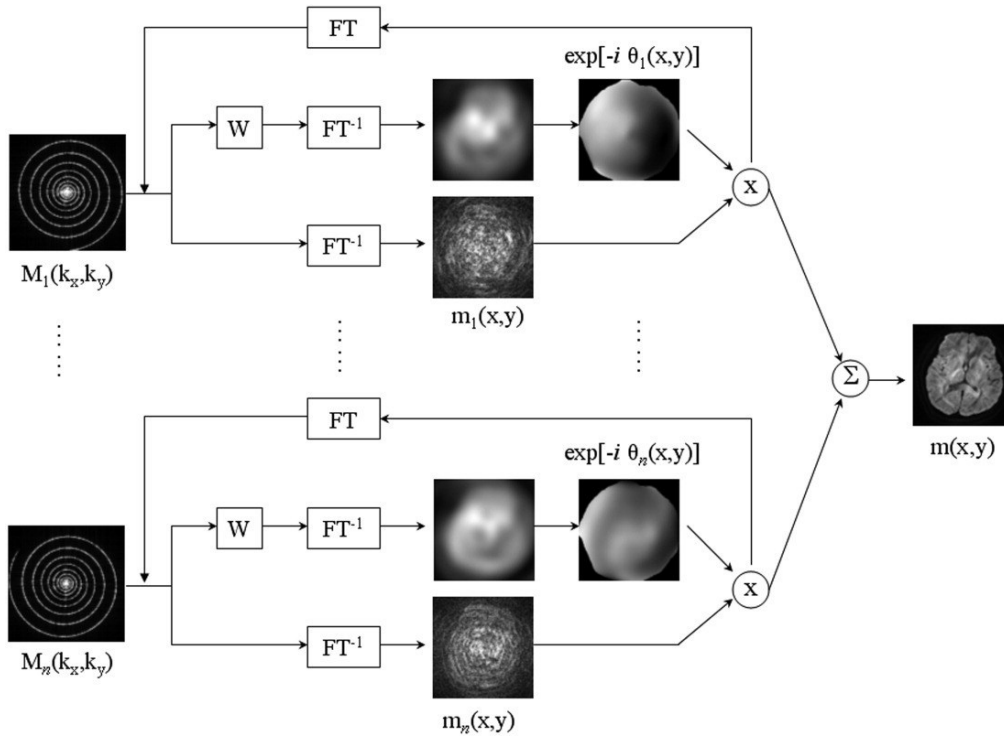


Figure 56: The SNAILS approach. After gridding, a single interleave spiral dataset, M_q , is copied. One of the copies is directly reconstructed using an FFT, while the other copy is filtered using W before FFT to create a low-resolution version of the image. Phase changes due to motion during diffusion encoding are assumed to be contained within the low-resolution phase of this filtered image. By multiplying the complex data of the unfiltered data with the conjugate phase of the filtered k-space, the motion-induced phase can be removed from each of the interleaves, allowing the corrected interleaves to be combined. The process can be repeated iteratively until no substantial change in the final phase is observed (denoted by the arrowing leading back to the original data after phase correction). Taken from [247].

7.2.3 Off-resonance Correction

A common problem in spiral imaging is blurring originating in off-resonance [270], [285] (see Section 6.3.2). The phase errors due to off-resonance accumulate with readout duration and so are particularly problematic if longer spirals are required to obtain higher resolution. Noll et al. proposed a method for correcting for this effect in 1991 based on a time-segmented method [286] and extended this with a frequency segmented approach [285]. While there have been multiple different approaches over the years [287]–[290] the frequency segmented method remains a popular choice and is described below (Figure 57).

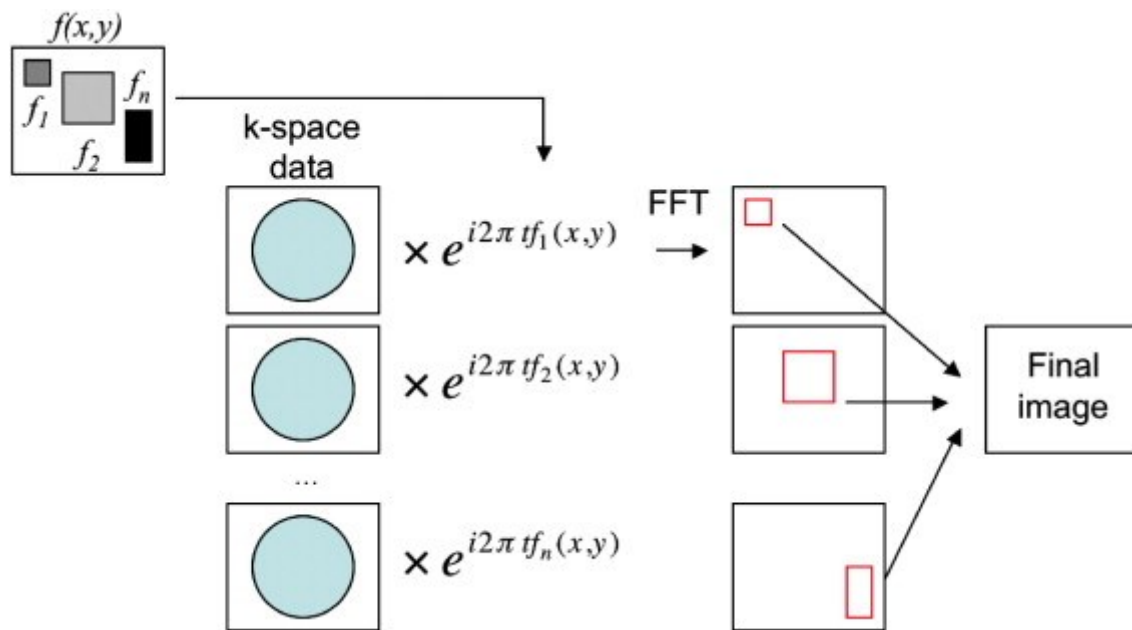


Figure 57: A schematic diagram of the frequency segmented off-resonance approach. Based on the field map $f(x, y)$ a range of f_1, f_2, f_n frequency bins is created. For each of these bins the original data is copied and multiplied with a correction for constant frequency offset $e^{i2\pi t f_n(x,y)}$. Then all bins undergo FFT and the final image can be created by selecting the local pixel of the bin that is closest to the frequency in the co registered field map. Taken from [263]

The basic requirement of the frequency segmented approach is the acquisition of a field map describing the spatial differences in Larmor frequency. This map can be calculated from two spiral (or other) acquisitions $S_1(x, y)$, $S_2(x, y)$ with a different data sampling delay $\Delta Sampling$. For gradient echo-based field maps, $\Delta Sampling$ is varied by increasing the TE, while for STEAM or SE approaches, off-resonant effects are rephased at the echo. As a result, the stimulated (or spin) echo is chosen to occur at the same relative timing and a delay in acquiring the data after the echo allows for the off resonant spins to dephase. The phase difference $\Delta\phi(x, y)$ is then calculated through:

$$\Delta\phi(x, y) = \arctan\left(\frac{\text{Imag}(S(x, y)_1 S(x, y)_2^*)}{\text{Real}(S(x, y)_1 S(x, y)_2^*)}\right) \quad 39$$

which can then be used to calculate the pixelwise Field Map (FM) $FM(x, y)$ in Hertz by using:

$$FM(x, y) = \frac{\Delta\phi(x, y)}{2\pi\Delta Sampling} \quad 40$$

which quantifies the underlying inhomogeneities of the magnetic field.

In the frequency segmented approach this FM is used by taking the global maximum and minimum values and creating a range of n frequency bins f_n in between. For each bin in this range the original ungridded spiral data is copied and a correction for a constant frequency offset of f_n is applied by multiplying the data by $e^{i 2\pi t f_n}$, where t is time. The data is then gridded and transferred to image space using an FFT (Figure 57). Now by pixelwise selection of the data corrected with the closest f_n based on the FM, the image blurring is much reduced.

Truncation artefacts can be evident with an insufficient number of bins and so n must be balanced against the increase in computational power required as more bins are used. Moriguchi et al. [291] suggested an empirical value for the appropriate number of bins while not requiring excessive computation:

$$4(f_{max} - f_{min})T_{acq} \quad 41$$

with $f_{max} - f_{min}$ the range of corrected frequencies and T_{acq} the duration of the readout. The truncation artefacts can be further suppressed by interpolating between the data from the two closest bins to any field map frequency.

7.2.4 T2* Correction

The previous chapter described the blurring that occurs due to T2* signal decay during long readouts. Gorodezky et al. [244] introduced a correction technique for use in spiral DT-CMR. After a single STEAM excitation two identical low-resolution spirals are acquired. The second spiral thus has a delay of ΔTE_{T2^*} . Importantly a refocussing gradient is used after the first spiral to ensure the same k-space data is sampled in both spirals. A mean T2* is then calculated by using

$$T2^* = \frac{\Delta TE_{T2^*}}{\log\left(\frac{\sum_{i=1}^N K_1}{\sum_{i=1}^N K_2}\right)} \quad 42$$

where K_j are the k-space samples of the first N points (this was chosen as 1000 in the initial work [244]).

Using this T2* value a correction that assuming a constant T2* can be used to correct the intensity of the spiral k-space data using:

$$k_{corr}(t) = k(t)_0 e^{\frac{t}{T2^*}} \quad 43$$

where $k(t)_0$ is the uncorrected signal before gridding. This approach relies on the assumption that due to the reduced FOV and blood suppressed STEAM preparation, the signal predominantly originates from the myocardium and so the sum of the first 1000 points is an estimate of the average myocardial signal. Other potential problems with this correction include the noise enhancement that is associated with this method.

8 Hypothesis

Chapter 2 laid out the clinical need for assessing rTOF patients using CMR. While other modalities such as echocardiography play an important role, CMR is considered a key part of rTOF monitoring, including for assessment of myocardial viability. Important work by Babu-Narayan et al. [67], showed that focal scar identified by LGE imaging correlates with adverse events such as sudden cardiac death. This study was published in 2006 and since then CMR methodologies have improved, including better LGE imaging and the rise in studies using T₁ mapping and ECV to assess fibrosis.

While LGE methods are now a gold standard for the assessment of focal fibrosis, the assessment of diffuse fibrosis has become a focus for the research community. This is particularly important clinically, as diffuse fibrosis is believed to be reversible via therapy and early detection could prove to be invaluable for risk management. While native T₁ mapping and ECV are promising approaches which may provide some insight into the microstructure of the myocardium including potentially the identification of diffuse fibrosis, current techniques are far from being reliable clinical tools for this application. There are, therefore, a lack of techniques that are able to generate contrast which enable reliable identification of diffuse fibrosis *in vivo*.

In CHD patients, including rTOF, the RV is often of particular interest and this is a more challenging target than the LV. Due to the relatively thin compact myocardium higher spatial resolution is required than when assessing the LV. The thin compact myocardium also means that blood pool signal often contaminates measurements of parameters such as T₁ in the RV, particularly when spatial resolution is limited. As a result, RV assessment requires excellent blood suppression, which is not generally available with current T₁ mapping methods.

A potentially useful method in assessing diffuse fibrosis is DT-CMR. Initial studies have shown that the microstructural information provided by DT-CMR may be a valuable tool in a range of pathologies (Section 5). In particular, the study of Nguyen et al. [292] showing a change in ADC in the presence of diffuse fibrosis in the LV is promising and provokes questions as to whether both MD and FA would be sensitive to the presence and extent of diffuse fibrosis.

A technique which may solve many of the problems associated with imaging the RV is the STEAM sequence. This sequence, described in previous chapters, offers excellent blood suppression and has been shown to work reliably for *in vivo* DT-CMR in multiple cardiac phases. In addition, it allows for the reduction of the FOV in both in-plane directions, which renders it well suited for use with efficient spiral trajectories. Spiral methods are, in turn, well suited for multiple interleave acquisitions in DT-CMR, as shown in Chapter 6 and 7, which facilitates high-resolution DT-CMR imaging.

Based on the above the following hypothesis of this thesis is:

Diffusion and T₁-based tissue characterisation of the right ventricle can be reproducibly and reliably performed using STEAM-based techniques.

Such methods would pave the way for future studies assessing the ability of these T₁ and diffusion-based techniques to detect diffuse fibrosis in the RV of patients with rTOF.

In order to assess this hypothesis, the work in the following chapters aims to:

- ***Develop an optimised spiral STEAM acquisition and reconstruction, including corrections to address off-resonance and spatially-varying T₂^{*} blurring.***
- ***Develop online reconstruction tools that provide images at the scanner, at the time of the scan, to provide methods suitable for use in clinical research studies.***
- ***Develop an ex vivo protocol that utilises the interleaved spiral design to achieve a higher resolution to reduce partial voluming effects in exploratory work into the RV microstructure of healthy and rTOF hearts.***
- ***Demonstrate the ability of the STEAM sequence to acquire native T₁ and DT-CMR parameters to provide reproducible results in healthy volunteers and to provide an assessment of the RV in rTOF patients.***

9 Simulations

9.1 Introduction

While several sources can contribute to artefacts in spiral MRI, as reviewed in Section 6.3.2, here the contributions of off-resonance and T_2^* decay during the readout are considered. Both field inhomogeneities and signal decay during the spiral readout due to T_2^* result in image blurring [263], [270]. In general, both off-resonance and T_2^* are spatially-varying parameters, causing a spatial variation in the resultant blurring. In previous work off-resonance related blurring was corrected by using the frequency segmented correction for field inhomogeneities and a spatially constant correction for T_2^* was performed based on an average T_2^* for the myocardium obtained in two short reference scans [245]. For *in vivo* DT-CMR data, the correction for spatially constant T_2^* was shown to increase a measure of sharpness and correction for off-resonance improved image quality. However, such *in vivo* studies lack a ground truth and the effect of spatial variations in T_2^* on spiral image quality has not been investigated. Here numerical simulations are used to investigate the effect of spatially-varying field inhomogeneities and T_2^* decay on spiral DT-CMR image quality and parameters. The implications of the related correction methods are also examined.

9.2 Methods

9.2.1 Simulating DT-CMR

To investigate the effects of T_2^* decay and field inhomogeneities on DT-CMR data using numerical simulations, a simple yet realistic ground truth is required. Thus, as shown in Figure 58 an annulus was created with an outer diameter of 70 mm and a thickness of 17 mm, resembling roughly the dimensions of a healthy LV imaged at the mid-ventricular level, during peak systole in the short axis plane. The pixel size was $2 \times 2 \text{ mm}^2$ and the FOV was $110 \times 110 \text{ mm}^2$ to match protocols used for *in vivo* interleaved spiral DT-CMR acquisitions later in this thesis. Pixels within the annulus were initially assigned to a constant signal intensity and those outside were nulled.

Within the annulus, a simulated diffusion tensor is generated for every pixel, based on typical results obtained *in vivo* with a STEAM sequence in the LV at peak-systole. The key DT-CMR characteristics were:

- The primary eigenvector, $\hat{e}_1$ is parallel to the local myocardial wall, i.e., $TA=0^\circ$. The HA rotates linearly from $+60^\circ$ at the epicardium to -60° at the endocardium.
- The secondary eigenvector is oriented perpendicular to $\hat{e}_1$ and the cross-myocyte plane. In this plane the angle previously described as E2A changes based on cardiac phase and is here assumed to be in a systolic configuration with a value of $+60^\circ$ [34].
- By mathematical definition the $\hat{e}_3$ is the cross product of the first two eigenvectors.
- The eigenvalues were spatially constant $[1.65, 0.85, 0.56] \times 10^{-3} \text{ mm}^2/\text{s}$ and selected to provide typical *in vivo* values $MD=1 \times 10^{-3} \text{ mm}^2/\text{s}$ and $FA=0.5$ [207].

Figure 58 shows the steps used to calculate the diffusion tensor at each pixel from the DT-CMR parameters defined above:

- 1) To allow a transmurally varying helical angle, n rings with a one-pixel thickness are defined. Each ring is associated with a HA ϕ linearly varying from $+60^\circ$ in the epicardium to -60° at the endocardium.
- 2) Given the circular nature of the synthetic dataset polar and spherical coordinates are advantageous when defining the eigenvectors. After transforming each pixel $P(x, y)$ into a polar representation (r_p, θ_p) with the centre of the annulus as the origin, the next step is to create a spherical coordinate system centred on $P(x, y)$. In the spherical coordinate system, θ_p can be rotated by $+90^\circ$ to define the first angular spherical coordinate θ_s of the local $\hat{e}_1$ and $r_s=1$ by definition.
- 3) The previous step ensures that due to θ_s , $\hat{e}_1$ is parallel to the local myocardial wall. The second spherical angle is then the HA, ϕ . $\hat{e}_1$ is then transformed into Cartesian coordinates.
- 4) To define $\hat{e}_2$ a supporting vector $\mathbf{h}$ is created through the cross product of a radial vector (the vector $\mathbf{p}$ from the centre of the annulus to the pixel) and $\hat{e}_1$. The cross-product of $\mathbf{p}$ and $\hat{e}_1$ is then the cross-myocyte direction, $\mathbf{h}$, (see Section 4.4 and Figure 58). As before, $\mathbf{h}$, is transformed into spherical coordinates (r_h, θ_h, ϕ_h) . Using ϕ_h of this transformation it is possible to define α by either adding or subtracting from -90° , while using θ_p to ensure that this new support angle is oriented correctly.
- 5) $\hat{e}_2$ is then calculated by transferring a spherical coordinate set of $(r=1, \theta=90+\beta, \phi=90)$ where β is E2A ($+60^\circ$) to Cartesian coordinates and rotating this set around the z and x

axes with the previous defined angles of α and θ_p . Calculating $\widehat{e}_3$ is simply the cross product of $\widehat{e}_1$ and $\widehat{e}_2$.

The tensors created with this approach can be inserted in Equation 12, scaled by the realistic eigenvalues, in combination with the 6 diffusion directions and b-values (150 s/mm², and 600 s/mm²) as in the *in vivo* case. Solving the equation for the diffusion weighted images (DWI), 6 images at both b=150 s/mm² and b=600 s/mm² are created making up the basis for the simulations (Figure 58).

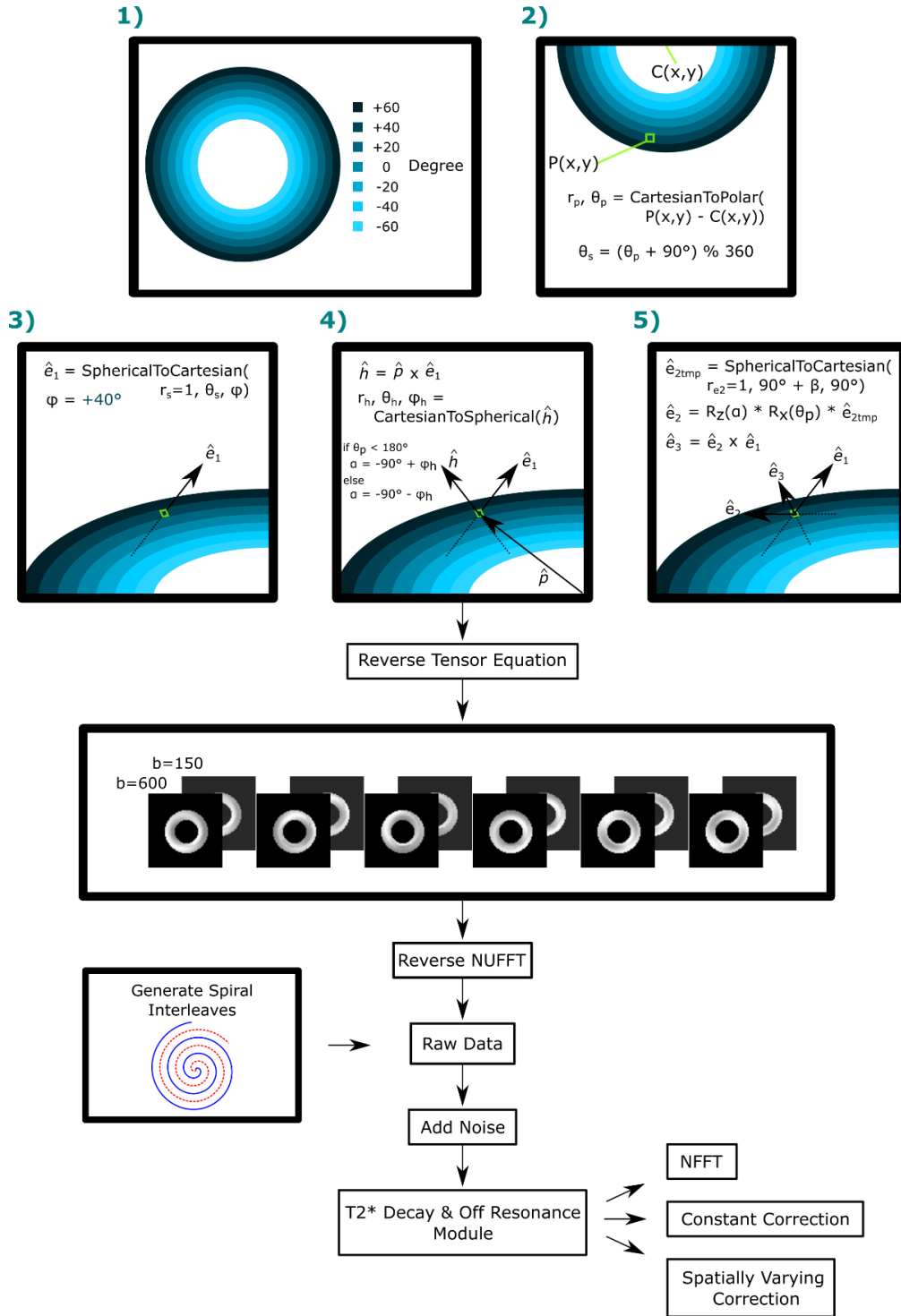


Figure 58: Diagram of the process used to simulate artificial spiral DT-CMR data. In 1-5) the process of generating a synthetic tensor typical of those obtained from DT-CMR in the myocardium is explained [$C(x,y)$ is the centre of the annulus, $P(x,y)$ is an arbitrary pixel of the annulus, r_p, θ_p are the polar coordinates of $P(x,y)$, θ_s is the first spherical angular coordinate of the local e_1 , φ is the HA, h is a supporting vector, r_h, θ_h, φ_h are the associated spherical coordinates to h , e_1, e_2, e_3 are the eigenvectors]. Following the generation of the tensor the Equation 12 can be used to generate DWI in image space. To transfer this dataset into raw k -space an inverse NUFFT algorithm is used together with a set of spiral trajectories. Following this realistic noise and $T2^*$ as well as field inhomogeneities can be simulated in k -space. In an artificial DT-CMR dataset this results in realistic signal decay patterns in scanner data space.

9.2.2 Generating Realistic Noise Values

Before adding noise to the dataset, each of the DWI must be transformed into spiral k-space paths using an inverse Non-Uniform Fast Fourier Transform (NUFFT) gridding operation as described in Chapter 7.2.1.

For these simulations, a single receive channel with white Gaussian noise in k-space is assumed.

To add noise to the spiral k-space data, complex Gaussian noise is added to each sample. The Gaussian distribution is centred at 0, while the standard deviation is variable and determines the SNR. The following algorithm selects the standard deviation required for a specified SNR, using the same algorithm used to measure SNR in *in vivo* data:

1. The spiral k-space data of one $b=600$ s/mm² direction is passed into a while loop, with a stop condition defined as reaching a specified SNR.
2. Each interleave of the raw data is copied 100 times.
3. For each of the copies complex Gaussian noise is added. The standard deviation of the noise distribution is a variable with the value of 0 in the first iteration. For each of the interleaves and for each of the 100 copies the noise seed used to generate the Gaussian noise is incremented.
4. Noisy interleaves are gridded and combined.
5. The SNR is calculated according to $SNR = \text{myocardial mean}(\frac{\text{mean}(\text{Image}[a])}{\text{std}(\text{Image}[a])})$ where a is the dimension along the 100 copies, to provide the SNR of each unaveraged image.
6. The standard deviation used for this iteration is increased and the next iteration of the loop is triggered, until the desired SNR is achieved.

A dataset with 6 diffusion directions, 2 x $b=150$ s/mm² averages and 8 x $b=600$ s/mm² averages was generated for each simulation at each SNR tested. For each image, the seed for the Gaussian random number generator was incremented.

9.2.3 Simulating Spatially-Varying T_2^* & Off-Resonance

To introduce both T_2^* decay and off-resonance related dephasing, simulated maps of T_2^* and off-resonance corresponding to the simulated LV geometry are required. The two pairs of T_2^* and off-resonance maps used in this simulation are firstly realistic maps extracted from an *in vivo* acquisition (Figure 59 a, b) and secondly artificial maps using a circumferential linear gradient in T_2^* or off-resonance (Figure 59 c, d).

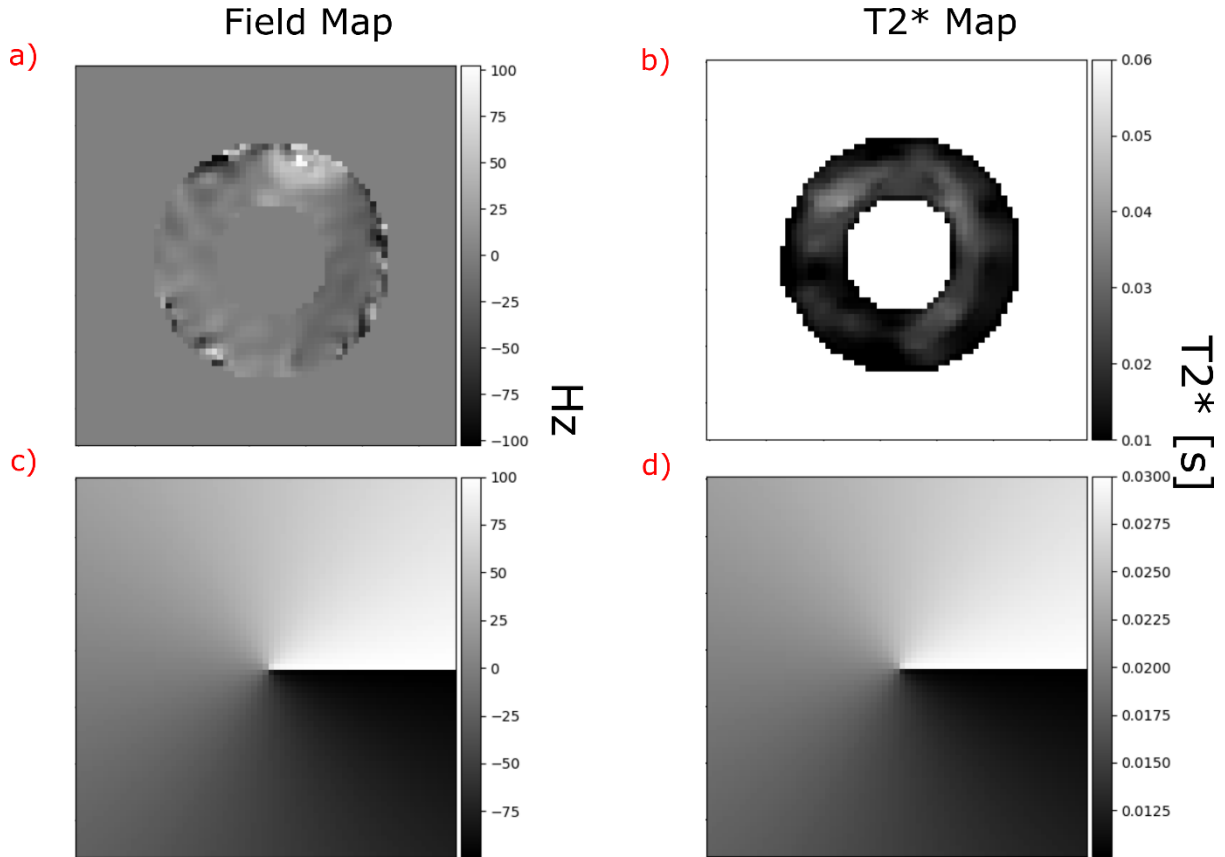


Figure 59: Field and T_2^* maps used in the simulation. A) is a field map acquired with a spiral STEAM approach *in vivo* and transformed to fit the LV annulus used here. The transformation was done by overlaying the real map and the simulated LV annulus, then by means of manual scaling/rotating and shearing the real map was adjusted so that the LV fitted the simulated annulus. b) shows a T_2^* map acquired with a typical product T_2^* mapping sequence on a 3T Siemens Skyra scanner *in vivo* and transformed to fit the simulated LV annulus in the same manner as the field map. c) and d) Linear circumferentially varying field and T_2^* maps. c) Varies from -100 to 100 Hz and d) covers a range from 10ms to 30ms. The discontinuity at 0-degrees radially (c,d), although non-physical, was included as a test of sharp localised changes.

The spatially-varying T_2^* related decay results in time varying changes in the spiral k-space signal. Here, the k-space signal is simulated piecewise by generating a series of signals corresponding to timepoints along the spiral path and combining these (Figure 60).

First the T_2^* map ($T_2^*[x, y]$) is used to create a series of decayed image precursors

$$I_{PC}[x, y, t] = e^{-t/T_2^*[x, y]} \quad 44$$

for a range of times, t , spanning the duration of the spiral readout. Each of these image precursors is multiplied with every DWI in the artificial DT-CMR dataset,

$$I_{decay}[x, y, t, d] = I_{PC}[x, y, t] * DWI[x, y, d] \quad 45$$

creating a series of images I_{decay} that show the decay pattern for one point in time of the spiral readout. Using an inverse NUFFT, these images are transformed to lie along spiral k-space paths $k_{spiral}[k, t, d]$

$$k_{spiral}[k, t, d] = NUFFT(I_{decay}[x, y, t, d], k_{trajectory}[k_x, k_y]) \quad 46$$

before combining the data for the multiple time points to form the final signal. The combination selects the first datapoint for the final spiral path from the first timepoint, $t=1$, then picks the second datapoint from $t=2$ resulting ultimately in a k-space spiral signal that includes the effects of the spatially-varying T_2^* decay.

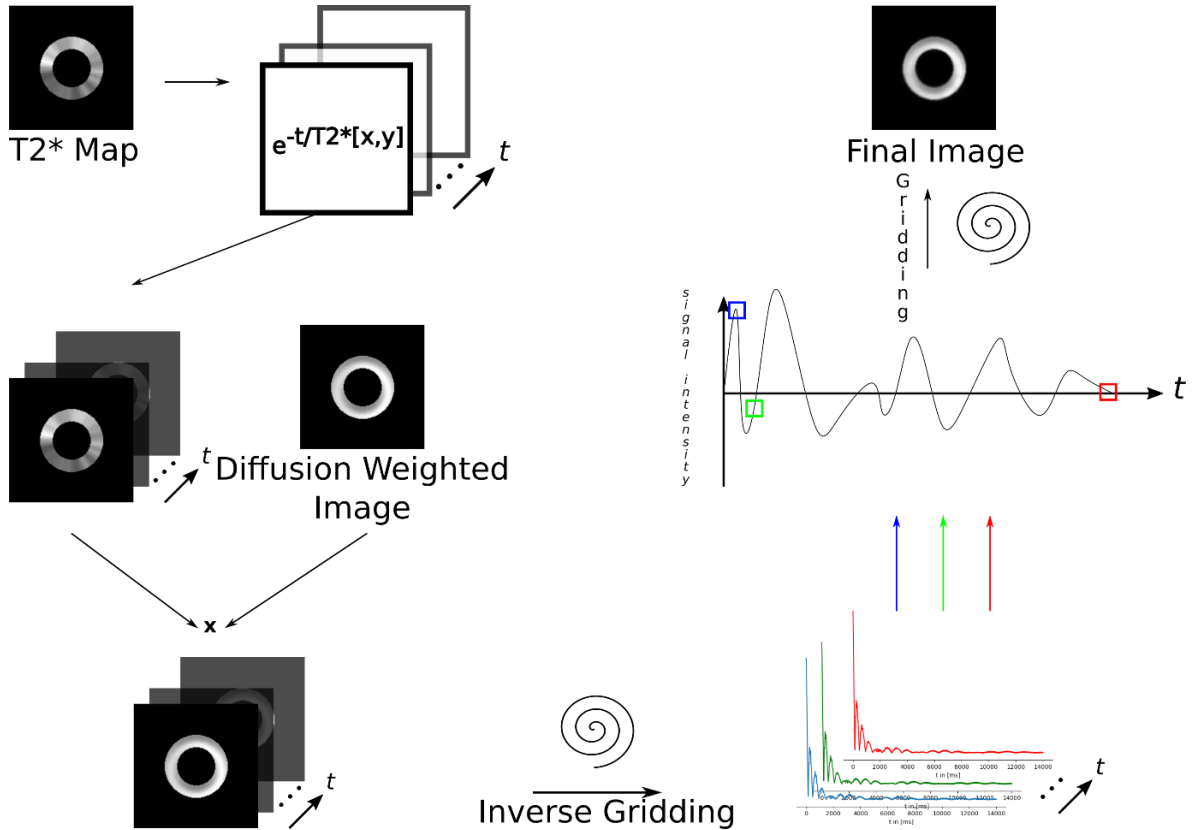


Figure 60: Simulation of spatially non uniform T_2^* decay. Starting with a T_2^* map and the DWIs a series of “decayed images” are calculated for each DWI based on the T_2^* related decay at each pixel for each time point along the spiral. Then the inverse NUFFT is performed and the final spiral k-space signal is formed by selecting the datapoints from the series of decayed spiral k-space signals based on the corresponding time along the final spiral path.

Field inhomogeneities were simulated using an inverse frequency segmented reconstruction [285] as shown in Figure 61. This simulation is based on the linearity of the Fourier transform. Each input pixel is separately and singly transferred to its same location in an otherwise empty matrix of the same size. Then through inverse NUFFT the contribution of this single pixel to the spiral k-space signal is calculated. The spiral k-space data corresponding to each single pixel is modified using the phase change corresponding the off-resonance frequency at the corresponding location in the field map. The final step is to sum all the individual spiral k-space paths together and thereby create a signal that encodes spatially-varying field inhomogeneities.

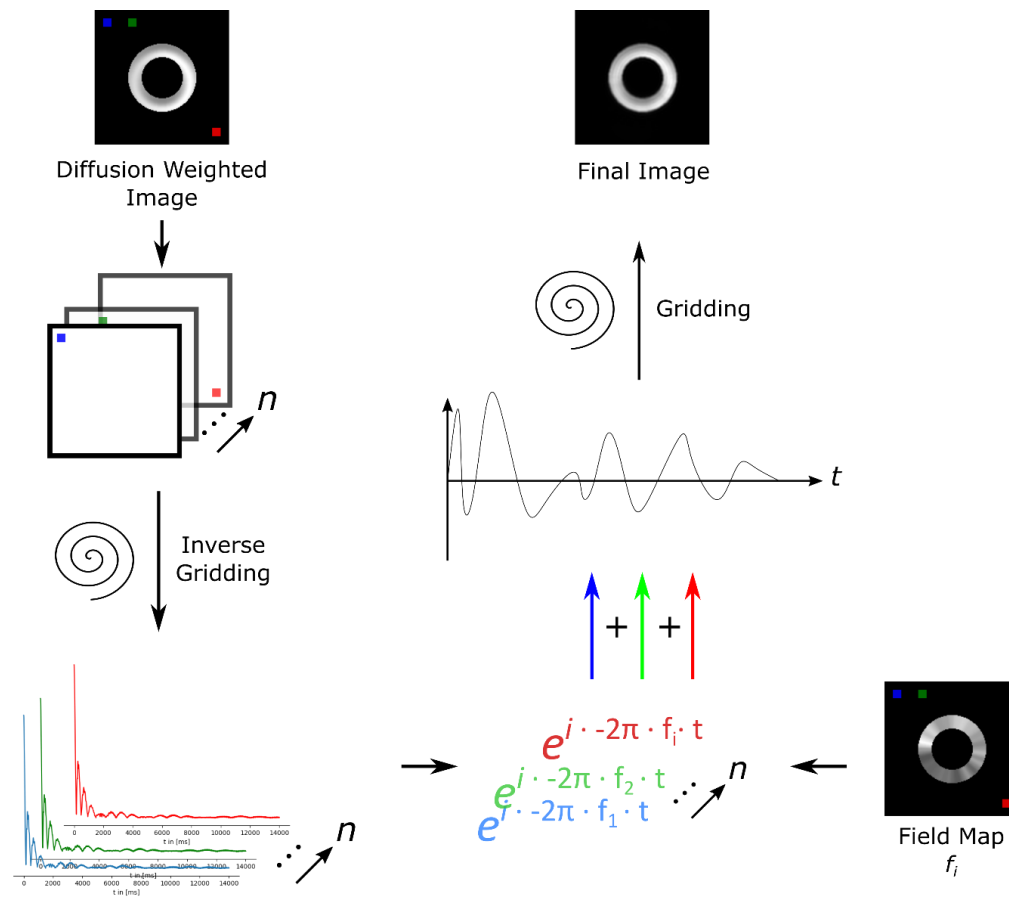


Figure 61: Simulation of spatially non uniform field inhomogeneities. Every pixel of the input image is copied into a separate zero filled matrix of the same size, creating a batch of n images. Here only three such pixels are shown as blue, green and red. Each of these images is then separately processed with an inverse NUFFT operation to generate n spiral k-space datasets. Using the off-resonance value from the corresponding pixel in a field map it is possible to modify the signal phase of the spiral k-space data based on a spatially constant off-resonance correction term $c = e^{j \cdot -2\pi \cdot f_i \cdot t}$. Next the n spiral k-space data sets are summed, resulting in one spiral k-space data set that includes the effects of spatially-varying field inhomogeneities.

To include the effects of both off-resonance and T_2^* decay it is possible to combine the two processes above.

9.2.4 Correcting for Spatially-Varying T_2^* & Off-Resonance

We recall here the last line of section 9.1, that this work ultimately aims to examine the effectiveness of the well-known correction methods for spatially variant T_2^* and off-resonance errors.

Therefore, to correct for the effects of T_2^* and off-resonance the segmented correction algorithm described in Chapter 7.2.3 is used. While the frequency segmented algorithm was developed for correcting spatially-varying off-resonance, we propose a novel alteration to allow for correction of spatially-varying T_2^* -related decay, as follows:

As shown in Figure 62 the spiral k-space data is replicated to produce n copies (same n as the n “bins” mentioned below). Each of these spiral k-space data copies is then corrected with a constant T_2^* correction term in a range spanning from the minimum T_2^* ($T_{2^*_{\min}}$) to the maximum T_2^* ($T_{2^*_{\max}}$) present in the T_2^* map. An NUFFT is used to create an image from the spiral k-space data in each copy. The pixel values of the T_2^* map are then binned into n bins, corresponding to the T_2^* values used in each of the n constant corrections. The final image is composed by pixel wise selection of the data based on the binned T_2^* map.

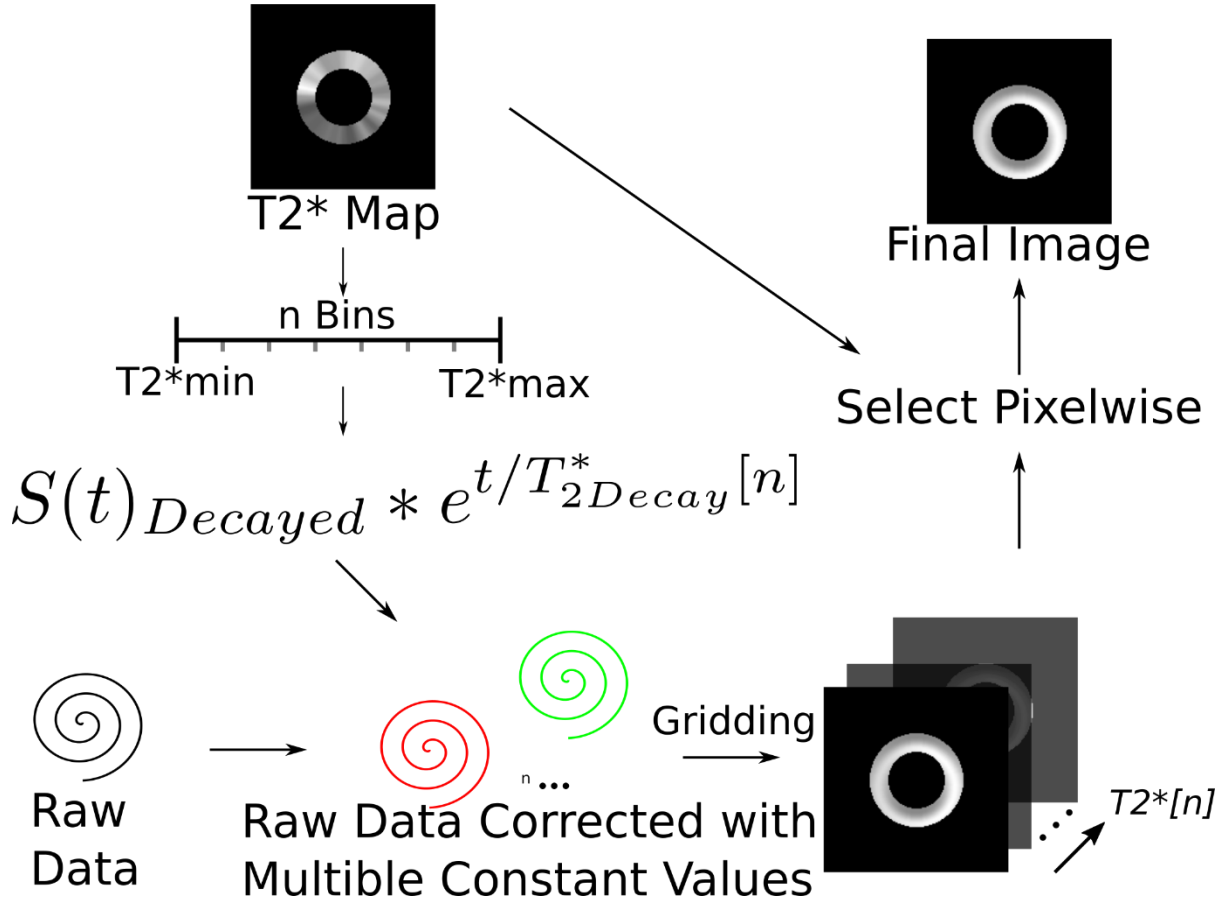


Figure 62: Proposed spatially-varying $T2^*$ correction. Starting with a measured $T2^*$ map a number of n separate bins is created. For each of these bins a spatially constant correction of the data is executed. The set of values used to correct is an equally spaced range from the minimum to the maximum values within the $T2^*$ map. After NUFFT of the constant $T2^*$ corrected copies of the spiral k -space data, a pixel wise data selection is performed to copy the data corrected with the $T2^*$ value closest to the corresponding value in the $T2^*$ map into the final image.

A correction for both off-resonance and $T2^*$ decay effects is possible. To do this, a matrix of corrected images is generated, in which each row is corrected with a constant frequency and each column with a constant $T2^*$ value. As a result, there is a squared relationship in terms of computational cost compared to a single spatial varying correction.

9.2.5 Post Processing

All simulated DT-CMR data was processed with the same purpose-built MATLAB tool described in Chapter 10.4.1.8. As the ground truth tensor and DT-CMR parameters are known, parameters such as pixel-wise Root Mean Square Error (RMSE) can be calculated. Mean error is also calculated by subtracting the respective mean myocardial value of a given parameter from the ground truth value (a positive value represents an overestimation of the parameter). For analysing image sharpness, the process described by Ahmad et al. [293] was implemented. Using an intensity profile p drawn perpendicular to the epicardial wall a sigmoid function f_{sigmoid} can be fitted by means of linear least square fitting to the resulting profile.

$$f_{\text{sigmoid}}(p) = \frac{a_1}{1 + 10^{s(a_0 - p)}} + a_2 \quad 47$$

with a_0 the centre of the sigmoid location, a_1 the vertical range and a_2 the vertical offset. The steepness parameter s of the sigmoid function is then used as measurement for sharpness. Here the perpendicular profiles were drawn on an interpolated (factor 2 zero filling in k-space) version of the diffusion weighted image. The intensity profiles were created by transforming the pixel coordinates to radial coordinates with the centre of the annulus as origin and creating radial lines out from the centre. Along each radial line a limited range of p starting outside epicardial border of the annulus and ending inside the myocardium was extracted.

9.2.6 Experiments

Validation of the Simulation and Correction Methods

To test the implementation of the proposed simulation and correction methods, both the T_2^* and off-resonance simulations were initially performed with a range of constant T_2^* and off-resonance values. This was achieved by filling every pixel in the parameter map (T_2^* and off-resonance) with the same value, while keeping every other aspect of the simulations the same.

Optimal number of bins

Optimising, for each of the T_2^* and off-resonance frequency corrections, the number of bins for both correction strategies is important to maximise the effectiveness of the correction, while minimising the computational cost. For these simulations, either the realistic T_2^* or off-resonance maps (Figure 59) were used and the following parameters were used in the simulation of imaging: SNR =15 based on *in vivo* studies [49], [179], resolution=2x2 mm², 2 spiral interleaves, FOV=190x190 mm² at the centre of k-space, which then linearly reduced to 110x110mm² at the outermost sampled k-space radius and spiral readout length=14.4 ms

(assuming a sampling dwell time of 2.5 μ s). Then each dataset was corrected 5 times with the corresponding spatially-varying correction algorithm (T_2^* or off-resonance) each time using a different number of off-resonance or T_2^* bins [3,6,9,12,15] covering the minimum to maximum values of off-resonance or T_2^* present in the maps.

Effectiveness of spatially-varying corrections

To determine the effectiveness of both spatially-varying correction methods (off-resonance and T_2^*), simulations for every off-resonance and T_2^* map (Figure 59) were repeated 30 times with different noise seed values (which allowed the assessment of the variability of the results). The SNR and spiral parameters were defined as above and the number of T_2^* or off-resonance was set to bins=9. Each simulation was then corrected with the corresponding method and all data was processed with the DT-CMR analysis software. Sharpness measures were obtained for the circumferentially varying maps (Figure 59 c, d) at every 5° along the simulated myocardial epicardial border, while for the maps based on real data (Figure 59 a, b) sharpness measurements were performed in three locations corresponding to regions that showed the most extreme off-resonance/ T_2^* decay patterns.

The effect of SNR on T_2^* and off-resonance correction

The impact of the image SNR on the efficacy of the correction was tested by running a range of simulations with varying SNR=[5,10,15,20] using the circumferential varying maps (c and d) with 30 simulation repeats and spiral parameters as above. For the correction 9 bins were used.

9.3 Results

9.3.1 Validation of the Simulation and Correction Methods

Figure 63 shows diffusion weighted images from the initial tests of the simulation using spatially constant T_2^* and off-resonance. The ground truth images in the left column of course are identical each time and are repeated to assist in visual comparison.

All uncorrected images demonstrate blurring when compared to the corresponding ground truth. This is most visible for the highest off-resonance frequency and the lowest T_2^* value. The corrected images do not appear blurred, however in the corrected $T_2^*=10$ ms and 15 ms simulations, the images appear noisier after correction.

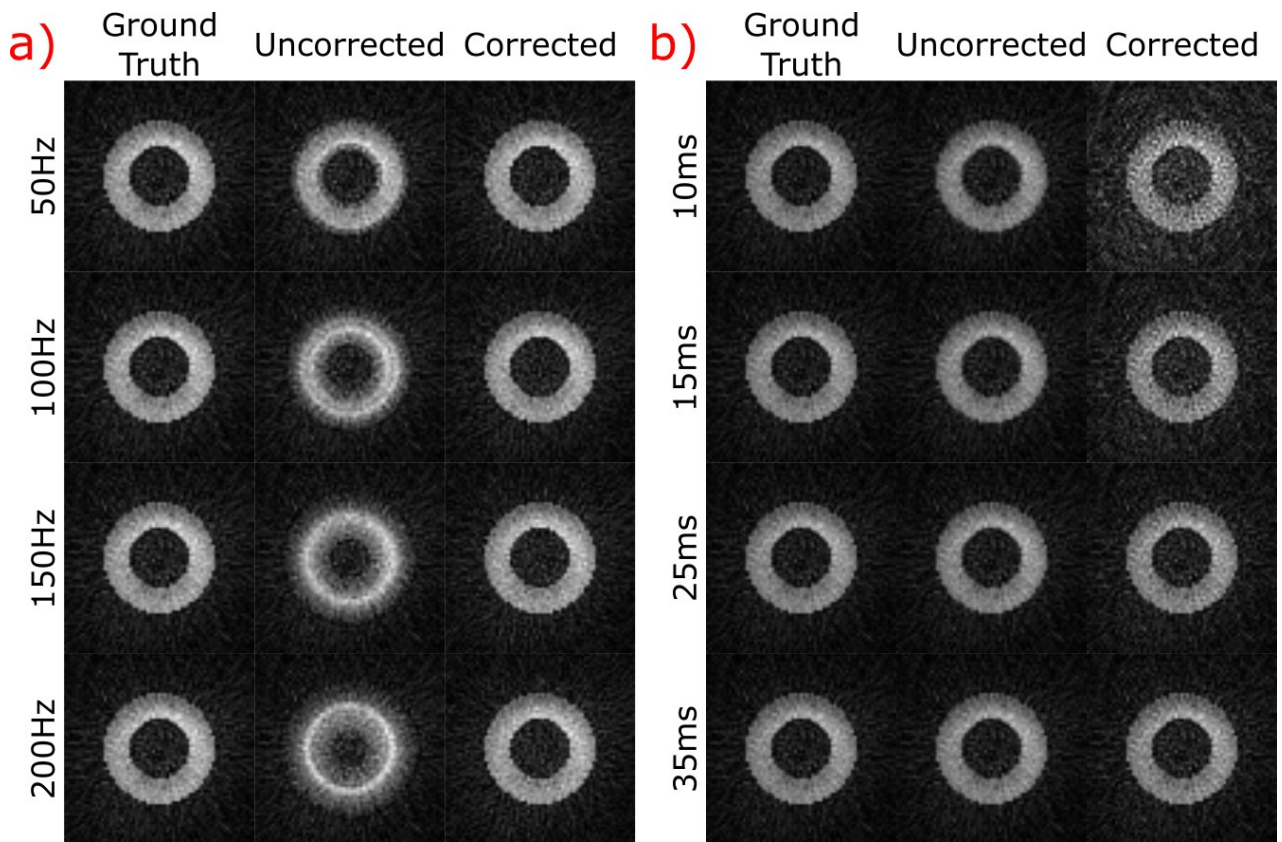


Figure 63: Diffusion weighted images of the ground truth, uncorrected (showing the effects of T_2^* or off-resonance) and spatially-varying corrected datasets. For these initial test simulations every pixel of the spatially-varying T_2^* or off-resonance maps is filled with a constant value. a) shows the off-resonance simulations with the simulated off-resonance value shown on the left, while b) shows the T_2^* simulations with the simulated T_2^* value shown on the left.

9.3.2 Optimal Number of Bins

Figure 64 shows the RMSE of the myocardial pixels for HA, E2A, MD, FA and the averaged diffusion weighted images plotted with the number off-resonance and T2* bins. In general, the RMSE in all parameters reduces with an increasing number of bins. The reduction in error appears to plateau or stop after the number of bins reaches 9. Figure 65 shows an exemplary DWI corrected using each of the different numbers of bins. There is a visible decrease in blurring from 3 bins to 6 bins. Based on these results, 9 bins were used in all subsequent reconstructions.

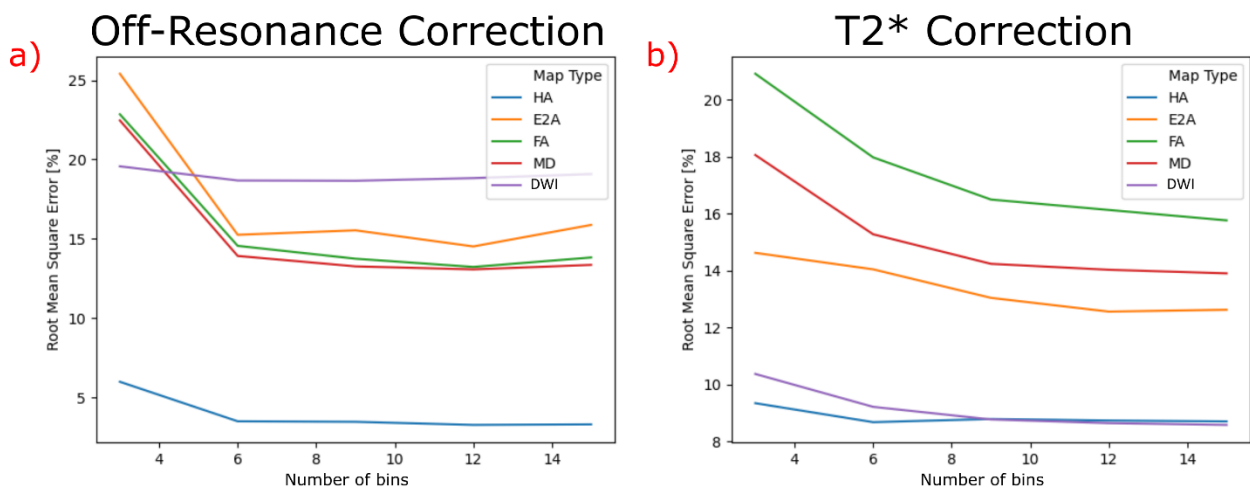


Figure 64: Results of simulations using realistic off-resonance (a) and T2*(b) maps for multiple number of bins. The x axis displays the number of bins used for the correction, while the y-axis displays the average myocardial RMSE as a percentage of the ground truth value. Errors are shown for HA, secondary eigenvector angulation (E2A), Fractional Anisotropy (FA), mean diffusivity (MD) and the averaged $b=600 \text{ s/mm}^2$ diffusion weighted image intensity (DWI).

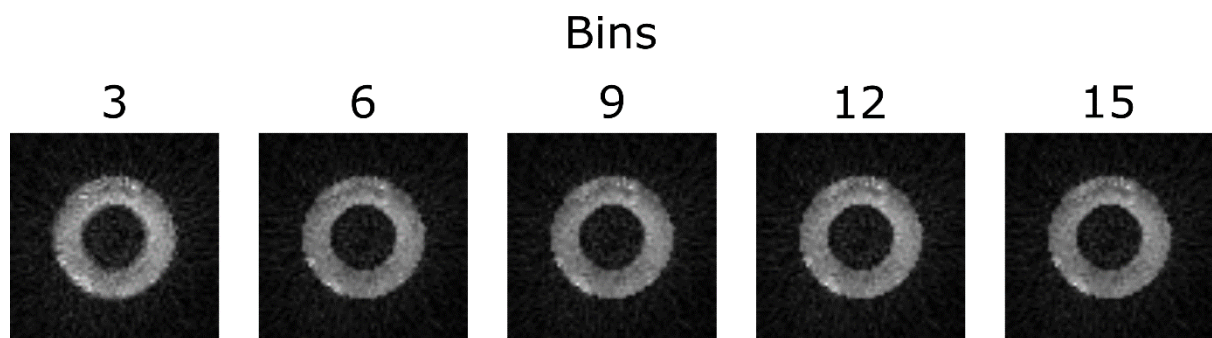


Figure 65: Off-resonance corrected DWI reconstructed with an increasing number of off-resonance bins.

9.3.3 Effectiveness of Spatial Varying Corrections

Figure 66 and Figure 67 show sharpness measurements from both the circumferential varying simulation and the realistic *in vivo* simulations. The reduced sharpness is visible in all uncorrected images (both off-resonance and T_2^*). The spatially-varying corrections perform well for both circumferential varying T_2^* and off-resonance, with sharpness curves approaching the ground truth results. The constant correction in the off-resonance example does not affect the sharpness as the mean myocardial off-resonance in this example is 0 Hz. In the T_2^* case the constant correction provides sharpness results close to the ground truth in a narrow central range (where the T_2^* in the map is close to the mean value used to correct) but results in over sharpened results or under sharpened results on either side of this area. In the circumferential off-resonance example (Figure 59 c) the sharp change of +100 Hz to -100 Hz results in an image region in which the correction is not able to fully recover the signal and instead results in a bright patch at 3 o'clock.

For the realistic maps (Figure 67) the data corrected with both spatially-varying corrections has the highest sharpness values when compared to the ground truth. However, the overall performance is poorer than in the circumferential varying simulations. The constant correction in the tests using the realistic maps also results in an increased sharpness when compared to the uncorrected diffusion weighted images.

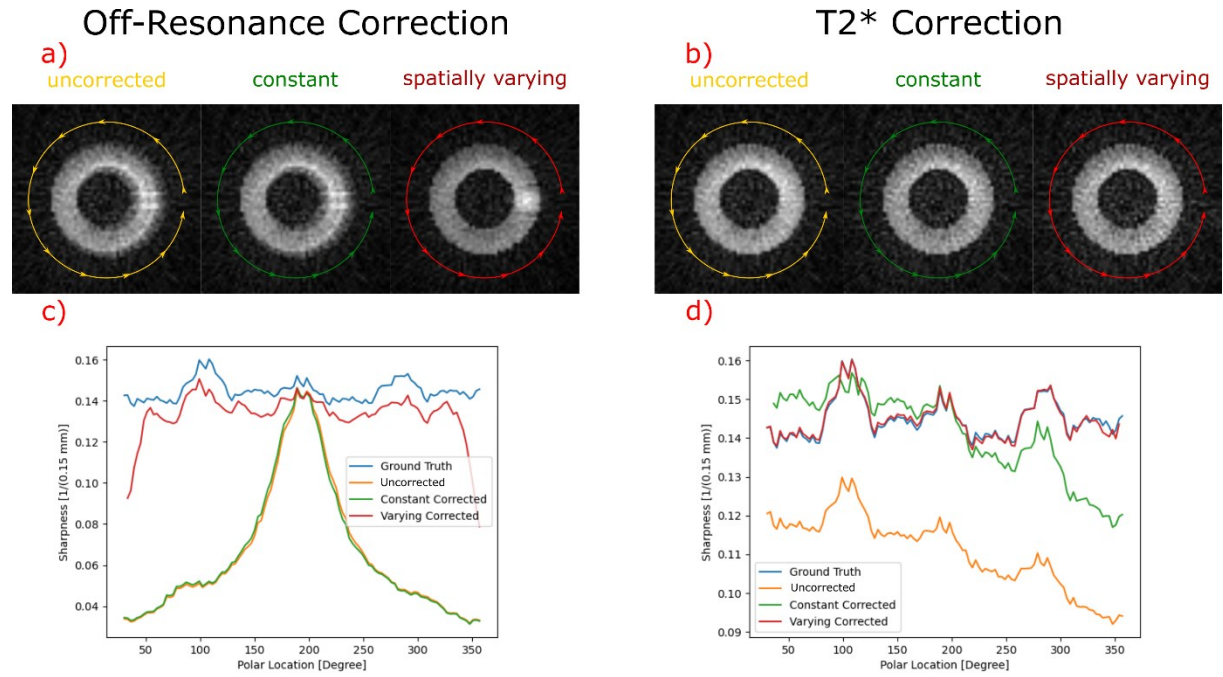
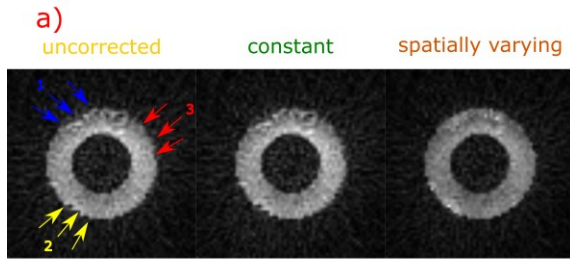


Figure 66: Sharpness measures of 1 of the simulated 30 repetitions of the circumferentially varying off-resonance (a, c) and T2*(b, d) maps. a) and b) show one average of the $b=600 \text{ s/mm}^2$ diffusion weighted images for the uncorrected data, the constant corrected data, and the spatially-varying corrected data. In each image the profile along which sharpness measures were taken is shown using arrows. c) and d) show the mean sharpness measurements for the ground truth (blue), uncorrected (yellow), constant corrected (green) and varying corrected (red). Here the x axis denotes the circumferential position around the epicardium, starting at the centre right (3 o'clock) for 0° and rotating anticlockwise as displayed in a & b.

Off-Resonance Correction



T2* Correction

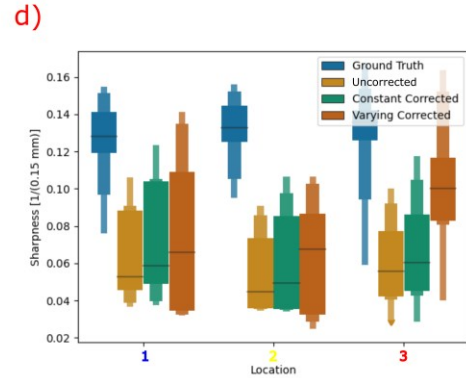
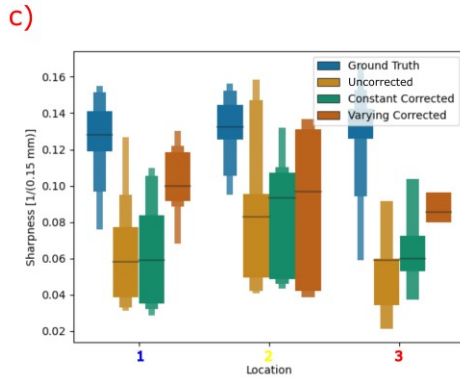
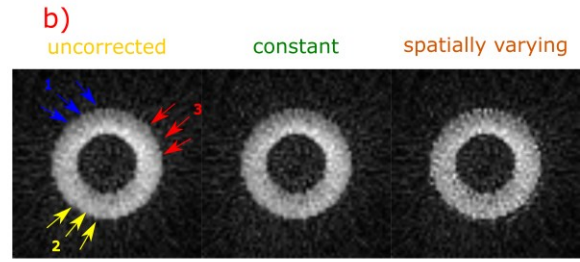


Figure 67: Sharpness measures of the simulated 30 repetitions of the realistic field (1) and T2*(2) maps. a) shows one average of the $b=600 \text{ s/mm}^2$ diffusion weighted image for the uncorrected data, the constant corrected data and the spatially-varying corrected data. The three locations where sharpness measures were obtained are highlighted with arrows. c) and d) show boxplots of the sharpness measures (larger number of quantiles, 6, than normal boxplots), where the three locations are shown on the x axis and the sharpness on the y-axis. For each location the ground truth (blue), uncorrected (yellow), constant corrected (green) and varying corrected (orange) are shown.

Further results on the effectiveness of spatially-varying corrections are presented next:

Figure 68-72 show the results of both the circumferential varying and realistic spatially-varying T2* and off-resonance simulations. Three different parameters (mean difference or bias, RMSE and standard deviation of the respective parameter in the myocardium) are shown for a range of DT-CMR parameters and for RMSE and SD in the diffusion weighted image data. The following sections summarise specific aspects of these results:

Off-resonance correction

The mean difference (bias) is reduced when using the spatially-varying off-resonance correction compared to both the uncorrected and constant corrected cases for all parameters evaluated apart from E2A and FA in the real field map examples, where there is a very small increase in the absolute bias (Figure 68.A and Figure 69.A).

The RMSE shows a substantial reduction after spatially-varying off-resonance correction for HA for both off-resonance maps and for the DWI when the circumferentially varying off-resonance map is used, while in all other parameters tested RMSE is increased (Figure 68.b and Figure 69.b).

Figure 68.c and Figure 69.c show that the standard deviation in the maps is reduced for the spatially off-resonance correction when compared to the other categories.

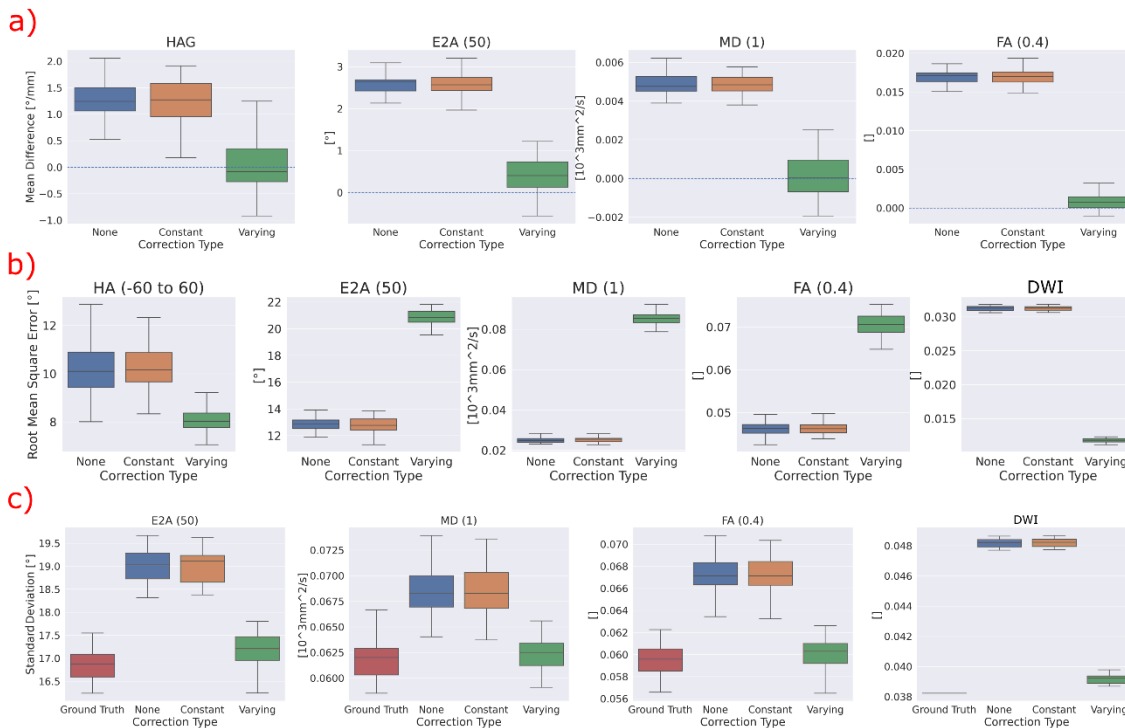


Figure 68: Results of simulations based on the circumferential off-resonance map. The box plots shown are generated from all 30 varying noise seed repetitions. In the title for HA, E2A, MD and FA the number in brackets represents the expected mean value in the myocardium a) Mean difference for HAG, E2A, MD and FA. Measurements are calculated for no correction, constant correction, and spatially-varying correction by subtracting the respective mean myocardial value from the ground truth value (a positive value represents an underestimation of the parameter). b) Pixelwise RMSE for HA, E2A, MD, FA and DWI. Measurements are calculated for no correction, constant correction, and spatially-varying correction by taking the respective average myocardial RMSE value as single data point. c) Myocardial standard deviation for E2A, MD, FA and DWI. Measurements are calculated for ground truth, no correction, constant correction, and spatially-varying correction.

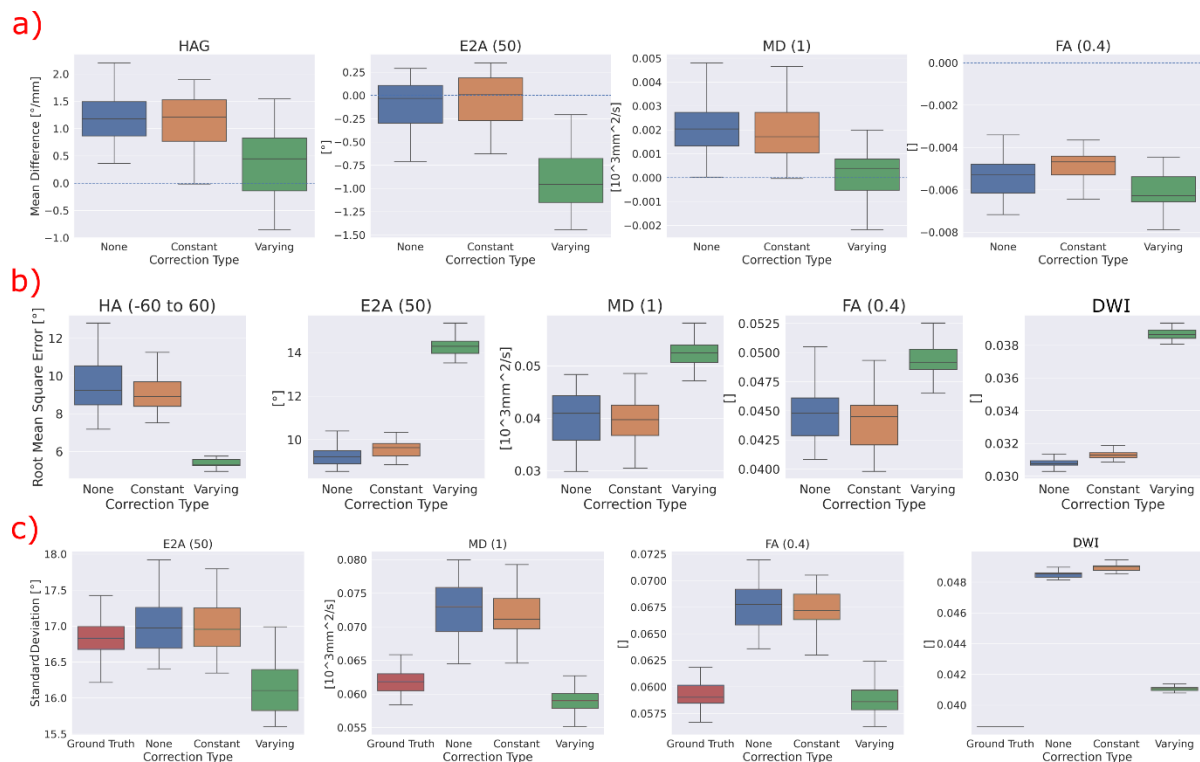


Figure 69: Results of simulations based on the realistic off-resonance map. For detailed description see Figure 68

T₂* correction

Figure 70.a and Figure 71.a show that the absolute value of the mean difference obtained after applying the constant and spatially-varying T₂* corrections, is reduced for E2A and MD; however, the mean difference increased for all other output maps from DT-CMR.

In Figure 70.b and Figure 71.b, the RMSE was unchanged by constant T₂* correction but it shows an increase in all spatially-varying T₂* corrected cases.

In Figure 70.c and Figure 71.c, the standard deviation for the spatially-varying correction of T₂* shows a significant increase in nearly all plots.

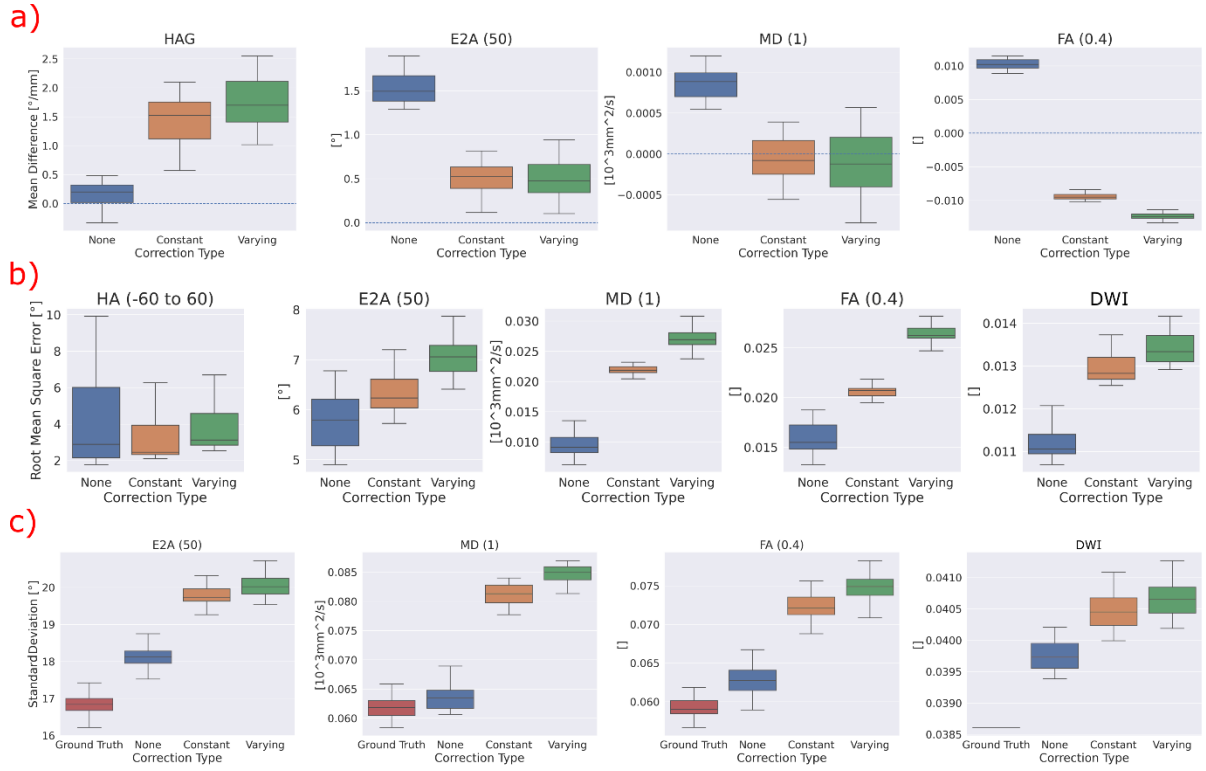


Figure 70: Results of simulations based on the circumferential T_2^* map. For detailed description see Figure 68

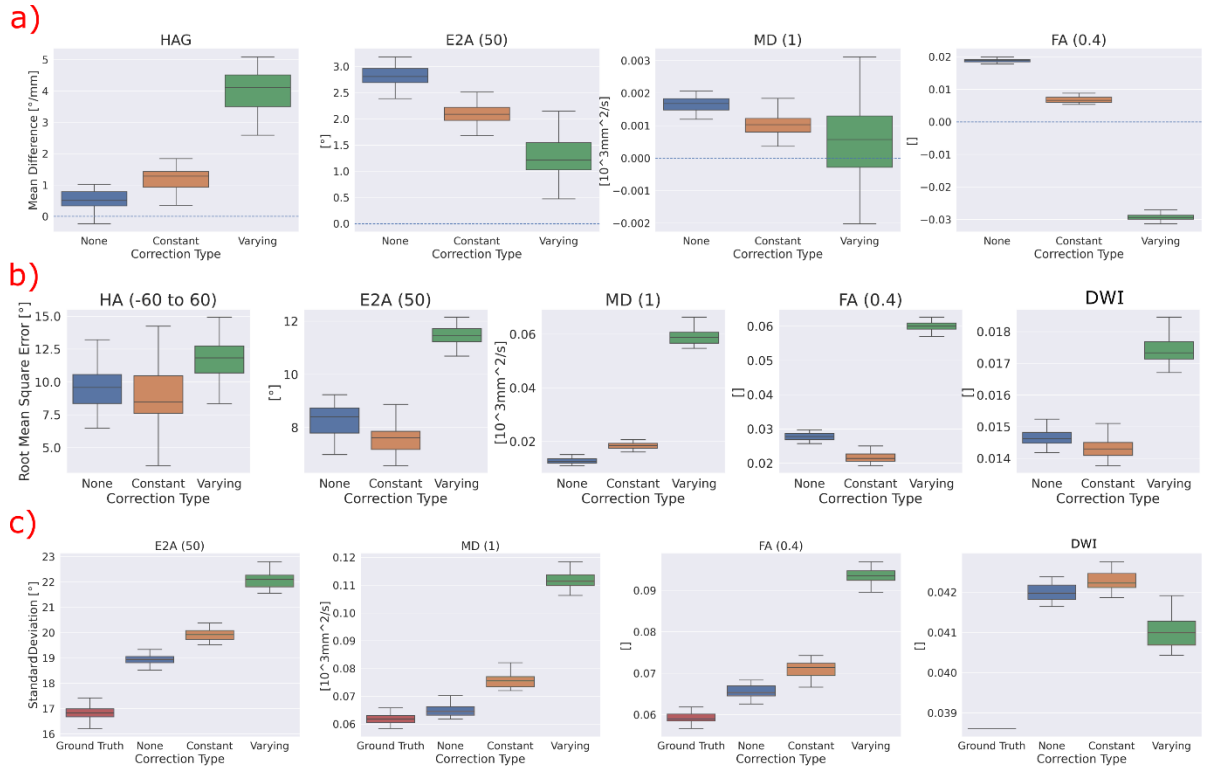


Figure 71: Results of simulations based on the real T_2^* map. For detailed description see Figure 68

9.3.4 The Effect of SNR on T2* and Off-Resonance Correction

Figure 72 (below) shows both the RMSE of the DT-CMR parameters, as well as the sharpness measures, for a set of simulations with SNR=[5, 10, 15, 20]. The overall trend for both spatially-varying off-resonance correction and T2* correction is for decreasing RMSE as SNR increases (Figure 72 a, b).

For the sharpness measures shown in Figure 72.c for off-resonance and in Figure 72.d for T2*, in general, the spatially-varying corrections result in sharpness measures closer to the ground truth as SNR increases. The constant correction was ineffective in the off-resonance results, as the mean myocardial value for this example is 0 Hz, while the constant T2* correction showed lower sharpening effects compared to the spatially-varying one.

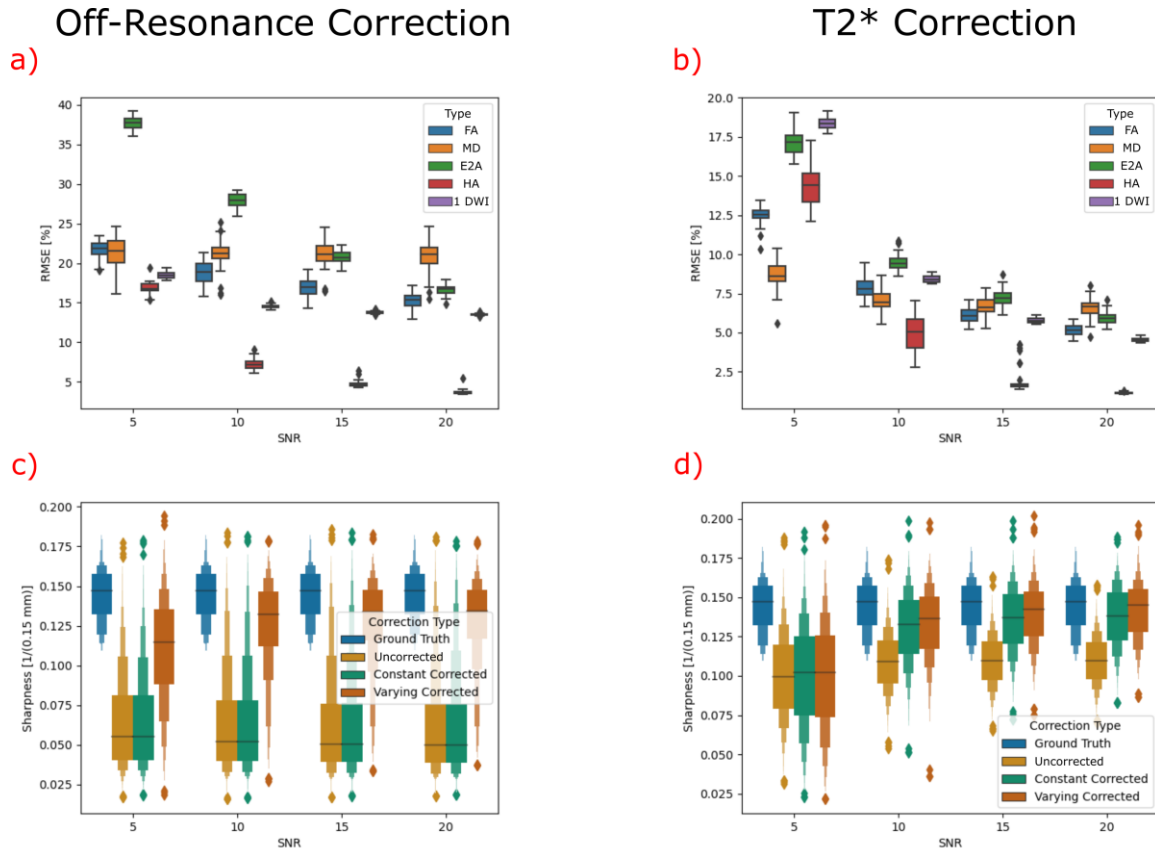


Figure 72: RMSE of DT-CMR parameters and DWI intensity after varying correction and DWI sharpness for different SNR levels= [5,10,15,20] in the circumferential varying simulations. In each case, boxplots are created from the 30 noise seed repetitions. a) and b) RMSE for FA, MD, E2A, HA and one DWI for the varying corrected data. c) off-resonance and d) T2* corrected results of sharpness measures for the ground truth, uncorrected, constant corrected and spatially-varying corrected datasets.

9.4 Discussion

The work in this chapter has shown the successful implementation of a computational simulation framework for spiral DT-CMR. It was shown that both spatially-varying T_2^* decay and off-resonance effects can be simulated and corrected for using the frequency segmented correction [285]. In addition, a novel spatially-varying segmented T_2^* correction, analogous to the frequency segmented correction was introduced.

The optimal bin number (n) for both correction methods was chosen as 9. A small number of bins (3) results in large errors (up to 10 %) in the final DT-CMR results and the error reduction when the number of bins > 9 is less than 1 %. Equation 41 would have resulted in the use of 12 bins. Considering the computational cost grows as a product of n for a single correction, it can be argued that any further increase in $9 < n$ is not required.

Both spatial correction methods presented here increase the sharpness of the diffusion weighted images. Areas of high off-resonance frequency show substantial improvement when compared to the uncorrected images. The same is true for the low T_2^* range (10-15 ms) in the circumferentially varying case. The constant correction only effectively corrects the image where the off-resonance or T_2^* is close to the mean value (which was used to correct). At the extreme values in the off-resonance case (approx. ± 100 Hz in locations 1 and 3) and in the T_2^* case (lowest value ~ 10 ms in location 1 Figure 67), the improved performance of the spatially-varying correction is most apparent. However, at sharply localised changes in frequency (e.g., the -100 Hz to +100 Hz edge in the circumferentially varying field map), there are large errors in the spatially-varying correction data. This is due to the artifact from highly-off-resonant pixels spreading beyond the pixel itself into adjacent pixels, which are corrected with different frequencies in regions with such a sharp localised error.

The error metrics in Figure 68 and Figure 69 show that the spatially-variant off-resonance correction leads to mean LV DT-CMR parameters closer to the ground truth compared to the uncorrected or constant corrected data. Similarly, the metrics suggest that the noise is not enhanced in the DT-CMR results after spatially-varying correction for off-resonance, as the standard deviation and the RMSE in the diffusion weighted images is lower than in the uncorrected and constant corrected datasets. While an increase in the RMSE in DT-CMR maps using the real field maps is apparent, this increase is small relative to the typical values of the DT-CMR parameters.

A different behaviour is observed in the error metrics after T_2^* correction (Figure 70 and Figure 71). Here a clear noise enhancement is evident after spatially-varying correction with substantially elevated RMSE and standard deviation in most cases compared to the uncorrected data. The only exception to these poorer results with spatially-varying T_2^* correction is for the standard deviation in the diffusion weighted images using the real T_2^* maps.

The noise enhancement of the T_2^* correction was also evident when investigating the correction methods at varying SNR levels (Figure 72). The spatially-varying off-resonance correction has a sharpening effect across the entire range of SNR (Figure 72.c), while the effectiveness of the T_2^* correction is lower when SNR is reduced (Figure 72.d). This noise enhancement of the T_2^* correction is explained by the suppression of signal at higher spatial frequencies due to T_2^* decay, while the level of noise stays constant. If now the higher spatial frequencies are enhanced in the correction, this will also increase the noise at higher spatial frequencies and so lead to reduced SNR.

9.5 Limitations

One of the main limitations of these simulation is that no investigation of the influence of the SNR or spatial resolution of the off-resonance and T_2^* maps was conducted. Considering that these are at the heart of the binning process, it is expected that inaccuracies or noise in these maps will have a significant impact on the final corrected DWI quality.

Further improvements to the simulation study presented here would be the investigation of different widths of the simulated annulus. In combination with different spatial resolutions (in both the maps and DWI) this could give an indication of the performance of the correction methods in difficult anatomies, such as the RV free wall.

The investigation of combining both spatial correction methods was not performed in the presented work. However, the noise enhancement as a consequence of the T_2^* correction and resultant reduction in the accuracy and precision of the DT-CMR means that T_2^* correction was not used in the rest of the work in this thesis, making an investigation of the combined correction redundant for the moment.

Interpolation between bins in the frequency segmented off-resonance correction is often used to avoid sharp transitions where the B_0 field map moves between bins. The presented simulations did not include this optimisation. While it can be argued that the interpolation would only improve the results future simulations should make use of this.

Finally, this simulation framework could be used to evaluate neural network-based approaches for off-resonance and T_2^* decay corrections as recently demonstrated in [294]. While these novel correction techniques seem unlikely to result in superior results when the off-resonance or T_2^* maps are good quality, they may show improvements in areas where the accompanying off-resonance map is noisy. Once trained, these networks also could significantly reduce computational cost, particularly in the combined correction case and would save a little scan time by avoiding the acquisition of field and/or T_2^* maps.

9.6 Conclusion

While this chapter has shown that the both the frequency segmented off-resonance and novel spatially-varying T_2^* correction result in sharper DWI, only the frequency segmented off-resonance method is recommended for spiral STEAM DT-CMR *in vivo*. Much time is spent to acquire multiple averages of a single slice to boost SNR in DT-CMR and the application of corrections that have a side-effect of reduced SNR cannot be advised. However, in future if higher SNR methods are used in combination with a long spiral readout, such as SE spiral DT-CMR, the spatially-varying T_2^* correction method proposed here could play an important role in mitigating blurring effects in addition to the frequency segmented off-resonance correction.

This work was presented on the Annual Meeting of the International Society for Magnetic Resonance in Medicine 2020 with the Abstract No. 5584 and on the Annual Meeting of the Society for Cardiovascular Magnetic Resonance 2020 with the program number P267.

10 Technical Development of Spiral DT-CMR Sequences

The following chapter covers all the technical development steps taken in the spiral DT-CMR sequence.

All data in this thesis was acquired using a 3T Vida system (Siemens Healthineers, Erlangen, Germany). The system was fitted with a gradient system that according to specification on each independent axis reaches a maximal amplitude of $G_{\max}=55$ mT/m and a maximal slew rate of 180 mT/m/ms. All *in vivo* experiments utilised the same 18 element anterior coil (Siemens Healthineers, Erlangen, Germany) and standard posterior spine array and or a 32-element head and neck coil (Siemens Healthineers, Erlangen, Germany) for phantom / *ex vivo* acquisitions.

10.1 Spiral Trajectory

The trajectories used in this thesis were calculated using a modified version of the variable density spiral waveform design from Brian Hargreaves [264]. Similar to other spiral design algorithms [267], [268], [295], the maximal slew rate, gradient amplitude and readout duration are the main constraints when designing a spiral for a given spatial resolution and FOV. Additionally, a polynomial function that allows manipulation of the FOV with increasing k-space radius can be supplied to generate a variable density sampling pattern. The spiral design algorithm was incorporated directly into the Siemens Integrated Development Environment for Applications (IDEA) framework and the Syngo Graphical User Interface (GUI), allowing for calculation of the spiral trajectory on the scanner. This implementation has the advantage over predefined calculation approaches where the gradients are calculated off-line in that the spiral parameters can be adjusted between sequence repeats, leading to quicker implementation/testing cycles.

In this work, a custom check was also implemented that transfers a spiral gradient design into the scanner system and checks the waveform against physical gradient hardware limits and the Peripheral Nerve Stimulation (PNS) model. If a design is chosen that cannot be executed on the scanner, the maximum slew rate and gradient amplitude are reduced by 1% and the new spiral design is transferred to the scanner for testing again. The aim is to avoid floating point conversion errors causing limits to be marginally broken.

Several sets of slew rate and gradient amplitude parameters for spirals designs were empirically tested in a range of typical *in vivo* imaging planes in a phantom. The spirals were run as part of the STEAM DT-CMR sequence described later in this chapter. Here the maximum prescribed slew rate to the spiral design algorithm that could be successfully run in all slice orientations was a of 150 mT/m/ms and a maximum gradient amplitude of 35 mT/m. These parameters resulted in a maximum gradient amplitude of 30 mT/m per gradient axis and a maximum slew rate of 156 mT/m/ms per axis in the spiral gradient waveforms. These values were used in all following work.

10.2 Sequence Development

10.2.1 In Vivo

For all *in vivo* DT-CMR acquisitions, a two interleave spiral design is used within a diffusion tensor STEAM sequence as introduced in [244]. Each spiral interleave is acquired in a separate stimulated echo, each of which runs over two cardiac cycles. Therefore, to keep breath-hold times in an acceptable range, a single average of 6 diffusion directions at one b value is split over two breath holds. Each breath hold consists of up to 18 RR intervals (9 stimulated echoes: 3 used for preparation scans and 6 used to acquire 2 interleaves in 3 diffusion encoding directions, as shown in Figure 73.A). The first stimulated echo was used to acquire data for coil sensitivity profiles, then the second and third stimulated echoes (RR-intervals 3-6) were used to acquire data for the B_0 field (off-resonance) maps.

In contrast to previous studies [244] a 1-2-1 binomial water excitation pulse [296] was used for the first 90° RF pulse to avoid exciting fat signal rather than using an additional fat saturation pulse (Figure 73.B). During initial testing, binomial water excitation was found to result in fewer artefacts in the spiral STEAM DT-CMR images than chemically selective fat saturation pulses. During each of the three RF pulses that create the stimulated echo a slice selective gradient $G_{\text{selective}(x, y, z)}$ is played out. In contrast to DT-CMR EPI sequences the FOV is reduced along both in-plane axes, as spiral imaging can take full advantage of a reduced FOV in two dimensions by either reducing the readout length or acquiring higher resolution data in the same duration. In both cardiac cycles of each stimulated echo, the diffusion gradients are run at the same time $T_{R\text{-Diff}}$ after the R wave and with the same gradient amplitude G and duration δ . The 6 diffusion encoding directions are based on sampling the corners of a cube in the scanner (rather than imaging plane) coordinate system (x, y, z) : $\sqrt{2}/2 * (0, -1, -1), (0, -1, 1), (-1, 0, 1), (-1, 0, -1), (-1, 1, 0)$ and $(-1, -1, 0)$. The time between the start of the first and the second diffusion gradient within one STEAM acquisition is denoted as the diffusion time Δ . The time between the second and third RF pulse is known as T_M and denotes the time during which the signal is stored along M_z , thus decaying according to T_1 . Based on the b value required, G and δ are altered (Section 4.2) assuming that the RR-interval, and therefore $\Delta=1000$ ms for *in vivo* scans. The heart rate dependence of b via Δ is accounted for in the calculation of the diffusion tensor, see Section 4.2. For *ex vivo* scans, the b-value is calculated based on the Δ used. For all *in vivo* acquisitions, a pair of b-values were used: a high $b=600$ s/mm² and for reference a low $b=150$ s/mm². A special case applies for the preparation scans (coil sensitivity

and field map acquisitions) in which $b=84 \text{ s/mm}^2$ is used to spoil the non-stimulated echo signal pathways [297], [298].

For the CSM data, single interleave constant density spirals are used. The parameters for these are shown in Table 5.

Data is acquired for a B_0 field map over two stimulated echoes (4 RR-intervals) using the acquisition scheme shown in Figure 73.C. Two single-shot spirals are acquired at each stimulated echo. The second spiral in each stimulated echo (spirals 2 and 4) is acquired at the same time in the cardiac cycle and a constant delay after the 3rd RF pulse of the stimulated echo. The first spiral in the first stimulated echo (spiral 1) is timed to acquire the central k-space data at the stimulated echo. The first spiral in the second stimulated echo (spiral 2) is delayed by time T_{Delta} from the stimulated echo to allow time for off-resonance related phase-accumulation. After both spiral 1 and 3 a rephasing gradient is run to move back to the centre of k-space prior to the second spiral. Spirals 2 and 4 are used to compensate spirals 1 and 3 respectively for motion induced phase. The corrected data from spirals 1 and 3 can then be used to calculate the field map according to Chapter 7.2.3.

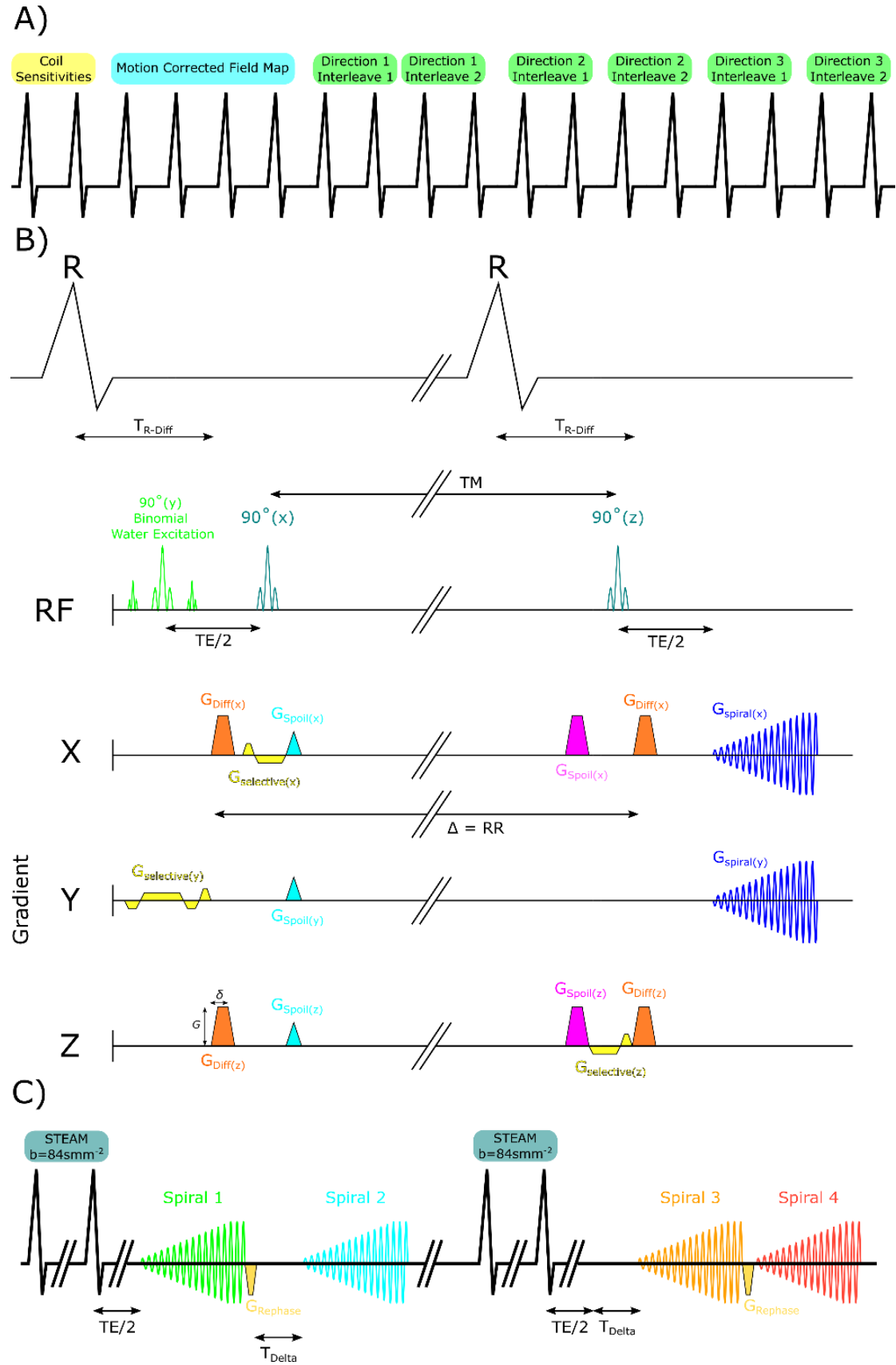


Figure 73: A schematic diagram of the spiral DT-CMR sequence used in vivo. A) Schematic showing a single DT-CMR breath-hold used to acquire 3 diffusion weighted images (3 diffusion encoding directions, 6 spiral interleaves). Of the total 18 RR intervals for each breath-hold, the first two are used to acquire coil sensitivity data, the next 4 for a Bo off-

resonance map, and the last 12 for the interleaved diffusion weighted data. B) The acquisition of a single diffusion encoded spiral interleave. During the first RR interval a binomial water excitation pulse (90°) is run with slice selection in one of the in-plane directions, followed by a diffusion gradient (G_{Diff}) and a 90° sinc RF pulse which is run along the other in-plane direction. After the second RF pulse the sequence waits for the next R-wave and then a delay time is run to ensure that the diffusion encoding (or spoiler gradients), G_{diff} , are run at the same time from the R-wave in both cardiac cycles. The third RF pulse is run before the second diffusion encoding gradient and the spiral readout is timed to ensure that the time between the peak of the first two RF pulses is the same as the time from the peak of the 3rd RF pulse to the acquisition of the k-space centre using the spiral readout. C) The sequence timings to acquire a field map with motion induced phase correction. After a STEAM preparation using spoiler gradients rather than diffusion encoding gradients a $4 \times 4 \text{ mm}^2$ spatial resolution single-shot constant-density spiral (Spiral 1) is run, followed by a rephasing gradient G_{Rephase} . Then after the time T_{Delta} a second single-shot constant density spiral (Spiral 2) with a resolution of 6 mm^2 is run. A similar scheme is used in the second stimulated echo (Spiral 3 and Spiral 4), with the first spiral (Spiral 3) of this pair now delayed by T_{Delta} to allow for off-resonance related dephasing, while the timing of the second spiral is maintained.

	<i>CSM</i>	<i>FM 1 + 3</i>	<i>FM 2 + 4</i>	<i>Main</i>
<i>Interleaves</i>	1	1	1	2
<i>Resolution [mm²]</i>	4x4	4x4	6x6	2x2
<i>Slice Thickness [mm]</i>	8	8	8	8
<i>Excited FOV [mm²]</i>	100x100	100x100	100x100	100x100
<i>FOV [mm²]</i>	110x110	110x110	110x110	Centre = 190x190 → Edge = 110x110
<i>Readout Duration [ms]</i>	8.6	8.6	4.7	14.4
<i>Dwell Time [μs]</i>	2.5	2.5	2.5	2.5
<i>TE [ms]</i>	14	FM 1 = 14, FM 3 = 17	26	14
<i>TR [ms]</i>	RR-Interval	RR-Interval	RR-Interval	RR-Interval
<i>Max Amplitude [mT/m]</i>	21.4	21	17.4	30.4
<i>Max Slew Rate [mT/m/ms]</i>	166	166	166	156

Table 5: Sequence Parameters used for in vivo spiral acquisitions.

Spirals 2 and 4 are single interleave constant-density spirals acquired at $6 \times 6 \text{ mm}^2$ spatial resolution (other sequence parameters shown in Table 5). Lower resolutions are used for spirals 2 and 4 as these spirals are only used to provide the motion induced phase information which is assumed to be contained within the lowest spatial frequencies. Spirals 1 and 3 are constant density single interleave spirals with a spatial resolution of $4 \times 4 \text{ mm}^2$ (other sequence parameters are shown in Table 5). Relative to the work of Gorodezky et al. [244] the order of the spiral readouts in each stimulated echo has been swapped, with the second spiral in each stimulated echo being used to acquire motion induced phase information. This ordering was chosen to minimise signal degeneration due to T_2^* decay in the inferolateral wall adjacent to the posterior vein of the LV [299] in the $4 \times 4 \text{ mm}^2$ spatial resolution images used to produce the field map. In this arrangement the data used for motion induced phase correction has reduced SNR and increased off-resonance and T_2^* related artefacts due to the increased signal dephasing during the longer echo times. In this way, the temporal relevance and image quality of the reference spirals (spirals 2 and 4) was partially sacrificed for improved image quality in the field map generating spirals (spirals 1 and 3).

$T_{\text{Delta}}=3 \text{ ms}$ allows off-resonance phase shift to accumulate compared to the image acquired without the T_{Delta} . The time 3 ms maps a phase difference of $\pm\pi$ to $\pm 166.7 \text{ Hz}$ between spiral 1 and 3, and so a range of off-resonance frequencies between -166.7 Hz to 166.7 Hz can be mapped without phase wrap. These correspond at $3T$ to distortions of B_0 in the range -1.31 ppm to $+1.31 \text{ ppm}$.

The spirals used to acquire the DT-CMR data were two interleave variable density spirals at a resolution of $2 \times 2 \text{ mm}^2$. The parameters for these are shown in Table 5.

10.2.2 Ex Vivo

All *ex vivo* acquisitions in this thesis are based on the same spiral design algorithm and principles as the *in vivo* acquisitions described above. As there is minimal movement of the sample, no motion-induced phase correction is performed. The resolution varies between the studies presented in Chapter 11, but the FOV (when all interleaves are combined) was consistent at $360 \times 360 \text{ mm}^2$ in the centre of k-space, linearly reducing to $180 \times 180 \text{ mm}^2$ at the edge. The number of interleaves is substantially higher (≥ 20) than for the *in vivo* protocols. This high number of interleaves allows for high-resolution images to be acquired while maintaining short spiral durations ($< 9 \text{ ms}$). The short spirals eliminate the need for the off-resonance corrections and reduce the severity of T_2^* related blurring, while providing relatively high SNR.

10.3 Image Planning

It is common in fields such as CHD to assess RV volumes and function and this is typically performed using a stack of Short Axis (SAX) images aligned perpendicular to the midline of the left ventricular blood pool or possibly axial images which have shown to provide improved reproducibility over a LV focussed image planes [300]–[302]. However, axial images and LV aligned slices do not in general provide slices that are perpendicular to the RV free wall due to its more complex curved shape. In general, this will lead to the RV free wall experiencing greater partial voluming and given the challenging imaging conditions in the RV, LV focussed or axial imaging planes cannot be recommended for sequences with lower spatial resolutions when the RV is of most interest. Directionally dependent parameters such as the microstructural orientations provided by DT-CMR are also often defined assuming that the imaging slice orientation is perpendicular to the local myocardial wall and are therefore dependent on the imaging slice orientation.

Here an image planning strategy was chosen that aims to maximise the area of the RV wall to which the imaging plane is perpendicular. However, it should be noted, that due to the crescent shape of the RV and the curvature in the long axis view, it is not possible to image in a plane that is perpendicular to the entire section of the RV free wall in a single slice. As shown in Figure 74, the RV SAX plane was planned based on a 4-chamber view, a RV 2-chamber axis and a RV outflow tract image and is not perfectly perpendicular in each view (the 4-chamber view and RV 2-chamber take precedence in this case).

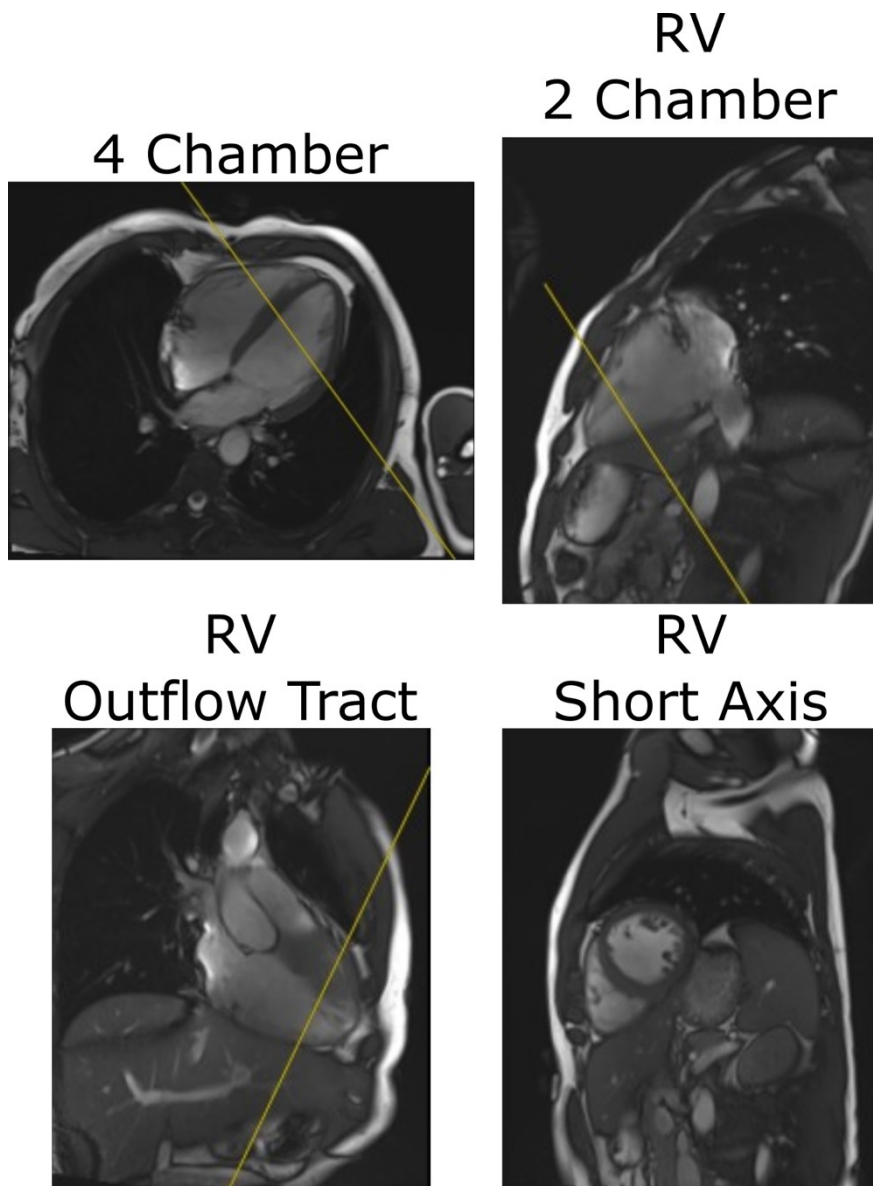


Figure 74: The three views (4 Chamber, RV 2 Chamber, RV Outflow Tract) from which the RV SAX imaging plane is planned. The location of the selected short axis plane is shown on each of the other images (yellow). The aim is to be as close to perpendicular to the RV free wall in all images as possible, with the 4 chamber and 2 chamber taking precedence in this example.

10.4 Image Reconstruction

The following section describes the reconstruction (Figure 75) of the spiral k-space data used in this thesis.

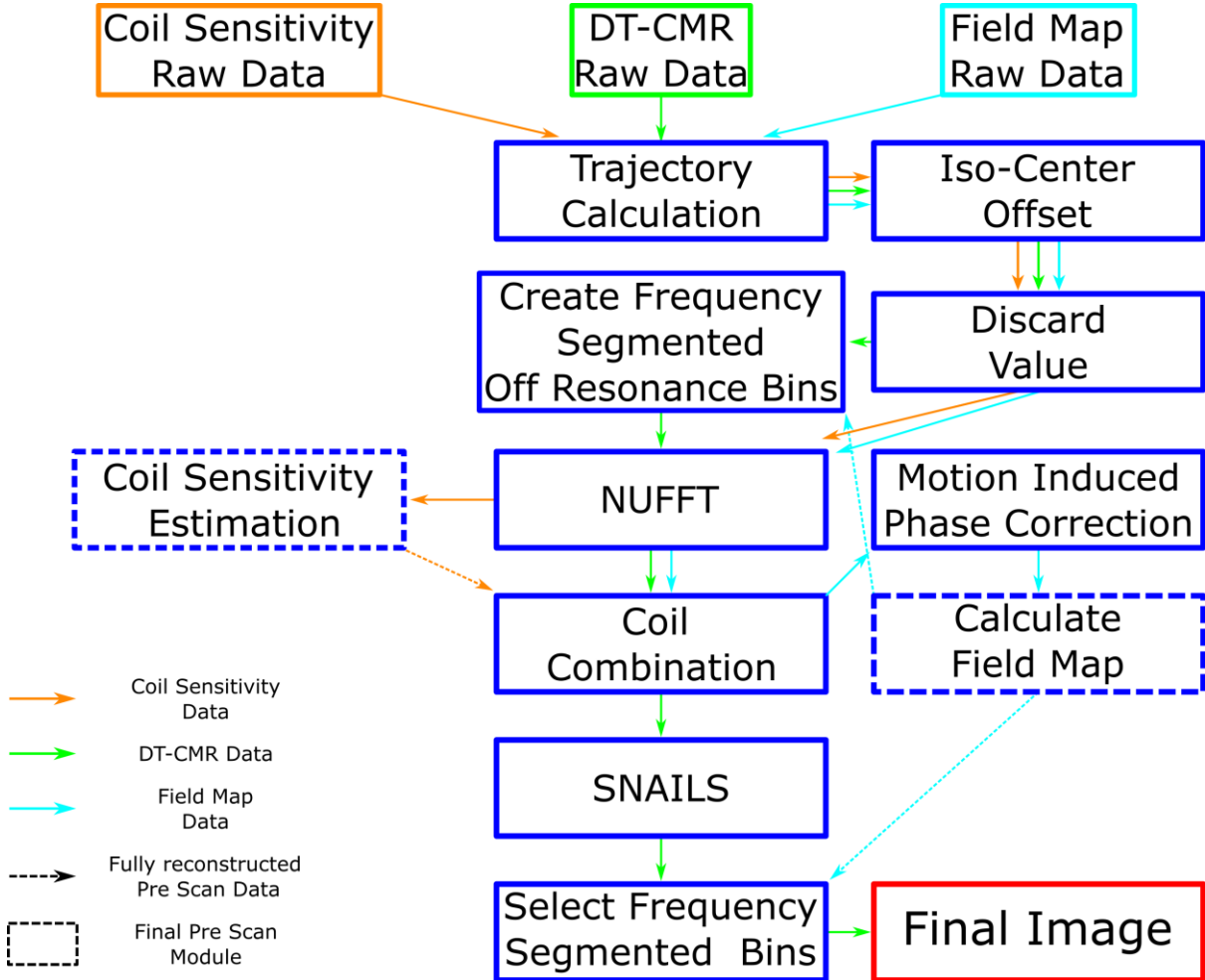


Figure 75: Flow chart showing the reconstruction of spiral DT-CMR data. Orange, green and turquoise respectively denote coil sensitivity, DT-CMR and field map raw data. Both dashed boxes represent temporary endpoints for the preparation (coil sensitivity and field map) data.

10.4.1 Methods

Here, a series of experiments are described that were used to optimise and validate the spiral DT-CMR STEAM sequence used in the following chapters.

10.4.1.1 Iso-Centre Offset

Cartesian or spiral acquisitions acquired with the centre of the FOV displaced from iso-centre in the in-plane directions (i.e., "in-plane FOV offset") require phase slopes to be applied to the k-space data (via the Fourier shift theorem) to shift the target FOV to align with the FOV shown in the final image matrix.

While for Cartesian acquisitions straightforward adjustment of the receiver phase and frequency using functions provided by the scanner manufacturer is used, for non-Cartesian sampling during time-varying gradients, such as spiral imaging, the correction is far less straightforward. Initial attempts to correct the receiver frequency and phase for spiral acquisitions in this work resulted in artefacts as these corrections are highly sensitive to small timing errors, particularly between the gradient waveform and the associated frequency-offset waveform. For sampling up and down readout gradient ramps in EPI, a timing correction is routinely applied in the EPI product source code as part of the forward-reverse echo alignment, but similar alignment functions are not generally available for the case of spiral imaging.

The Fourier shift theorem states that a shift $\Delta_{x,y}$ in the image space signal $S(x, y)$ results in a linear phase term $\Delta\Phi_{x,y}$ in the k-space signal $s(k_{x,y})$ where $k_{x,y}$ are the x and y k-space locations (here spiral x and y trajectories)

$$F\{S(x - \Delta_x, y - \Delta_y)\} = e^{-j\Delta(\phi_x + \phi_y)} s(k_{x,y}) \quad 48$$

Here we use information provided by the scanner to provide the displacements in the in-plane co-ordinates allowing for Δ_x and Δ_y to be determined. Now altering equation A1-A9 from [303] for spiral imaging

$$\Delta\phi_x = 2\pi\Delta_x \left[k_x - \left(\frac{k_{x\max} - 1}{2} \right) \right] \frac{1}{k_{x\max}} \quad 49$$

$$\Delta\phi_y = 2\pi\Delta_y \left[k_y - \left(\frac{k_{y\max} - 1}{2} \right) \right] \frac{1}{k_{y\max}} \quad 50$$

with $k_{x\max}/k_{y\max}$ being the maximal extent of the spiral trajectories in the respective axes, thereby allowing the centre of the FOV to be shifted to the image centre. However small delays in the timing of the gradient experienced by the tissue due to hardware imperfections will result in image errors due to the resultant misalignment of this phase shift. To correct for this misalignment, an alignment factor is defined that determines which spiral k-space data sample is considered to be the first point when applying the phase shift operation.

To evaluate the correct alignment value for the offset correction a cylindrical agar phantom (8 cm diameter, 40 g/L agar in tap water) [304] was imaged with two different zonal selective FOVs (40x40 mm² and 100x100 mm²) at increasing displacements from isocentre. The x displacement here describes a displacement in the sagittal plane's slice-vector direction, the y along the coronal plane's slice-vector direction and z along the transverse plane's slice-vector direction. Displacements of 0 mm, 50 mm and 75 mm were selected to cover the typical range of displacements expected for *in vivo* cardiac imaging centred on the mid-ventricle, while still allowing the phantom to be imaged inside the 32-channel head coil. While other receive coils such as the anterior array or built-in body coil would have allowed for greater displacements, the reduced receive homogeneity and lower SNR of these alternatives made identifying subtle artefacts more challenging. No off-resonance correction and SNAILS correction were performed due to negligible off-resonance and motion within the phantom.

10.4.1.2 Discard

Modern clinical MRI scanners are optimized to compensate for and/or minimize eddy current effects for the trapezoidal gradient waveforms commonly used in Cartesian acquisitions, which are also very robust to small timing errors between gradients and dwell time of the Analog-Digital (A-D) converter. However, spiral trajectories are especially sensitive to residual small gradient timing errors that result in a misalignment of the data sampled in the A-D converter and the gradient waveforms experienced by the imaged sample, causing artefacts when left uncorrected. To correct for this misalignment, the following steps were taken:

1. Data sampling in all spiral acquisitions was programmed to start 10 μ s before starting the spiral gradients. This ensures that the data at the centre of k-space is always collected.
2. The initial N datapoints are discarded to align the data and spiral trajectory. A phantom calibration scan is used to determine the correct discard value (N) which will align the data and the spiral trajectory.
3. Using this discard value obtained from the calibration, any spiral can be corrected by discarding the first N data samples.

To identify the ideal discard value the *in vivo* sequence (Chapter 10.2.1) was used to image in a plane perpendicular to the axis of the 8 cm diameter cylindrical agar phantom (placed at isocentre and imaged using a 32-element head coil to achieve a uniform coil response after channel combination. A zonal selective FOV of 40x40 mm² was used to investigate the ideal discard value. No off-resonance correction or SNAILS correction were performed.

10.4.1.3 NUFFT/Gridding

To interpolate the k-space data acquired along a spiral trajectory onto a Cartesian grid and transform the data into image space a NUFFT algorithm is used. Here we use the Flatiron Institute NUFFT [305], [306] implementation, which is a fast and efficient algorithm. In all reconstructions the spiral was gridded onto a matrix with a factor 2 oversampling, before then being cropped to the final size (which is selected based on reconstructed FOV*interpolation factor/resolution). The spiral trajectories were scaled so that they cover half the diameter of the final matrix. This results in an interpolation of the final images by a factor of 2 and is equivalent to the k-space zero-filling that is often performed in reconstruction of Cartesian data.

10.4.1.4 Coil Sensitivity Estimation and Coil Combination

Roemer et al. [277], [307] have shown that by combining the receive coil channels S_c weighted by the inverse of the spatial sensitivity m_c^* of the receive coils

$$I[x, y] = \sum_c^{N \text{ Coils}} m_c^* S_c \quad 51$$

it is possible to yield improvements in SNR bias at low SNR when compared to a Sum Of Squares (SOS) coil combination approach. Also, a suppression of background noise is achieved by this method. To generate the spatial coil sensitivity weightings the fully sampled preparation scan described in Section 10.2.1 is used. The data from this preparation scan is used with the algorithm presented by Inati et al. [308] to generate the coil sensitivity maps. Inati's [308] algorithm is an extension of the relative coil sensitivity approach originally developed by Walsh [309]. By adding a constraint that the phase progression must be smooth it is possible to avoid artefacts in areas where the SNR is low.

10.4.1.5 Motion-Induced Phase Correction (SNAILS)

To correct for motion induced phase in the *in vivo* DT-CMR data, the SNAILS algorithm described in Chapter 7.2.2 was used. The Gaussian kernel used to extract a low-resolution phase image from the data (assumed to contain the motion induced phase) was defined based on a full width half max of 30 % of the sampled k-space region for all *in vivo* acquisitions. This value was determined empirically by reconstructing every dataset with increasing kernel size as shown in Figure 76. 30 % was the value that visually resulted in all images minimizing motion induced phase cancellation artefact without excessive noise amplification.

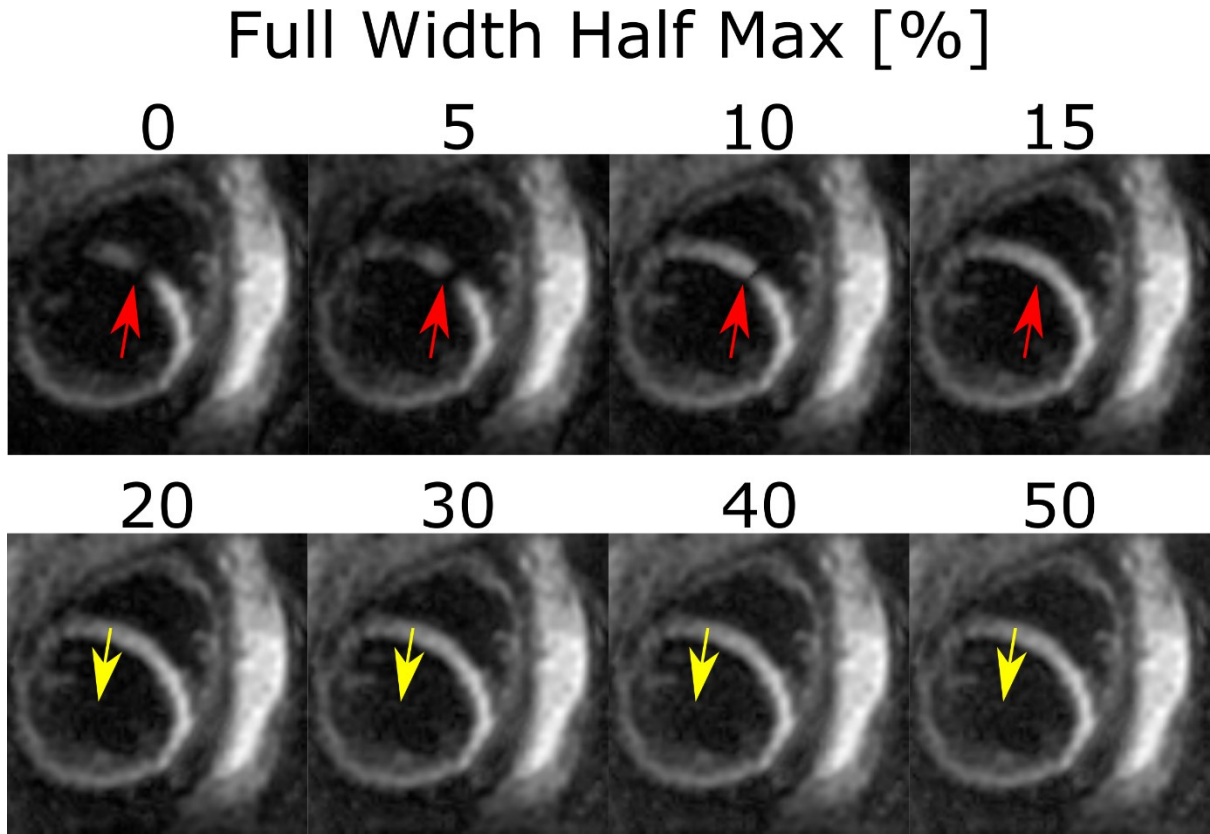


Figure 76: Shown is the same interleaved spiral dataset reconstructed with varying SNAIL kernel size. The red arrow shows the reduction in motion induced phase artefact with increasing kernel size. The yellow arrow shows the increase in background noise.

10.4.1.6 Field Map Calculation/Field Correction

To correct for B_0 inhomogeneities, the frequency segmented reconstruction scheme described in Chapter 7.2.3 was used in combination with the B_0 field maps. The optimal bin size was determined to be 9 based on simulations in Chapter 9. In contrast to the original implementation [285], here the data in the final image is interpolated from the data in neighbouring bins, to avoid sharp transitions where the B_0 field map moves between bins. The interpolation is performed by a linear function which weights the signal from the two neighbouring bins based on the B_0 field map value at each pixel.

To validate the B_0 field map data acquisition (Section 10.2.1), field map calculation and the correction of the spiral imaging data for off-resonance artefacts, the 8 cm cylindrical agar phantom was imaged at isocentre in a 32-element head coil. To generate off-resonance effects, the excitation frequency was manually altered after careful shimming with the second order shim system. The excitation frequency was varied in steps of 20 Hz between -120 Hz to +120 Hz off-resonance. Further, by manipulating the shim currents in the x and y gradients a linearly varying off-resonance was generated with off-resonance frequencies Δf varying between -120 Hz to +120 Hz. No SNAILS correction of the DT-CMR data was performed since no motion is occurring during the scan.

Based on the results of 10.5.1 and 10.5.2, for this field-map correction testing the discard value for the reconstruction was set at 8. The iso centre offset and alignment were used with an alignment value of 9.

10.4.1.7 Online Reconstruction

One major drawback of many spiral-based sequences is a lack of image reconstruction methods online at the scanner. Many studies use off-line retrospective reconstruction, leaving the scientist/clinician/technologist scanning “blind”; acquisition problems, such as a poor shim, a misplaced slice or an imperfectly selected acquisition window cannot be identified and corrected while the patient is still in the scanner. Offline reconstructions, therefore, frequently lead to subjects being rescanned or datapoints being deleted in a study.

Implementing the whole reconstruction within the manufacturer’s reconstruction framework can be difficult as much of the manufacturer’s code may be unavailable making these frameworks inflexible. It may also be difficult to incorporate additional external libraries such as those required for NUFFT and the supported programming language is usually limited to C/C++.

One alternative to the manufacturer reconstruction software is the Gadgetron framework [310]. The Gadgetron is a manufacturer independent nominally open-source MRI reconstruction software developed by the NIH and is well-suited for spiral reconstructions. It allows for the raw data of the scan to be converted to the open ISMRMD format [311] and be sent via a SSH tunnel to a remote reconstruction server. The Gadgetron reconstruction framework contains a range of tools for reconstructing data from a variety of sequences and k-space trajectories. After reconstruction, the data is then sent back into the scanner host where it can be displayed as usual and sent to other servers (e.g., Picture Archive and Communication Systems, PACS). While open source and highly customizable, for this project the C/C++ reconstruction framework used on the Gadgetron server was found to be rigid and therefore require major revisions to be tailored to the needs of the sequence used here. The version of the Gadgetron available also suffered from a memory leak in the implementation of the NUFFT library, which in combination with high numbers of bins used for the frequency segmented reconstruction (factor of n more gridding operations), often resulted in a corrupted output.

Having spent considerable time developing a Gadgetron implementation, a third solution is presented in this thesis. After exporting the raw data using the export mechanisms of the Gadgetron, a Gadgetron module was written that exports the data to a mongoDB database [312] running on a Docker swarm cluster [313] (Figure 77). This not only takes advantage of the highly optimised read and write speed of a clustered service architecture, but also allows for applications to access the data in a widely used and well supported format (mongoDB). All the raw data is then available on the cluster and a reconstruction was developed in Python. Together with a frontend written as a Dash Plotly [314] webserver, this setup allows for online reconstruction (reconstruction time <30 seconds for a single DT-CMR breath-hold) and visualisation next to the scanner using a laptop and web browser. Furthermore, this allows for more straightforward development and testing cycles due to the high-level functions and interfaces provided by Dash and Python. This setup takes advantage of both the flexibility and speed of the Gadgetron in terms of exporting data from a proprietary manufacturer system and the ease of use and high-level visualisation features of Python.

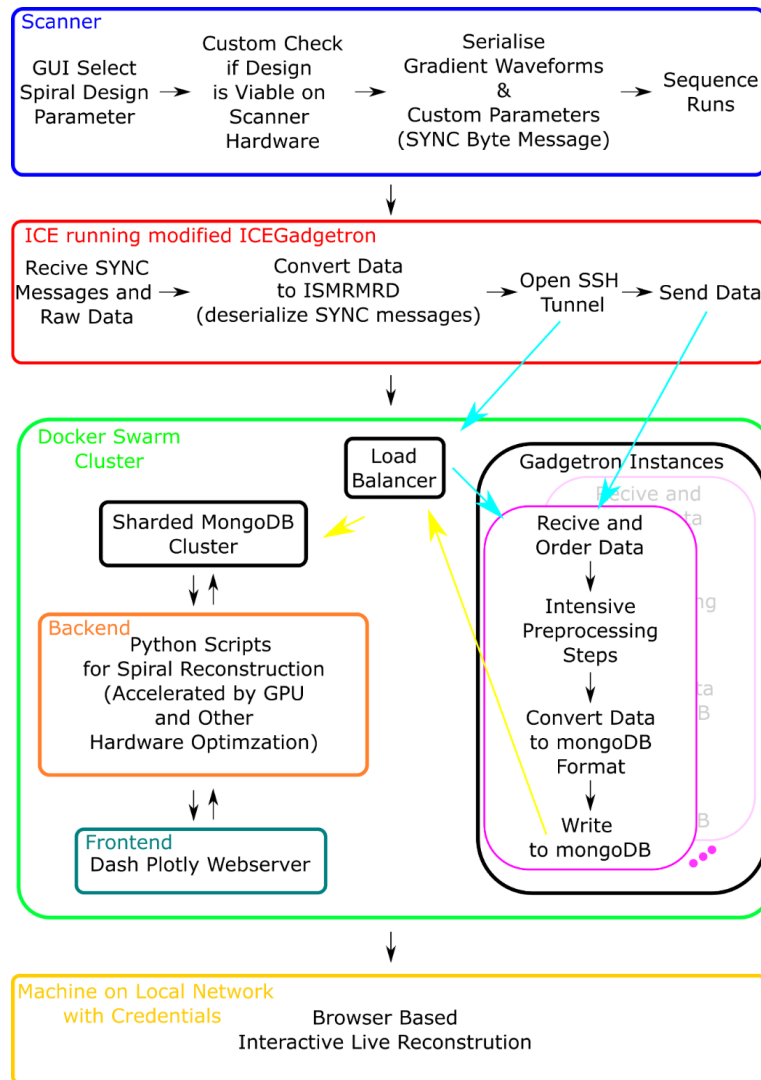


Figure 77: Flow Chart showing data flow and processing steps. The blue box shows the steps that are run on scanner hardware, including the selection of spiral design parameters, the subsequent calculation and checking of the gradients and the data export to the Siemens reconstruction server. The red box includes the functions that are run in the Siemens reconstruction framework. Here the ICEGadgetron program provided by NIH was modified to serialize the custom SYNC message and transform it into a message conforming to the ISMRMD standard. The creation of a SSH tunnel to an external Gadgetron reconstruction server is shown, as well as the subsequent transfer of all data to this server. The light green box denotes the Docker Swarm Cluster, which runs all reconstruction, data storage and visualisation tasks in a microservice architecture. The central component of this cluster is the load balancer which routes requests to idle instances of the individual components. For the data coming from the ICEGadgetron module this means selecting one of the idle Gadgetron reconstruction servers. The selected server runs a custom reconstruction chain that receives and orders the spiral data, does pre-processing steps (discard, centre alignment, trajectory calculation from the gradients) and stores the data into a mongoDB running in the same cluster. The orange box within the Docker Swarm Cluster represents the collection of Python reconstruction scripts that are responsible for all the main spiral reconstruction steps, such as NUFFT, field map correction and coil combination. The respective instances have access to hardware acceleration which is passed through to their respective Docker container. The teal box in the cluster shows the frontend, which is running a webserver instance of Dash Plotly to visualise and interact with the reconstruction and the data received live from the scanner.

10.4.1.8 DT-CMR Processing

To generate all DT-CMR parameter maps shown in this work the same MATLAB Diffusion Toolbox used in other work [24], [50], [196], [221] was used. The toolbox provides following steps in order to generate the final DT-CMR parameter maps:

1. **Image Crop:** To simplify all following processing steps a manual image crop on a single image is used to crop all raw images in the dataset.
2. **Frame Rejection:** The frame rejection steps allow for DWI with obvious artefacts, typically due to motion to be discarded at the start of every analysis.
3. **Motion Registration:** Images are registered using a rigid translation [315] to the first frame of the acquisition.
4. **Foreground Segmentation:** To segment the myocardial signal from the background a manual threshold with subsequent manual correction is performed based on an averaged image of all the DWI.
5. **Centroid Selection:** The centroid of the ventricle of interest is manually defined
6. **Myocardial Region Segmentation:** The diffusion tensor is calculated for every pixel within the thresholded region. The dependence of the b-value on the RR-interval is accounted for in the tensor calculation using metadata from the DICOM files. An approximation of the HA is then calculated for each pixel using the centroid. The endocardium, epicardium and right ventricular insertion points are defined by manual segmentation on this estimated HA map. Previous work has found that the removal of the papillary muscles and portion of the septum considered to be a part of the RV myocardium is easier when performed on this approximate HA map than on the DWI.
7. **Parameter map calculation:** Finally, pixelwise maps of parameters including eigenvalues, MD, FA, HA, IA (see below) and E2A are calculated.

This processing tool was developed within the CMR Unit at Royal Brompton Hospital. However, the tool was developed for the LV and has some notable shortcomings when used for RV analysis, including the definition of HA used. The HA definition was based on the LV shape and assumes a smooth epicardial contour, which is not applicable in the RV where the sharp corner in the contours causes artefacts in the HA map. As a result, in all work where the RV orientational data is explored, we define the Inclination Angle (IA) for use as an alternative. The IA depicts the angle between the $\hat{e}_i$ and the image plane without projection. As a result, IA does not require the definition of the epicardial surface. However, one problem that remains is that the polarity of the IA depends on the position of the pixel relative to the centroid (Figure 78). When the centroid is placed in the RV blood pool the polarity of the IA in the septum is inverted relative to the case when the centroid is placed in the LV blood pool. When the centroid is placed in the LV blood pool, there are often regions of the RV free wall where the IA changes relative to the case when the centroid is placed in the RV. To solve this mismatch IA maps calculated with the centroid placed in the LV blood pool and the RV blood pool were merged. By repeating the analysis with identical segmentations and rejected frames but switching the centroid from the LV blood pool to the RV blood pool, two IA maps were created. These two maps were merged with IA data for the RV free wall taken from the RV centric analysis and data for the septum taken from the LV centric analysis (Figure 78). The transition between the LV and RV centric data was located at the inferior and anterior insertion points. A linear interpolation of pixel values in the IA maps was used to reduce the displayed pixel size, in contrast to the output of the original analysis methods which used a nearest neighbour approach.

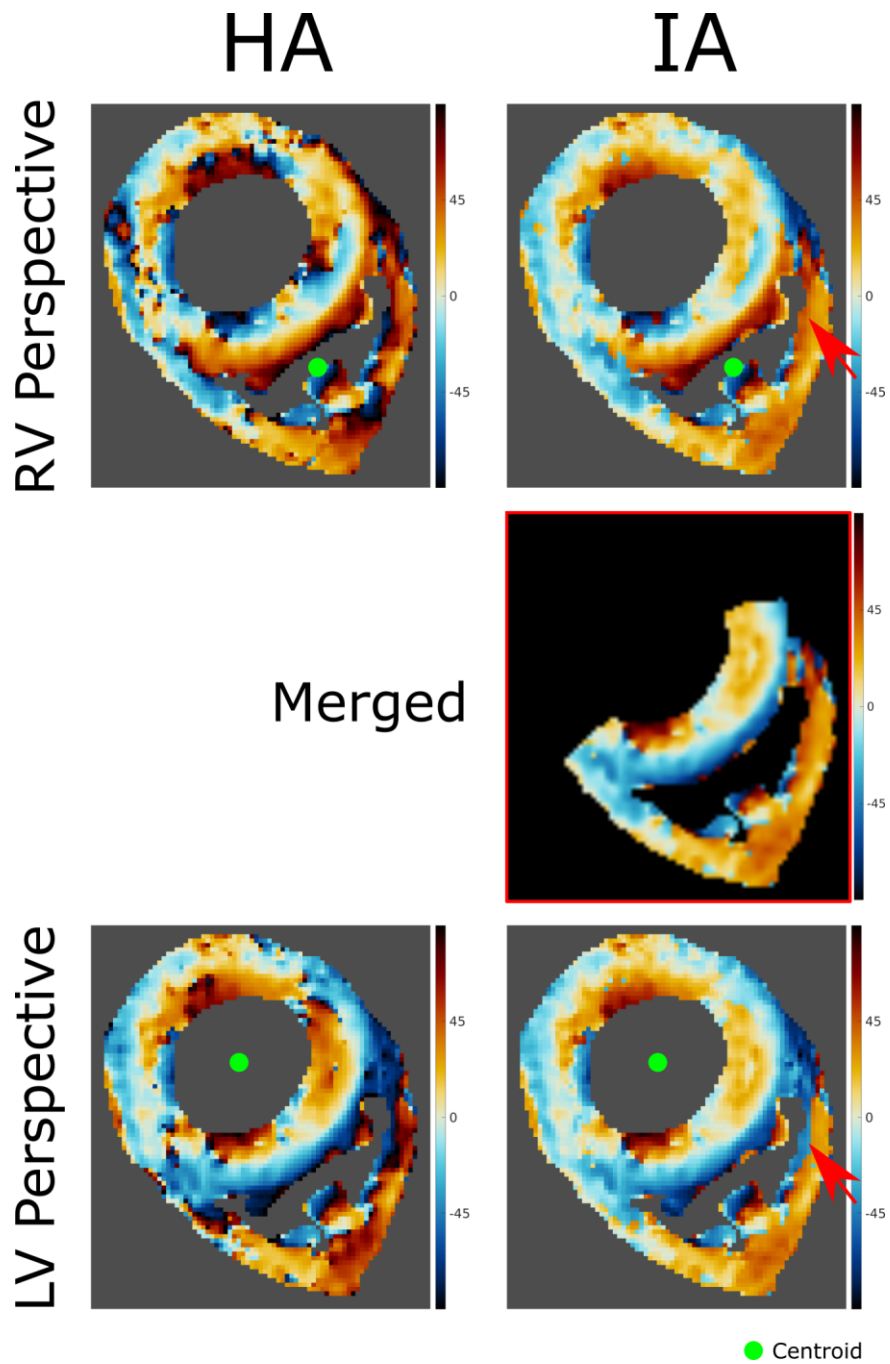


Figure 78: HA and IA maps from DT-CMR processing with the centroid located in the LV blood pool and in the RV blood pool. To avoid bias through using a LV centric analysis in the RV free wall a merged version of both analysis is used. The septal section in the merged map is taken from the LV centric analysis while the RV uses the RV centric data. The red arrows point to differences in the IA between the respective analyses.

10.5 Results from Phantom Validations

10.5.1 Iso-Centre Offset

The results of the iso-centre offset test are shown in Figure 79. Misalignment of the off-centre correction and the spiral data results in a region of signal loss at the phantom edge and halo-like signal around the edge of $\sim 180^\circ$ of the phantom. The severity of the misalignment artefact is more severe as the displacement from iso-centre increases and is lowest at an alignment value of 8 in x and y and 10 for the z direction. Residual artefacts when using the selected alignment value are minimal for offsets of 50 mm in x and y, but slightly larger for 75 mm offsets or z-offsets

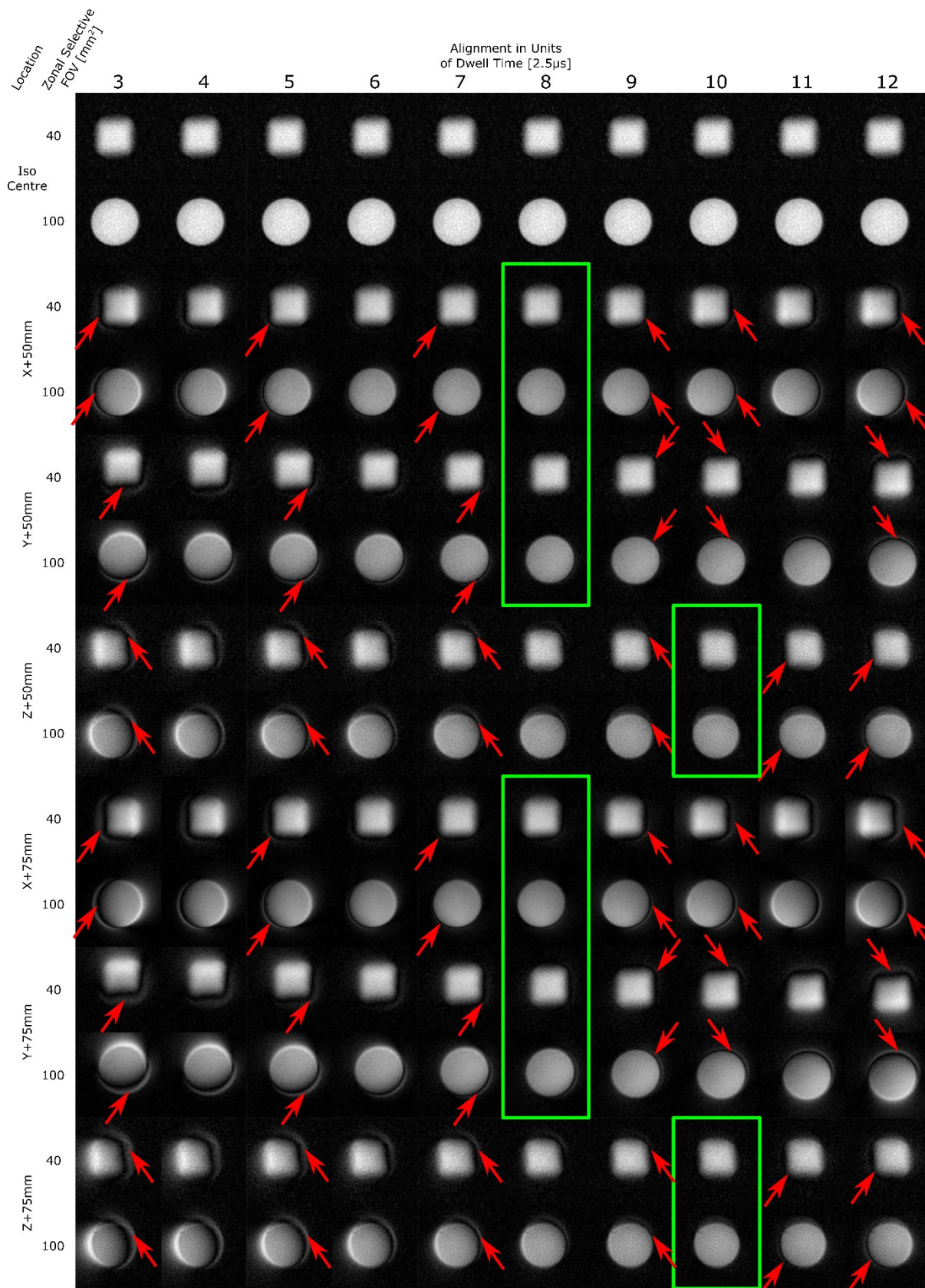


Figure 79: Phantom experiment showing optimisation of center offset alignment for two protocols (40×40 mm² excited FOV [cropped to enhance visibility of arteact], and 100×100 mm² excited FOV). The data shown was aquired with offsets (50 mm, 75 mm) in x,y,z scanner axis and reconstructed with alignment values from 3 to 12.

10.5.2 Discard Value

The results of the discard experiment are shown in Figure 8o. With a discard of 8 samples, the edges of the excited FOV in the 40×40 mm² acquisition are aligned with the principal Cartesian axes, suggesting that this value is optimal.

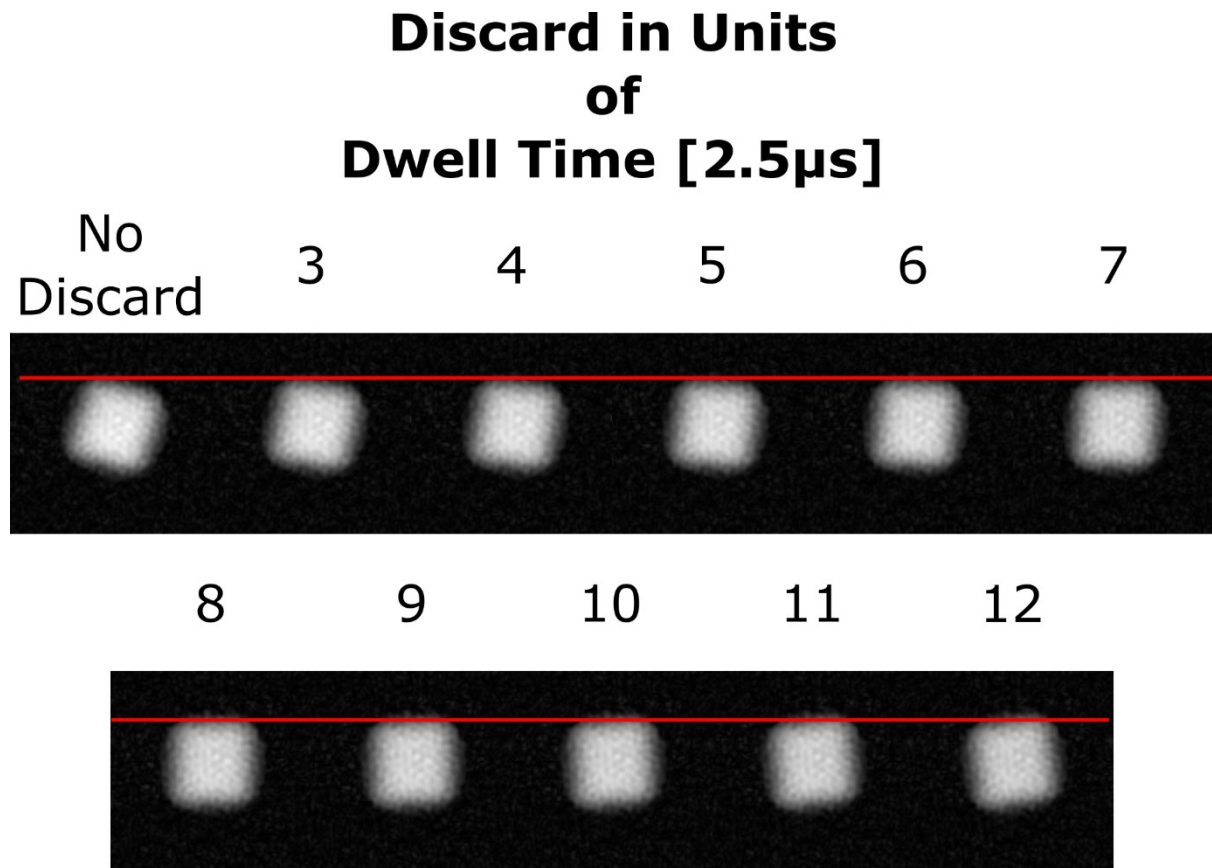


Figure 8o: Reconstructions of spiral images acquired in a uniform phantom with varying numbers of the initial spiral points discarded. Using a reduced stimulated echo FOV of 40×40 mm² (in a cylindrical phantom of diameter 80 mm) when the edge of the stimulated echo FOV aligns with the principal Cartesian axis, the discard value is optimal. A discard value of 8 was selected as optimal.

10.5.3 Off-Resonance Correction

Figure 81 shows the results of the off-resonance experiment. The calculated field maps match in every case the manually added off-resonance value. The correction sharpens the uncorrected image in every case to provide a similar appearance compared to the ground truth (0 Hz).

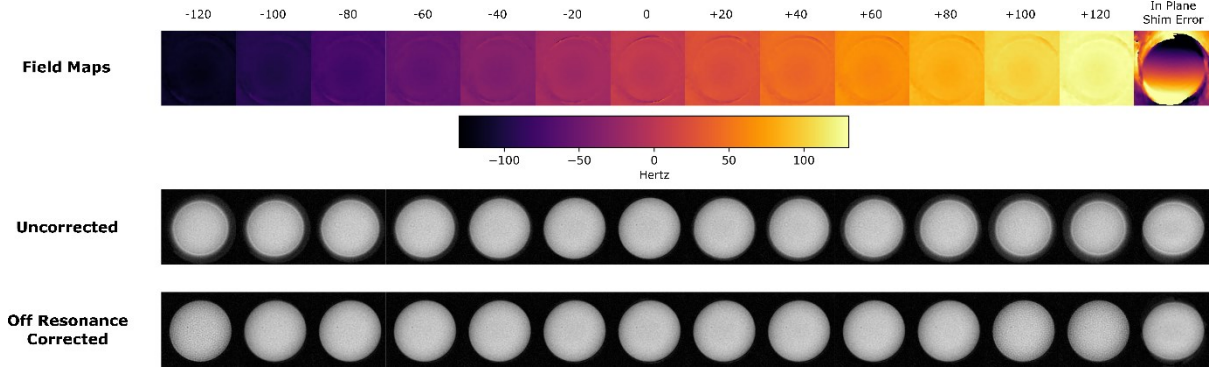


Figure 81: The performance of the STEAM spiral field mapping technique and off-resonance correction used in this work. Images were acquired with a range of off-resonance excitations and a linear (bottom to top) slope in off-resonance. Field maps (top row) and spiral images both without (middle row) and with off-resonance correction (bottom row) were reconstructed. The field map accurately measures off-resonance, and the off-resonance correction effectively removes the off-resonance related blurring.

10.5.4 Discussion

In this section, we have described the implementation and optimisation of the interleaved spiral DT-CMR sequence and reconstruction. Tests showed that an alignment value of 9 dwell-time units is the most appropriate choice to align the acquired spiral k-space data with the phase shifts required to place the target FOV in the centre of the reconstructed imaging matrix. This value is optimal for the sequence implementation and MRI scanner hardware used in this thesis and is not generalisable. The artefact due to imperfect alignment is increasingly severe with increasing off-isocentre shift of the imaging plane. During placement of DT-CMR subjects on the scanner table, particular attention was paid to ensuring that the location of the heart was as close to isocentre as possible. However, subject specific variations in anatomical orientation cannot be adjusted for. As a result, the selected imaging plane is in general oblique and off isocentre. Oblique imaging planes require the spiral gradient waveforms to be played out on multiple physical axes. The optimal alignment value on the x and y axis was found to be 8 and the optimal value for the z axis is 10. Thus, the use of 9 as a compromise value provided minimal artefacts across the range of most subjects without using plane-specific reconstruction adjustments. It was further assumed that this value did not

change based on spiral design, as long as the dwell time and the initial delay time of the A-D converter were kept constant.

An optimal discard value results in temporal alignment of the A-D converter sampling points with the spiral gradient waveform. Correct alignment ensures that the two in plane axes are represented horizontally and vertically in the final image. Most usefully, the in-plane zone-selection gradients applied on those same two in plane gradient axes act as exact indicators of these directions and therefore the edges of the square excited FOV appear aligned with the principal axes of the imaging matrix. (Without those in-plane selection gradients, it is necessary to ensure a flat surface of a phantom positioned within the reduced FOV is supported completely orthogonally). The optimal discard value of 8 A-D converter dwell-time units found for the sequence implementation and hardware used in this work was used in all subsequent reconstructions.

The off-resonance test showed that both the field map implementation and the off-resonance correction performed as expected in the scanner environment. It was further demonstrated that off-resonance frequencies up to ± 120 Hz can be sufficiently resolved. For *in vivo* imaging, the range of off-resonance frequency corrections applied was limited to -120 Hz to +120 Hz. As such the results presented here provide validation of the method for off-resonance measurement and correction.

10.5.5 Spiral Resolution Validation

Any acquisition on an MRI system is subject to a number of factors that potentially result in a discrepancy between desired (prescribed) resolution and the true acquired resolution. In conventional Cartesian imaging this can be factors such as the design of the pulse sequence and the reconstruction steps. In non-Cartesian acquisitions effects such as imperfect gradient systems, T_2^* filtering, off-resonance [270], [316] and reconstruction parameters[283] can alter the effective resolution.

A potential method to measure the resolution is via the use of gradient-field sensors [317], [318], however the application of these is limited as the true A-D converter sampling rate has to be known and often the required equipment is not readily available to researchers. Another way to estimate true pixel size is through the use of resolution phantoms in which various known sized objects are imaged. Via the modulation transfer function, it is then possible to obtain the point spread function. This however can be affected by slice-misalignment partial volume effects and reconstruction algorithms [283] and so struggle to determine the true encoded resolution of the spatial encoding.

The aim of the following section was therefore to measure the acquired resolution via the spin-warp [319] (“k-space”) coverage of any sequence (the DT-CMR spiral sequence is of particular interest here), using the array of k-space data peaks when imaging a phantom with a regular grid shape (this work differs from the work using grids for measuring geometric accuracy [320]). This method allows to measure the physically encoded resolution rather than the final image display resolution. This differentiation is vital as it means the proposed method is not measuring alterations due to reconstruction steps, but the pure physical limit of the high spatial frequencies present in the data.

10.5.5.1 Theory

The Fourier transform of a RECT function in image space is a SINC function in k-space.

$$A * RECT\left(\frac{x - x_0}{W}\right) = \begin{cases} A, & \left|\frac{x - x_0}{W}\right| \leq \frac{1}{2} \\ 0, & \text{otherwise} \end{cases} \quad 52$$

$$\mathcal{F}\left[A * RECT\left(\frac{x - x_0}{W}\right)\right] = A * W * SINC(\pi * f * W) * e^{-i * 2\pi * f * x_0} \quad 53$$

with A the signal amplitude, x the distance, x_0 the centre and W the width of the RECT function.

Thus, if considering the basic relation of

$$\Delta w = FOV / N_{cycles} \quad 54$$

with Δw the spacing between sampled points it is possible to calculate how many harmonic peaks of the spatial RECT wave result from a certain resolution.

10.5.5.2 Methods

To validate the resolution of the spiral design used for *in vivo* imaging in this thesis, a grid phantom with the design shown in Figure 82 was designed and manufactured by the Department of Chemistry at King's College London. The final acrylic phantom was created using a CnC milling process and measurements with vernier callipers were unable to detect any discrepancy between the specified and manufactured dimensions. Clear cast acrylic was chosen, as it has a magnetic susceptibility very close to that of water ($(\chi - \chi_{H_2O})/ppm = -0.023$, $\rho / (g / cm^3) = 1.19$ [321]) and therefore susceptibility artefacts should be minimal. For imaging the phantom was suspended in a container filled with jelly (water filled phantoms often result in flow artefacts due to the vibrations induced by the diffusion gradients). To achieve a uniform coil sensitivity response, the in-built scanner body coil was used, as the phantom did not fit into the head coil which would have provided preferential SNR whilst also achieving sufficient spatial coil sensitivity uniformity.

For initial validation of the setup a standard 2D product Cartesian SE sequence was used to image the phantom with following parameters [user interface nominal values: resolution=0.547 mm², FOV=140 mm², slice thickness=4 mm, TR=2 s, TE=10 ms, 6 averages]. The image was reconstructed by forming the raw data into the displayed k-space matrix (no reconstruction pipeline).

The spiral iteration of this experiment was performed using the *in vivo* sequence with nominal control software parameters (as in Table 5) and to null any signal outside the grid the zonal selective FOV was used. Reconstruction was limited to the gridding operation and the discard of the first 8 points.

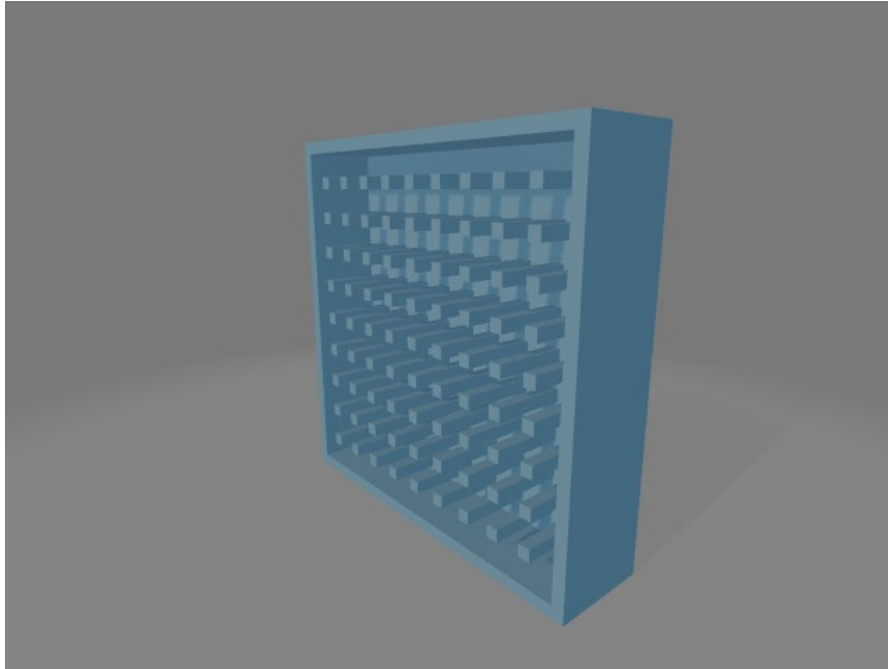


Figure 82: 3D rendering of the resolution phantom developed in this work. The width and height of the overall phantom are each 155 mm with a depth of 20 mm. Each direction is separated into 9 rods with an in-plane dimensions of 5 mm², which are spaced 10 mm apart.

10.5.5.3 Results

The T₁ of the jelly was measured to be 1s, while the T₂^{*} was measured to be 50 ms.

In Figure 83 the image space and k-space image of the Cartesian acquisition is shown. In both k_x and k_y there were 27.8±0.2 peaks across k-space.

In Figure 84 the spiral experiment is shown. The k-space here was the FFT of the final complex image, thus the “zero filled” region (factor 2) was not filled with zeros due to imperfections of the FFT operation. When counting the peaks across the fraction where no zero filling was performed it was apparent that the 3rd harmonic peak was missing (since it was unfortunately zero due to the selected ratio of the pillars to gaps). However, it was still possible to measure an estimated 8.0±0.1 peaks across the filled k-space.

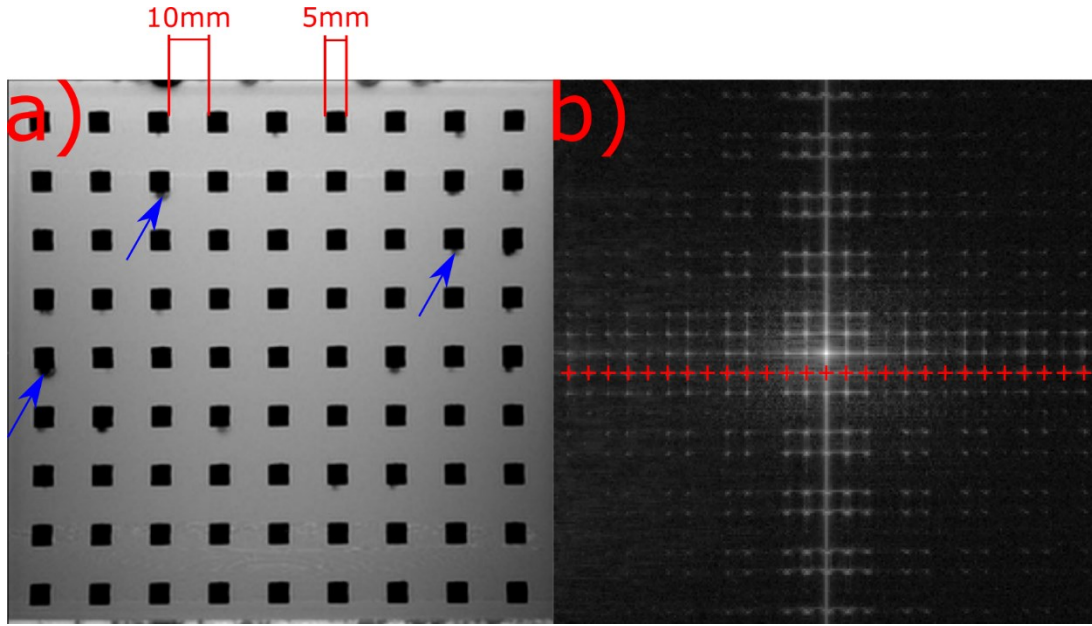


Figure 83: a) Image space Siemens' product 2D acquisition of the grid resolution phantom. FOV was selected to be 140 mm² at a resolution of 0.547 mm². b) K-space data of Siemens 2D scan, displayed on a log scale. The artefacts visible (blue arrow) in image space originate from residual air bubbles in the jelly. The red markers in k-space show the harmonic peaks.

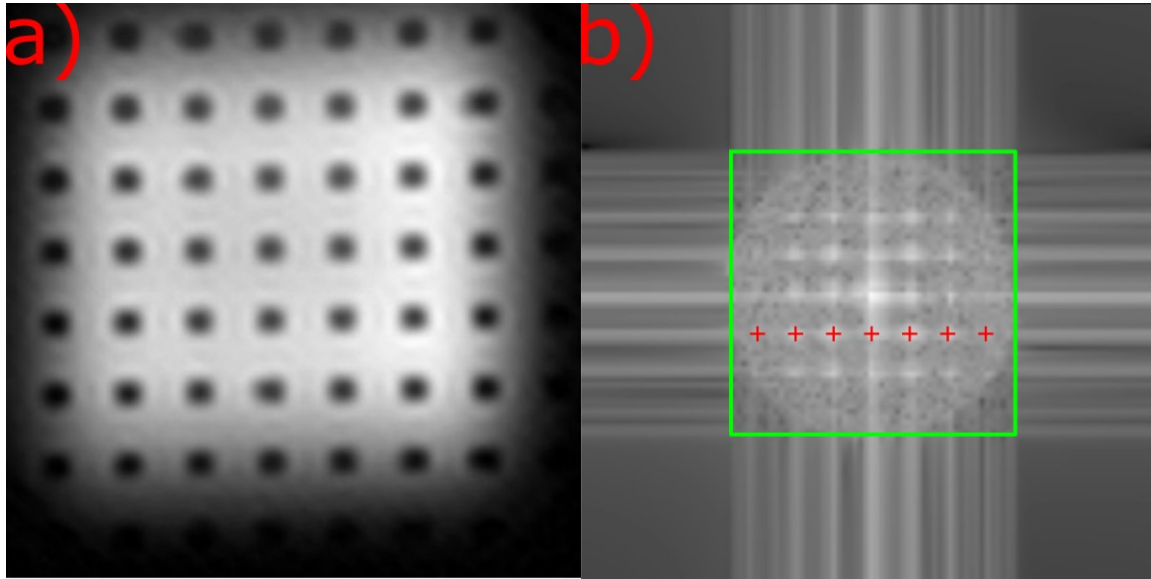


Figure 84: Spiral resolution phantom scan. a) The magnitude image space. b) The magnitude of k-space is displaced on a logarithmic scale. The red markers in k-space show the harmonics, while the green box bounds the sampled circular region of sampled k-space.

10.5.5.4 Discussion

The grid had a basic wavelength of 15 mm (120 mm/8) which was assumed to have negligible error compared to the peak-counting estimate. Thus, when taking into account the relationship described in 10.5.5.1, the following result for the resolution in the Cartesian experiment was derived:

$$\frac{15 \text{ mm}}{27.8 \pm 0.2} = 0.54 \pm 0.004 \text{ mm} \quad 55$$

concluding that the Siemens standard clinical sequence achieved a slightly better resolution than the prescribed 0.547 mm.

From Figure 84.b it is visible that the 3rd harmonic in the spiral case was nulled, this can be confirmed by a simple demonstration shown in Figure 85 where the 10:5 mm profile of one in plane dimension was simulated and Fourier transformed; this shows the missing third harmonic peak as in the k-space Figure 83.b and Figure 84.b. Perhaps a better design would have been a ratio of 4:11 mm, as shown in Figure 86. which leads to a k-space representation in which none of the harmonic peaks is exactly nulled. Overall, this method needed further work, but investigating the obvious use of a more extreme pulse ratio to generate more consistent harmonic amplitudes led to concerns about whether their SNR would be reduced too far, and there was time to make only one grid phantom.

Nonetheless, from this experiment, the following spiral acquisition k-space path resolution could be estimated

$$\frac{15 \text{ mm}}{8 \pm 1.25} = 1.88 \pm 0.02 \text{ mm} \quad 56$$

Thus, achieving approximately 0.1mm finer resolution than originally planned. While there may be some impact of gradient nonlinearity on these measures, given the small region excited at iso-centre (max 140x140 mm²) we assume a negligible impact of gradient nonlinearity on these results.

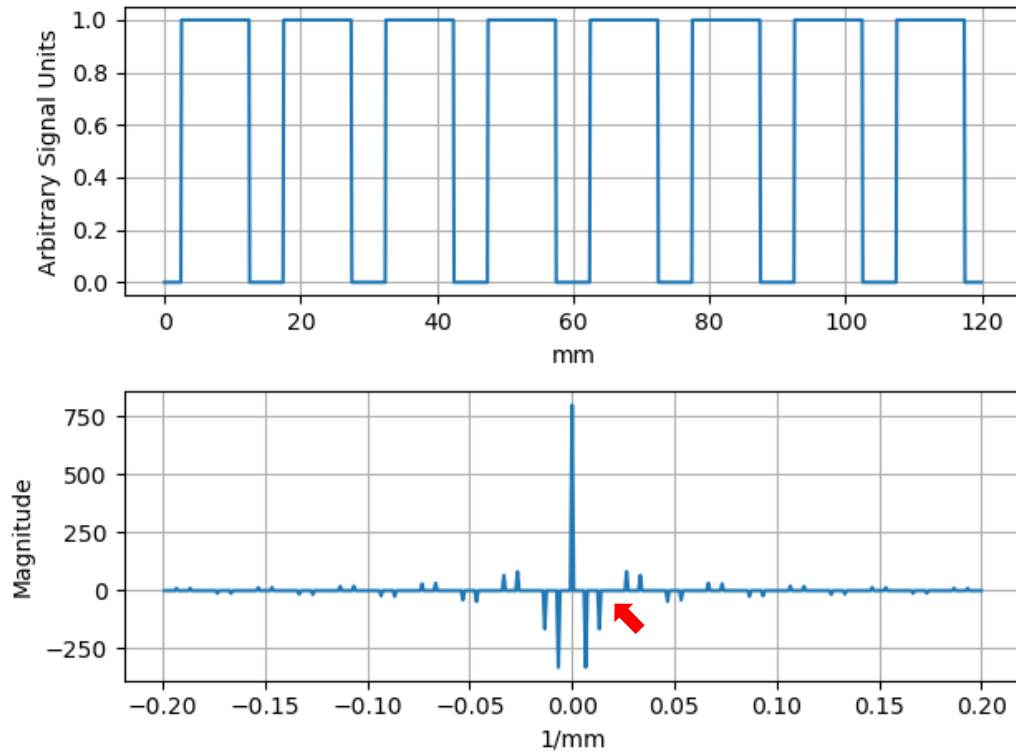


Figure 85: Fourier transform of resolution phantom RECT waveform showing the nulled peak at every 3rd harmonic. The red arrow is showing the position of the nulled peak.

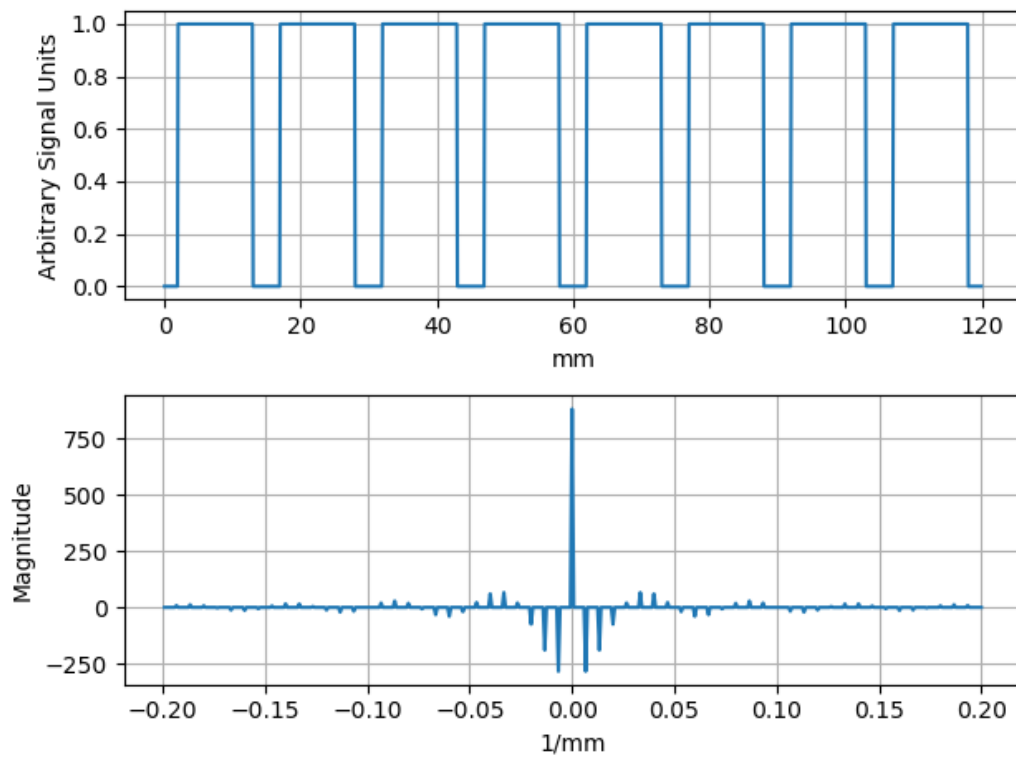


Figure 86: Fourier transform of RECT waveform without zero nulling point at the 3rd harmonic. Spacing is 11 mm signal with a 4 mm gap.

10.5.5.5 Conclusion

Using this novel phantom-based approach, it was possible to directly measure the extent of k-space sampled by the scanner, bypassing any image reconstruction effects and also any acquisition difficulties such as slice partial volume degradation of sharp edges in detailed resolution phantoms. The phantom is low cost to produce, image acquisition is relatively straightforward and the subsequent image processing does not require specialist algorithms. However, while the simplicity of this is an asset, the effects of the image reconstruction algorithms or effects such as T_2^* and off-resonance on the modulation transfer function are not assessed with this approach. This novel experiment provides a fast and uncomplicated way for the sequence designer to check if the scanner accurately plays out the desired waveforms for spatial encoding.

10.6 Influence of Point Spread Function

The effect of sampling schemes in k-space, image reconstruction algorithms, off-resonance, signal decay, partial volume effects and system imperfections on image spatial resolution can be described via the Point Spread Function (PSF). To provide some insights into the ability and limitation of the sequences used in this work to resolve the thin-walled RV (5-6mm in systole) a simple simulation was performed investigate the PSF of both the EPI and the spiral sequence.

10.6.1 Method

The PSF simulation was based on the Fourier transform of a delta function (a perfect PSF), which is a uniform signal in k-space. Data in k-space were replaced with $1+0i$ and a basic reconstruction was simulated (inverse Fourier transform for EPI and a NUFFT for the spiral data). As no coil sensitivity profiles were available, parallel imaging was not simulated, but the reduction in the echo train length provided by SENSE (factor 2) in the EPI protocol used in vivo was simulated by reducing the simulated echo spacing by a factor of 2. The simulation used similar readout parameters for EPI and spiral as the *in vivo* acquisitions, with the simulated maximum k-space extent corresponding to $2.8 \times 2.8 \text{ mm}^2$ for the EPI sequence and $2 \times 2 \text{ mm}^2$ for the spiral sequence. The simulated field of view for the EPI acquisition was reduced to $67.5 \times 180 \text{ mm}^2$ instead of $135 \times 360 \text{ mm}^2$ in order to adjust for the missing parallel reconstruction factor along the phase encode direction (frequency encode direction was adjusted to maintain same matrix ratio). For both methods, the effects of a range of constant T_2^* values [15ms, 25ms, 35ms, 1000ms] and off resonance frequencies [0Hz, 5Hz, 10Hz, 20Hz] was also simulated based on the methods described in chapter 9. To allow side-by-side

comparisons, k-space data from both methods was zero filled to provide a simulated reconstructed resolution of 1mm^2 .

10.6.2 Results

Figure 87 shows the 2D PSFs calculated for both sequences without the effects of off-resonance or T_2^* decay. While the spiral PSF appears circularly symmetric, the EPI sequence shows side lobes radiating out along the frequency and phase encode directions. In Figure 88 intensity profiles of these simulations are provided. In the case of the EPI simulation, the profiles were calculated along the phase encode direction, since the effects of off-resonance and T_2^* are predominantly observed in this direction. Figure 88 also shows a measurement of the Full Width Half Max (FWHM) of the PSF obtained from the intensity profile, normalised by the nominal spatial resolution (1.8mm for the spiral and 2.8mm for the EPI sequence).

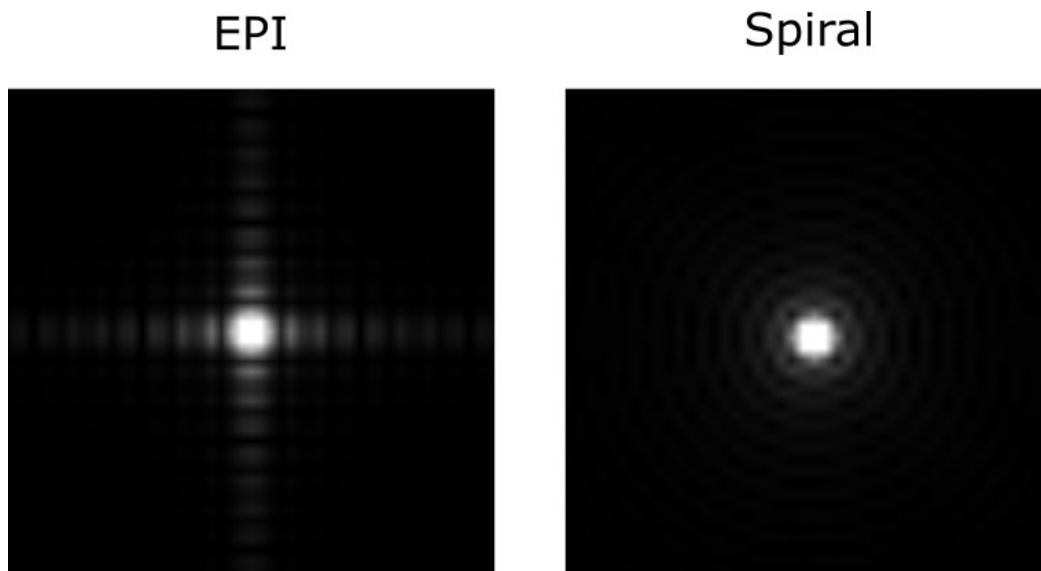


Figure 87: 2D PSF from simulated EPI and spiral sequence with constant off-resonance $=0\text{Hz}$ and $T_2^=1000\text{ms}$. Both images are cropped to the same sized central region in image space to aid visualisation.*

From Figure 88 it is evident that the spiral sequence has a slightly narrower PSF in each case when compared to the EPI. However, when comparing resolution normalised FWHM values it is clear that the EPI results in a narrower PSF for a given prescribed spatial resolution. The spiral trajectory and reconstruction blurs signals by 2.27 times the nominal resolution (at 50% of the maximum intensity) in the best case (no off resonance and long T_2^*) and by 2.58 in the worst-case (high off resonance, short T_2^*). The FWHM of the EPI PSF is narrower at 1.53 x nominal spatial resolution in the best-case scenario and 1.58 in the worst-case scenario.

Both increasing off-resonance and a reduction in T_2^* result in a widening of the PSF. In both cases, small increases in the FWHM are observed, but there is a clear increase in the width of the tails of the PSF. It should be noted that this effect is asymmetric for the EPI sequence as off-resonance and T_2^* related blurring effects have a much-reduced effect in the readout direction.

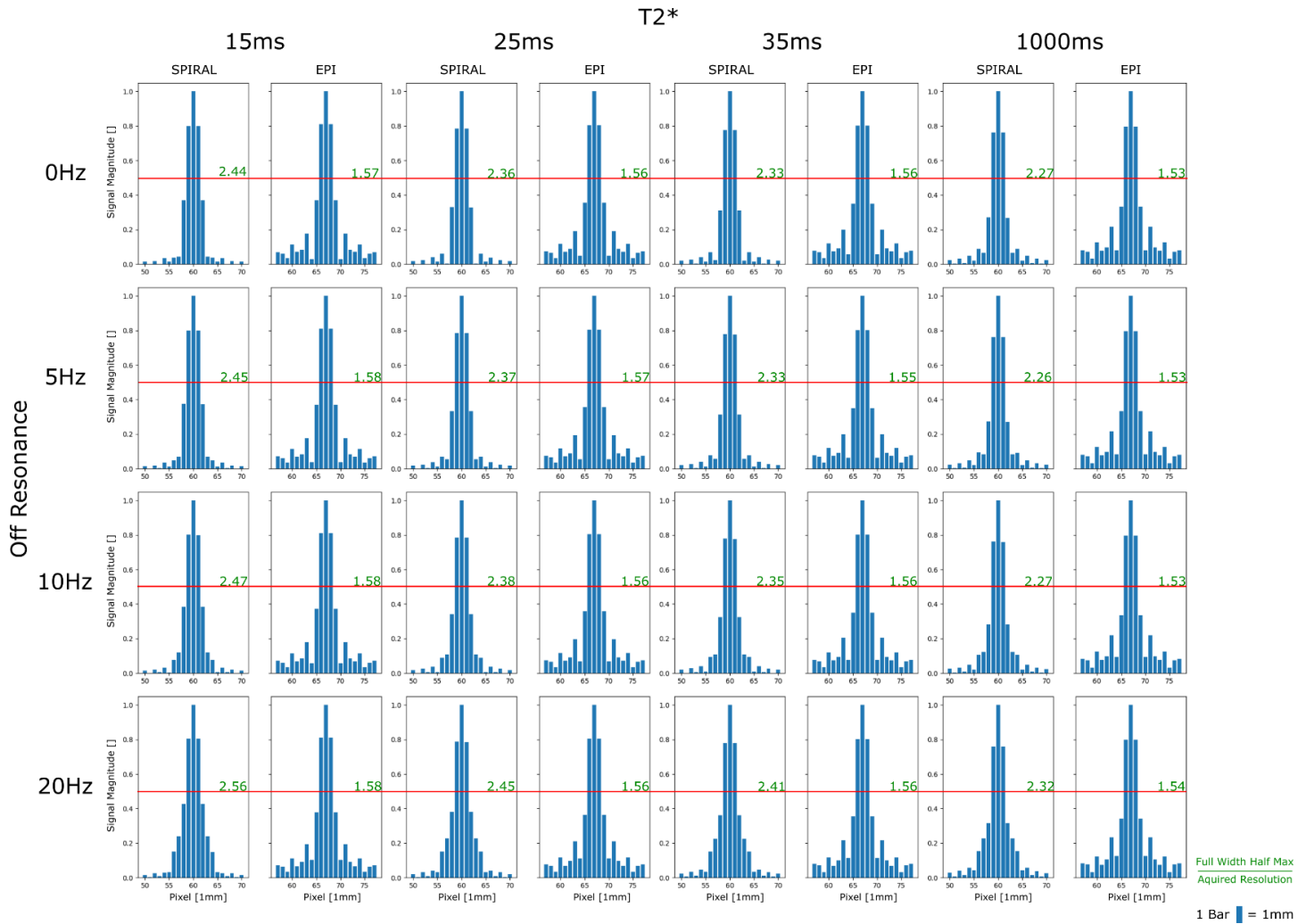


Figure 88: Intensity profiles through the PSF for both simulated EPI and spiral sequences using similar parameters to the in vivo image acquisitions (Chapter 12). Results are shown for a range of constant simulated T_2^* [15ms, 25ms, 35ms, 1000ms] and off resonance frequencies [0Hz, 5Hz, 10Hz, 20Hz]. The red line denotes 50% of the signal magnitude, which was used in the calculation of the FWHM normalised by the nominal acquired resolution (values were calculated using a linear interpolation between pixel surrounding the 50% signal magnitude).

10.6.3 Discussion

The width of the PSF means that at a nominal acquired resolution of $1.8 \times 1.8 \text{ mm}^2$ for the spiral sequence, the minimum distance between two infinitely small objects that would allow separation of the objects would be $2.27 \times 2 \text{ mm} = 4.5 \text{ mm}$. For the EPI sequence, the equivalent distance would be $1.53 \times 2.8 \text{ mm} = 4.2 \text{ mm}$. In both cases, this is in the absence of off-resonance or T_2^* related blurring. The implications of this are that we can only really resolve a maximum of less than two distinct microstructural states transmurally across the average RV wall (5-6 mm). This will limit the sensitivity of DT-CMR methods to transmural changes in microstructure and should be taken into account when interpreting the data presented in this work. As discussed above, off-resonance and finite T_2^* result in the width of the PSF increasing for the spiral sequence in both in-plane directions, but only in the phase encode direction for the EPI sequence. This may have implications for the optimal phase encode direction in future EPI studies. In future the nominal resolution would need to be increased to 1.3 mm and 0.8 mm for the EPI and spiral sequences respectively, this would allow resolution of three different transmural microstructural states and as such aid in the sensitivity to transmural changes in RV DT-CMR.

11 Ex Vivo DT-CMR

11.1 Introduction

Ex vivo DT-CMR is a method that has proven useful when investigating cardiomyocyte microstructure without the confounding effects of motion (cardiac and respiratory), strain, off-resonance, partial voluming (through higher spatial resolutions). While a number of other methods have been used to assess cardiac microstructure [30], [47] only DT-CMR approaches are viable for both *in vivo* imaging and *ex vivo* imaging of large mammalian hearts. Further, *ex vivo* DT-CMR is relatively non-destructive, can potentially provide whole heart data and can be used to validate *in vivo* data acquired with similar sequences.

Recent advances [244] using interleaved spiral DT-CMR have enabled *in vivo* acquisitions at higher spatial resolutions. The ability to easily segment a spiral acquisition into multiple spiral interleaves to acquire high-resolution data also means that interleaved spiral STEAM acquisitions may be better suited to *ex vivo* DT-CMR than single-shot EPI methods that are often used at present [299]. The aim of the following chapter is to modify and optimise an interleaved spiral acquisition to generate high-resolution *ex vivo* DT-CMR data in the right ventricle.

11.2 Methods

All acquisitions in this chapter were performed on a on a clinical 3T scanner (Siemens Vida) fitted with a 32-channel head coil (use of knee coil was considered but no test coil could be procured). In total 4 Formalin fixed hearts were scanned of which one was a porcine heart used for initial optimisation, two healthy human hearts (Heart 1[male, age at death 54, fixation time 10 years], Heart 2 [male, age at death 53, fixation time 10 years]) and one rTOF heart (male, age at death 61, fixation time 8 years, Surgery VSD closure & PV outflow enlargement). All hearts were immersion fixed and retained in Formalin. In preparation for imaging, the hearts were drained of fixative, rinsed, and patted dry. To reduce susceptibility artefacts while imaging, hearts were suspended in a perfluorinated polyether (Fomblin) for imaging. Hearts were supported within a cylindrical plastic container using melamine foam (Magic Eraser sponges). The long axis of the heart was parallel to the container cylinder axis, which was aligned vertically in the scanner to minimise the risk of leaking during long scans. The containers were supported within the head coil using foam padding and sandbags to reduce vibration and minimise the risk of sample movement. The imaging plane was aligned with the RV short axis, as described in Chapter 10.3 aiming to image a mid-ventricular slice.

The same STEAM sequence as covered in Chapter 10.2.2 was used here with modifications. The main difference was that the zonal selective field of view generated through the change in slice selective encoding during the 90° pulses was switched off (all pulses are slice selective in the through plane direction). No field map was acquired due to the smaller off-resonance effects found in the *ex vivo* setting and the shorter spiral readout durations that were used are less sensitive to off-resonance.

All spiral reconstruction and postprocessing was performed using the methods described in Chapter 10. No correction for motion-induced phase or sample movement (image registration) was performed as the sample was static. All spiral trajectories were designed with a FOV (after combining all spiral interleaves) linearly reducing from 360x360 mm² at the centre of k-space to 180x180 mm² at the k-space edge. Initial tests demonstrated higher quality images when the central k-space data was oversampled in this way. Due to the design of the sequence, all acquisitions were triggered using a simulated ECG signal with period 1500ms to allow for a high proportion of Mz to have recovered between sequence repeats.

The DT-CMR parameters shown in the results section of this chapter are E1, E2, E3, E2A, MD, FA. Further the HA is shown in early experiments, while in later experiments IA is used. This was due to an upgrade in the processing software aimed at better representing structures in the RV. However, the experiments where HA was used are for the initial optimisation of sequence parameters and a change to IA would not change any of the findings of this work.

SNR measures were obtained using a through-time method where k indexes the averaging used:

$$\bar{I}(x, y) = \frac{\sum_{k=1}^{Averages} I(x, y, k)}{Averages} \quad 57$$

$$\sigma(x, y) = \sqrt{\frac{1}{Averages - 1} \sum_{k=1}^{Averages} (I(x, y, k) - \bar{I}(x, y, k))^2} \quad 58$$

$$SNR_{Direction}(x, y) = \frac{\bar{I}(x, y)}{\sigma(x, y)} \quad 59$$

with $\bar{I}$ the raw data images of a single high diffusion direction at the pixel locations x and y. Using this method, it is possible to generate a pixel wise SNR map for each of the 6 high b value directions. To combine the 6 directions into a final pixel wise map the geometric mean (where n here indexes the 6 directions)

$$SNR(x, y) = \sqrt{\prod_{n=1}^6 SNR_{Direction}(x, y, n)} \quad 60$$

was used. All region-based measures were then collected from this map. Additional to this SNR assessment, DT specific data quality metrics are used in the following. The transmural change in HA is assumed to be linear in the LV [185]; as such, the mean coefficient of determination R^2 of a linear fit to transmural HA profiles in the LV allows inference of the quality of the underlying diffusion data (increase in R^2 = increase in underlying quality) [185], [187]. Additionally, to this measure, the standard deviation of the transverse angle in the LV can be used to assess DT data quality. This is due to the observation that in healthy LV myocardium, the transverse angle value should be close to 0° and so a larger standard deviation of this parameter is an indicator of deteriorating diffusion data quality [184], [187].

11.2.1 Protocol Optimisation

The initial optimisation of the *ex vivo* spiral DT-CMR methods was performed on the porcine heart. Data quality was evaluated using DT-CMR parameters as described above

11.2.1.1 Optimal Coil Combination Method

A Roemer type [277], [307] combination of receive coil channels weighted by the inverse of the spatial sensitivity of the receive coils (the coil sensitivity maps, CSM) results in improvements in SNR, particularly in suppressing background signal. However, coil combination using a coil sensitivity weighted approach requires the time-consuming acquisition of CSM.

We therefore compare 4 approaches:

1. SOS coil combination
2. CSM weighted combination with the CSM acquired using a separate STEAM as performed *in vivo* with spoiler gradients replacing the diffusion gradients to eliminate gradient echo signals from the third RF pulse and suppressing blood signal
3. CSM acquired using separate gradient echo scans using a flip angle of 90°
4. CSM obtained directly from the STEAM imaging data

The key sequence parameters for these tests are summarised in Table 6. One advantage of the GRE acquisition compared to the STEAM is that each interleave requires half the time (1RR trigger) to be acquired, as well as providing a better SNR. All coil sensitivity maps were calculated using the algorithm proposed by Inati et al. [308]. DWI were acquired with 30 averages of $b=600 \text{ s/mm}^2$ and 5 averages of $b=100 \text{ s/mm}^2$, 6 diffusion directions, $\Delta=300 \text{ ms}$ (this shorter diffusion time than commonly used *in vivo* was used to boost the low SNR in fixed *ex vivo* hearts via a reduction in T_1 related signal loss during TM). The four methods of coil combination listed above were compared to identify the optimal coil combination strategy for *ex vivo* DT-CMR.

Acquisition Name	Interleaves	Resolution [mm ²]	Slice Thickness [mm]	FOV [mm ²]	Readout Duration [ms]	TE [ms]	TR [ms]
CSM separate STEAM	15	2x2	2	180x180	2.8	19	1500
CSM separate gradient echo scans	15	2x2	2	180x180	2.8	1.7	1500
Main Data	35	1x1	2	Centre = 360x360 → Edge = 180x180	5.5	19	1500

Table 6: Sequence parameters of the sequences used to determine the optimal coil combination strategy.

11.2.1.2 Optimise b Value

Data were acquired with 30 averages of $b=500, 1000, 1250, 1500, 2000, 2500$ s/mm² and 5 averages of $b=100$ s/mm² to investigate effects of the b-value on *ex vivo* DT-CMR. Other sequence parameters were [6 diffusion directions, spiral interleaves=35, spiral readout duration=5.5 ms, resolution=1x1 mm², slice thickness=2 mm, $\Delta=300$ ms, TR=1500 ms, TE=24 ms]

11.2.1.3 Optimise Averages/Interleaves

To identify the most time-effective combination of averages and number of spiral interleaves, data was acquired with 50 averages at $b=1250$ s/mm² and 15 averages at $b=100$ s/mm² for spirals with 20, 25, 30, 35 and 40 interleaves. Other sequence parameters were [6 diffusion directions, spiral readout duration=[9.5, 7.6, 6.4, 5.5, 4.9] ms respectively, resolution=1x1 mm², slice thickness=2 mm, $\Delta=300$ ms, TR=1500 ms, TE=21 ms]. For each interleaved dataset, a varying number of averages [40, 32, 23, 20] was processed to match the acquisition duration (2hours 15 min) between averages and interleaves.

11.2.1.4 Compare the Optimal Spiral Protocol to EPI

For comparison with an adaptation of the single shot EPI methods typically used for *in vivo* imaging at the Royal Brompton Hospital, the optimised spiral protocol shown in Table 7 was used. The acquisition duration for this protocol was 2 hours per slice. To match the total acquisition duration with a matched resolution, slice thickness and b-value by the single shot EPI method, the protocol shown in Table 7 was used, with the number of averages increased to provide matched acquisition time. Single shot EPI images were reconstructed using the product reconstruction to produce magnitude and phase images to support complex averaging: Images acquired with the same b-value and diffusion encoding direction were combined using complex averaging without phase correction. Complex averaging was performed by a purpose-built Python script. All images were processed with the same DT-CMR processing tool as described in the methods Chapter 10.4.1.8 .

	<i>EPI</i>	<i>SPIRAL</i>
<i>Averages $b=1250$ [s/mm²]</i>	700	40
<i>Averages $b=100$ [s/mm²]</i>	120	7
<i>Interleaves</i>	-	20
<i>Resolution [mm²]</i>	1x1	1x1
<i>Slice Thickness [mm]</i>	2	2
<i>FOV [mm²]</i>	84(Phase) x 320(Frequency)	Centre = 360x360 → Edge = 180x180
<i>Readout Duration [ms]</i>	84	9.5
<i>TE [ms]</i>	111	21
<i>TR [ms]</i>	1500	1500
<i>Δ [ms]</i>	300	300
<i>Parallel Imaging</i>	SENSE	-
<i>Dwell Time [μs]</i>	1.7	2.5

Table 7: Sequence parameters of time matched spiral and EPI DT-CMR protocols.

11.2.1.5 The Effect of Diffusion Time

The previous tests were performed to optimise acquisition parameters before applying the techniques in healthy human hearts. Initial tests in a healthy human *ex vivo* heart demonstrated poor quality images due to low SNR. One method of achieving improved SNR in STEAM acquisitions is to reduce the mixing time, T_M , during which the signal available for imaging decays with T_1 . The T_1 of formalin fixed myocardium is shorter than *in vivo* myocardium (see Section 13.3.4) and a reduction in T_M is therefore an effective method of improving SNR *ex vivo*. However, the relative sensitivity of the DT-CMR results to different length scales is dependent on the diffusion time, Δ , which is equal to T_M + the time from the centre of the first diffusion gradient to the centre of the 2nd RF pulse (approx. 4.7ms) + the time from the centre of the 3rd RF pulse to the centre of the second diffusion gradient (approx. 5.7ms). Kim et al. [322] demonstrated that changes in diffusion time(Δ) can result in changes in the secondary and tertiary eigenvector in muscle tissue. As a result, experiments were performed to assess the effects of Δ on the DT-CMR results in fixed *ex vivo* hearts. The protocol was set to acquire 50 averages of $b = 1250 \text{ s/mm}^2$ and 8 averages of $b = 100 \text{ s/mm}^2$ for a range of different Δ values = 100, 200, 300, 500, 700 and 1000 ms, with other parameters fixed as in Table 2.

11.2.2 Evaluation of the Optimised *Ex Vivo* Protocol

11.2.2.1 Healthy Human 1

For this heart, three different in-plane resolutions [$1 \times 1 \text{ mm}^2$, $1.5 \times 1.5 \text{ mm}^2$, $2 \times 2 \text{ mm}^2$] all with a slice thickness of 2 mm and the parameters in Table 8 were acquired in a mid-ventricular short axis slice to demonstrate the effect of the spatial resolution on the ability to assess the fine structure of the thin right ventricle.

11.2.2.2 Healthy Human 2

Three consecutive mid ventricular 2mm slices were acquired in this heart using the parameters in Table 8. To allow better delineation of potential compact myocardium an anatomical TSE sequence with 10 averages was acquired covering the same mid ventricular location (Table 8). In order to further understand signal behaviour, a T_1 map and a T_2 map were acquired in the mid slice using the parameters in Table 8.

11.2.2.3 rTOF

Three consecutive mid ventricular 2mm slices were acquired in this heart using the parameters in Table 8. The same anatomical, T₁ and T₂ protocol used for the 2nd healthy human heart were used here for the mid slice.

	Healthy 1 DT-CMR	Healthy 2 DT-CMR	TOF DT-CMR	TSE slow inversion recovery T1 mapping	Spin Echo T2 mapping	TSE anatomical
Averages $b=1250$ [s/mm ²]	120	120	120	-	-	-
Averages $b=100$ [s/mm ²]	15	15	15	-	-	-
Interleaves	20	20	20	-	-	-
Resolution [mm ²]	1x1, 1.5x1.5, 2x2	1x1	1x1	1.72x1.72	1.17x1.17	0.7x0.7
Slice Thickness [mm]	2	2	2	5	8	0.6
FOV [mm ²]	Centre = 360x360 → Edge = 180x180	Centre = 360x360 → Edge = 180x180	Centre = 360x360 → Edge = 180x180	107 (Phase) x 160 (Frequency)	150 (Phase) x 300 (Frequency)	107 (Phase) x 160 (Frequency)
Readout Duration [ms]	9.5, 4.5, 3.2	9.5	9.5	-	-	-
TE [ms]	21	21	21	15	7.7, 9, 10, 12, 14, 16, 19, 22, 25, 28, 31, 35, 40, 45, 50, 60, 70, 80, 100, 120, 140, 160, 200, 250	13
TR [ms]	1500	1500	1500	3000	1500	9000
Δ [ms]	100	100	100	-	-	-
Pixel Bandwidth [Hz]	-	-	-	130	781	225
TI [ms]	-	-	-	30, 50, 70, 90, 110, 130, 150, 170, 200, 250, 300, 350, 500, 600, 800, 1000, 1500, 2000	-	-

Table 8: Sequence parameters deployed in healthy and rTOF hearts. Both the spiral DT-CMR protocols and the supporting sequences (T1, T2 and anatomical) are shown.

11.3 Results

11.3.1 Protocol Optimisation in the porcine heart

Figure 89.a shows the E2A, HA, FA and MD for all 4 coil combination strategies. Results appear visually similar for all techniques apart from SOS combination, which shows lower overall MD and higher noise levels in the E2A and HA maps. This visual assessment is supported by Figure 89.c and Figure 89.b, where SOS data show lower mean transmural HA R^2 and higher transverse angle standard deviation compared to the other 3 coil combination methods.

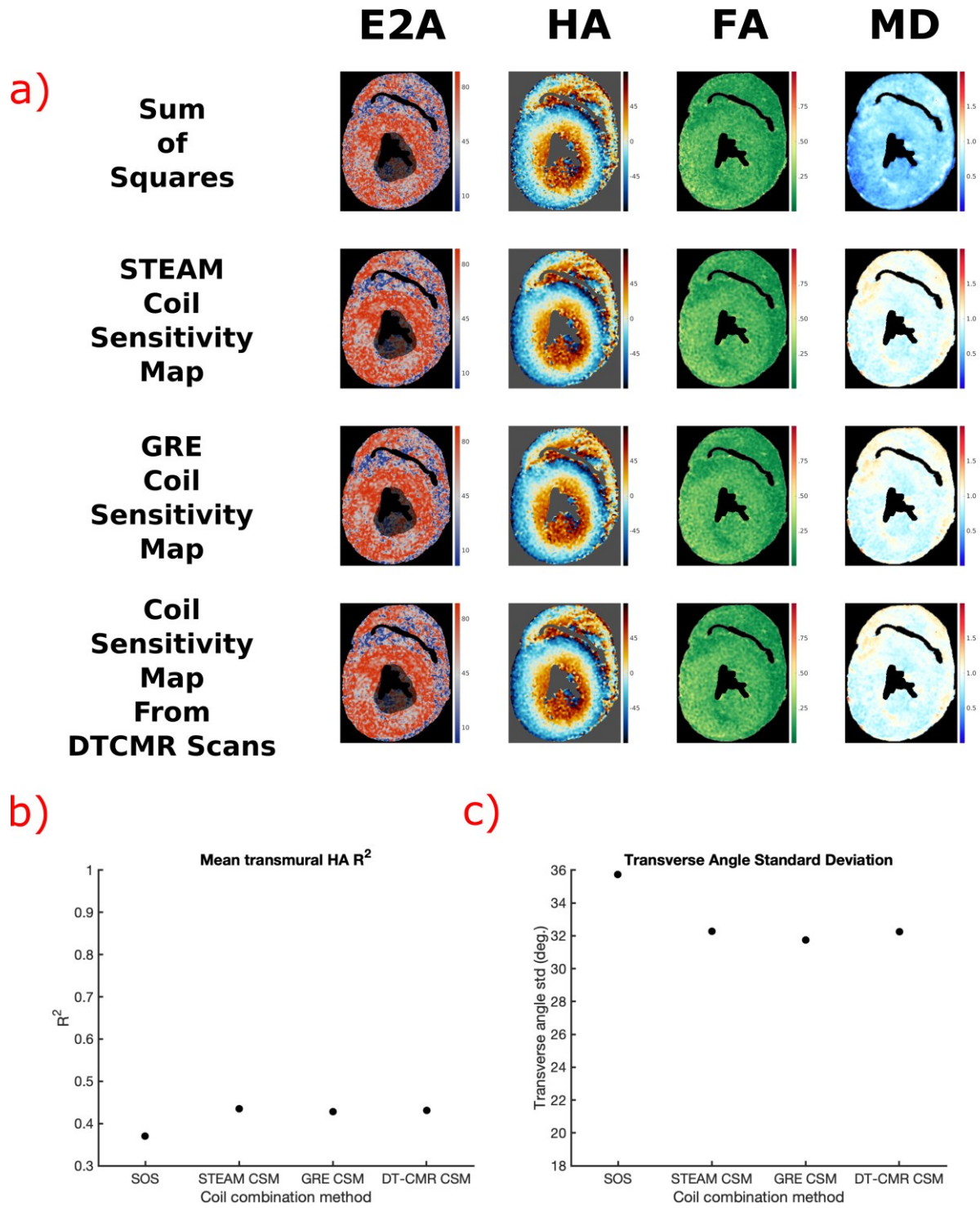


Figure 89: The results of the investigation into the effect of coil combination strategies on porcine heart ex vivo DT-CMR data. a) DT-CMR maps (absolute second eigenvector angulation (E2A [$^{\circ}$]), HA [$^{\circ}$], FA [$^{\circ}$], MD [10^{-3} mm 2 /s])) for the same dataset using different coil combination strategies (Sum of Squares, STEAM-based spiral data acquired in separate dedicated coil sensitivity scans, gradient echo spiral data acquired separately for coil sensitivity data, extraction of the coil sensitivity data from the diffusion encoded spiral STEAM data. b) Plot of mean transmural HA R^2 for the data shown in (a). c) Plot of transverse angle standard deviation of the data shown in (a). Reproduced from [323]

The results of the b value tests are shown in Figure 90.a. Visibly the least noisy DT-CMR maps are those from the $b=1000 \text{ s/mm}^2$ and $b=1250 \text{ s/mm}^2$ data. The mean transmural R^2 plots (Figure 90.b) and the transverse angle standard deviation (Figure 90.c) plots show a maximum and minimum respectively around $b=1000\text{--}1250 \text{ s/mm}^2$ supporting this as the optimal range for this *ex vivo* protocol.

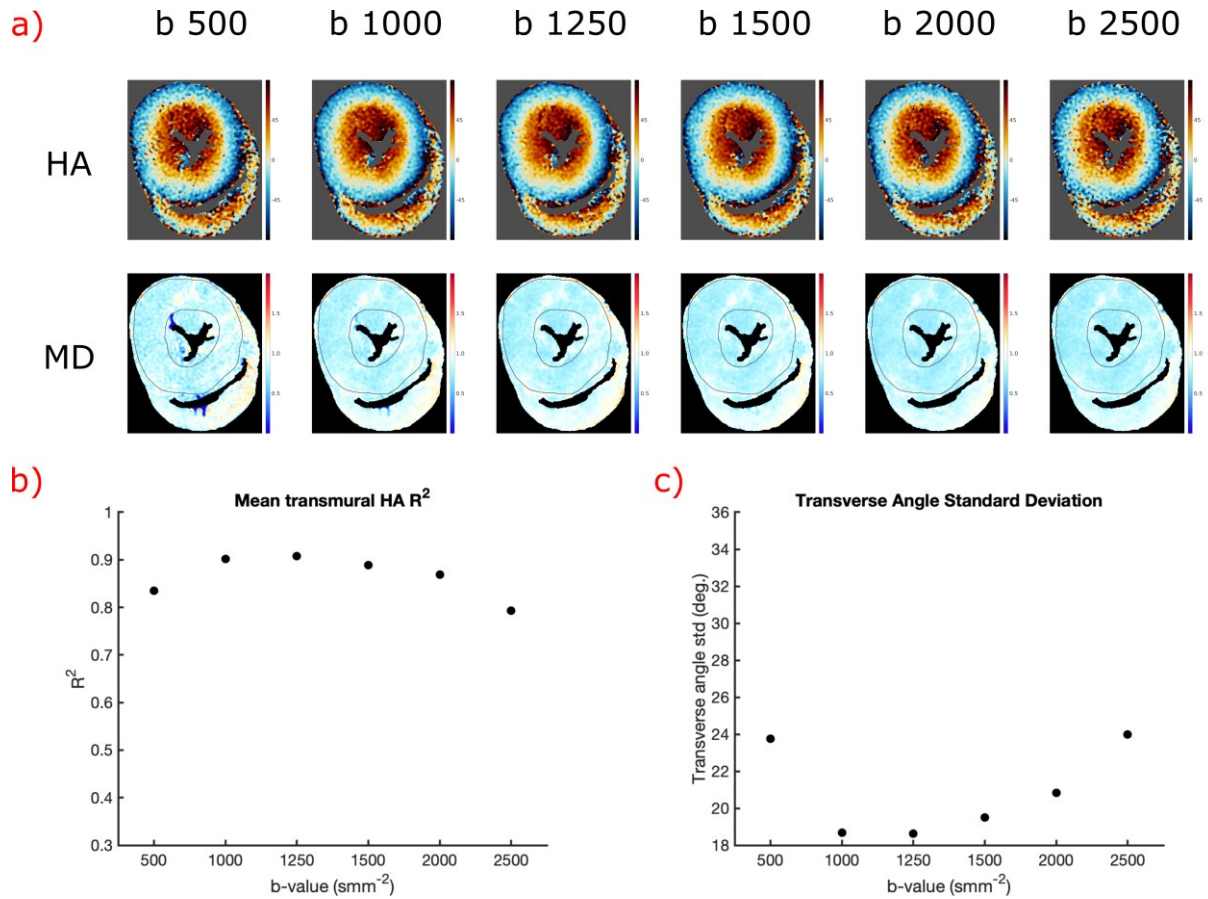


Figure 90: a) DT-CMR (HA [$^{\circ}$], MD [$10^{-3} \text{ mm}^2/\text{s}$]) maps showing the effect of the main b value in the porcine heart *ex vivo* spiral STEAM data. All data was acquired with the matched sequence parameters b) Plot of mean R^2 of the transmural variation in HA with b-value for the data shown in (a). c) Plot of standard deviation of the transverse angle for the data shown in (a). Reproduced from [323]

Figure 91 shows synthetic $b=0$ s/mm² images calculated from the $b=100$ s/mm² and $b=1250$ s/mm² in the tensor calculation and HA maps with an increasing number of spiral interleaves and a fixed 50 averages. An off-resonance artefact caused by air or thrombus in a coronary artery (Figure 91.a) decreases in size with an increasing number of interleaves (shorter spiral interleaves). However, there is visually little change in the HA maps. This suggestion that longer spiral interleaves do not result in substantial artefacts in the DT-CMR parameter maps for the range tested is supported by the mean transmural HA R^2 and the transverse angle standard deviation which change very little between the different numbers of interleaves (Figure 91.c, Figure 91.d).

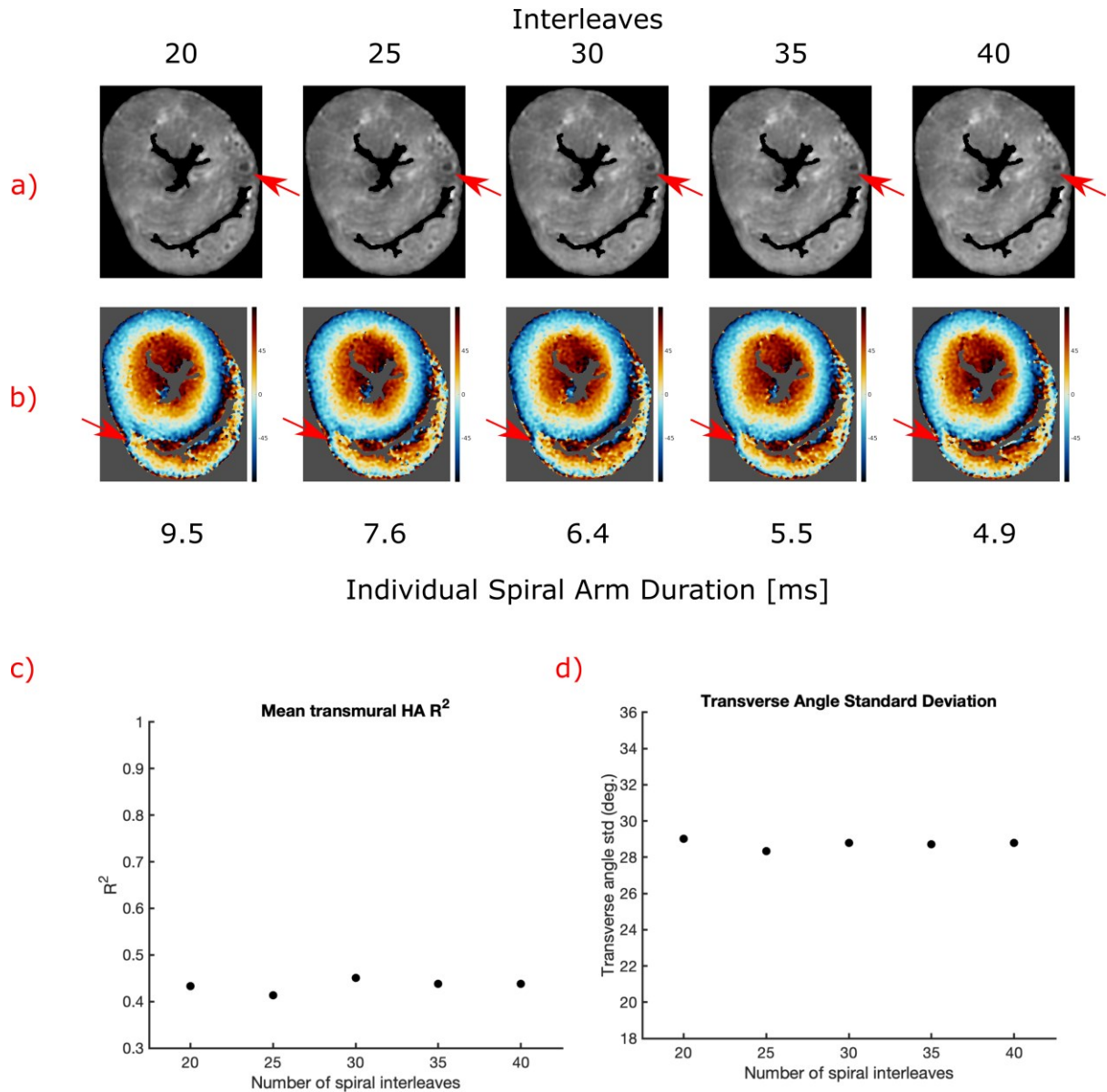


Figure 91: Calculated porcine heart images (a) with corresponding HA [°] (b) maps of the same mid ventricular slice in a Formalin fixed porcine heart for varying numbers of spiral interleaves with acquisition-time-matched field of view, spatial resolution, and number of averages. The values under row (b) show the duration of a single spiral interleave. Red arrows in A indicate an off-resonance artefact caused by thrombus or air in the coronary circulation that becomes more severe with increasing spiral duration. Red arrows in (b) show decreasing artefact in the HA with reduced spiral duration c) Plot of mean R^2 of the transmural variation in HA with b-value for the data shown in (a). d) Plot of standard deviation of the transverse angle for the data shown in (a). Reproduced from [323]

When investigating the most time effective combination of interleaves and averages (Figure 92) the DT-CMR maps appear smoother as the number of interleaves decreases and the number of averages increases. The mean transmurals HA R^2 is maximum and transverse angle standard deviation is minimum at the lowest number of interleaves.

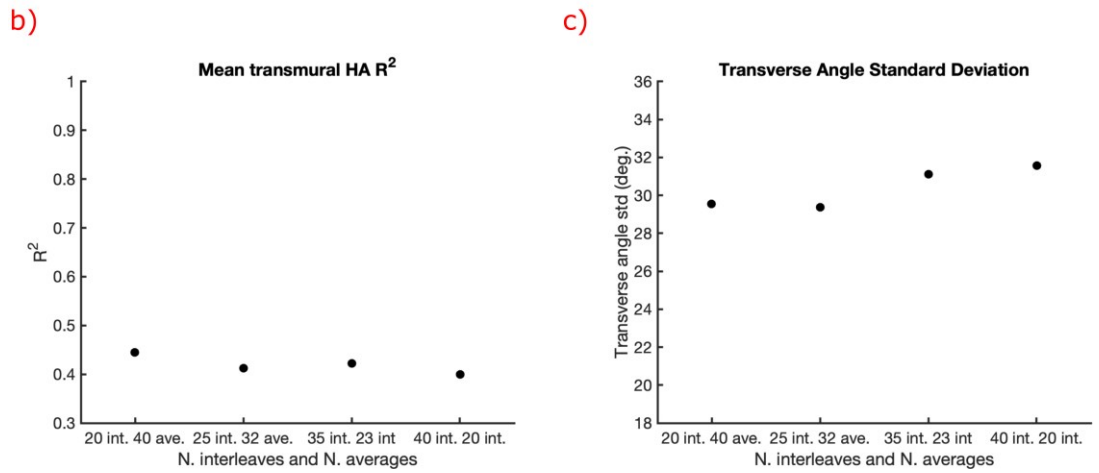
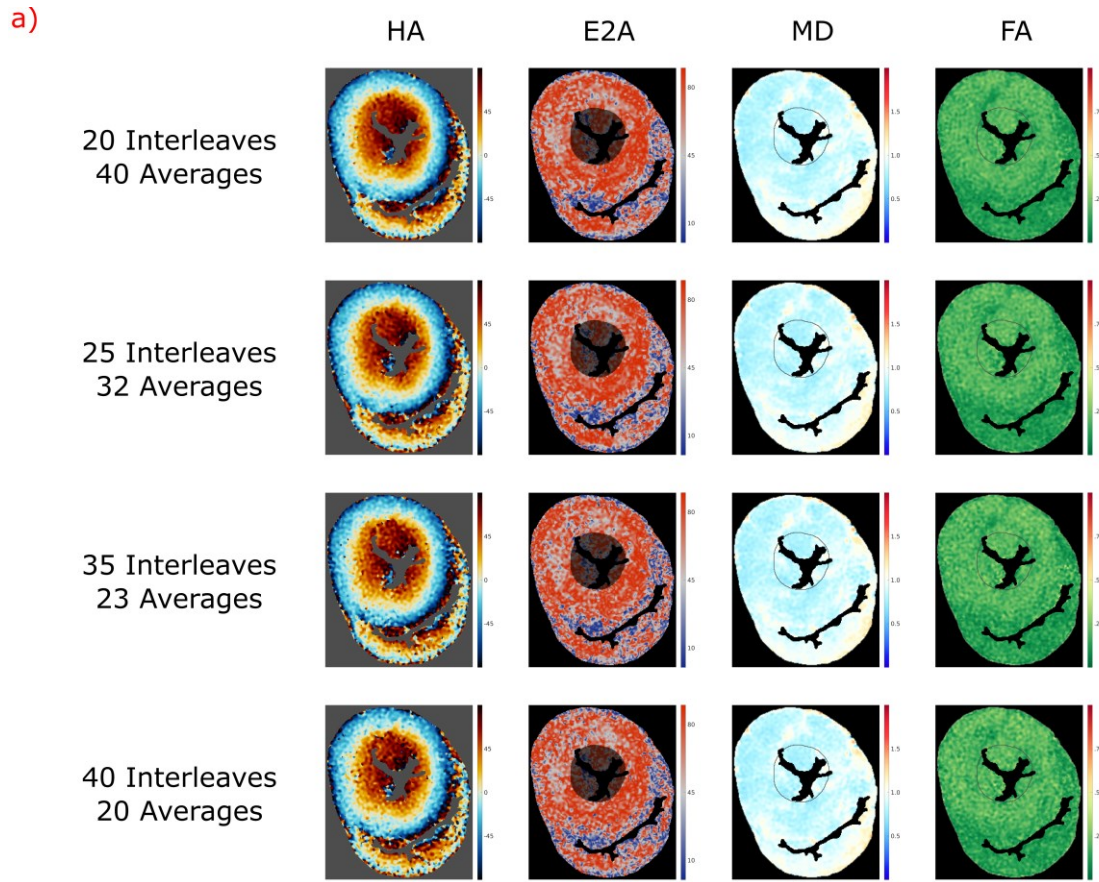


Figure 92: In the porcine heart for protocol optimization: a) DT-CMR maps (HA[°], E2A [°], MD[10^{-3} mm²/s], FA [°]) reconstructed from data acquired with similar total acquisition duration but increasing numbers of spiral interleaves and decreasing numbers of averages. Total acquisition time was approximately 2h for each dataset. b) Plot of mean R^2 of the transmural variation in HA with b-value for the data shown in (a). c) Plot of standard deviation of the transverse angle for the data shown in (a). DT-CMR maps appear slightly smoother and both the HA R^2 and standard deviation of the transverse angle are consistent with improvements in image quality with more averages and fewer interleaves. Reproduced from [323].

Figure 93 shows DT-CMR maps obtained from both the EPI and spiral data with an acquisition duration of 2 h/slice for both techniques. The maps from the interleaved spiral data show a clear improvement in image quality with reduced noise in these maps.

The results of the tests assessing the effects of Δ are shown in Figure 94. The difference between all maps (IA, E2A, MD, FA) at each value of Δ is small (Figure 94), but a general increase in MD and FA can be observed as Δ increases. The $\Delta=700$ ms and $\Delta=1000$ ms results show a less smooth structure, but the regional patterns for each map are similar to those obtained with other Δ values. This can also be seen in the accompanied violin plots, which show values for three different regions (Figure 95).

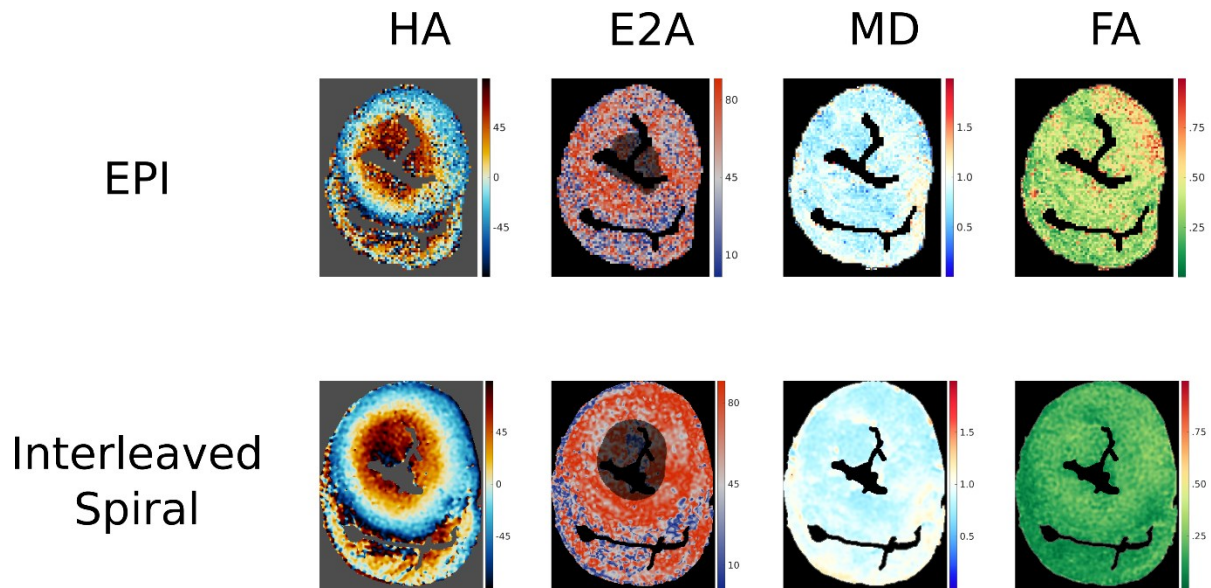


Figure 93: Comparison of HA[°], E2A[°], MD[10⁻³ mm²/s] and FA[] for a single midventricular slice in a porcine ex vivo heart using a single-shot EPI readout and an interleaved spiral readout. Both using the same STEAM approach, multiple averages (both using complex averaging) and the same total acquisition time of 2 hours per slice. Reproduced from [323].

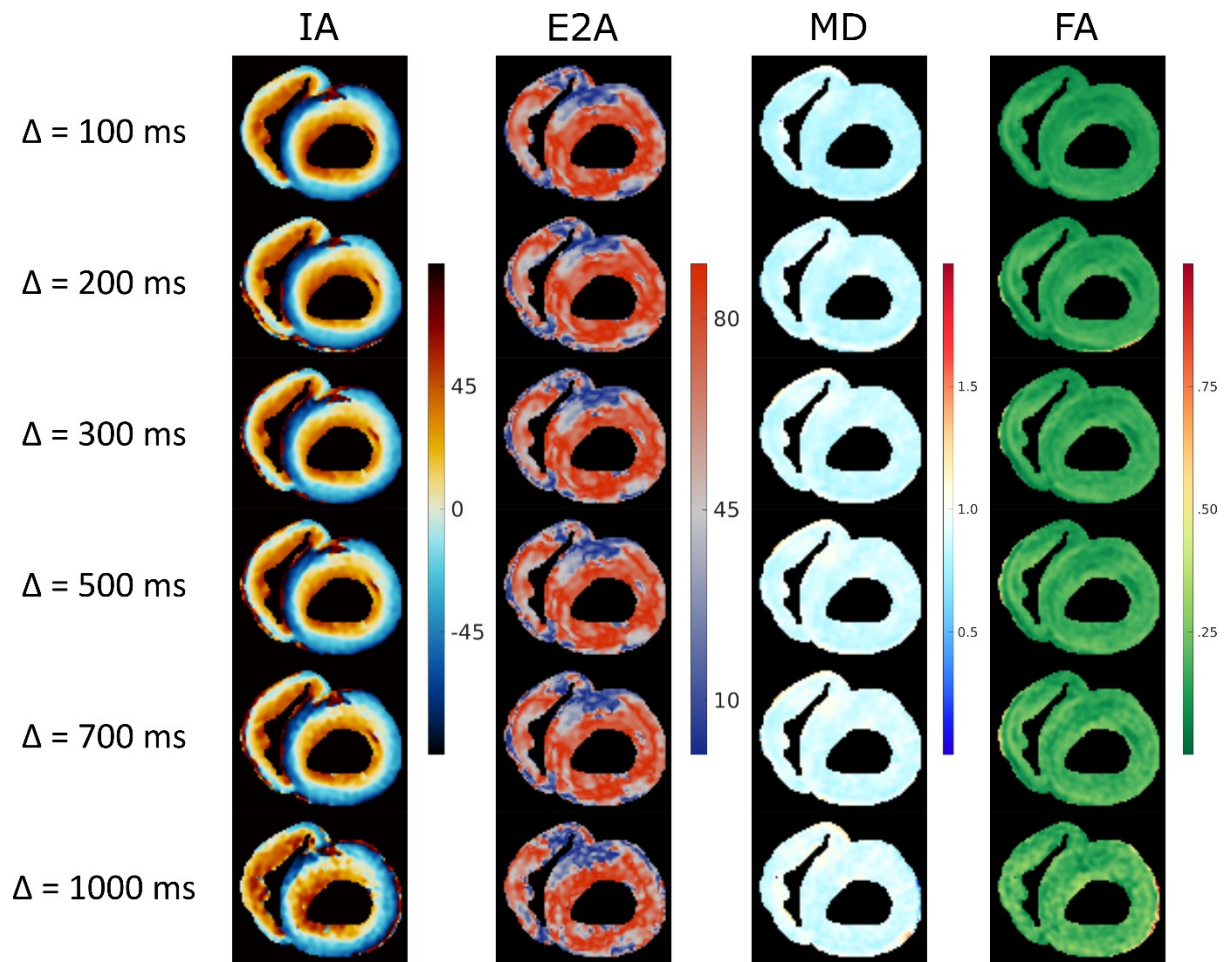
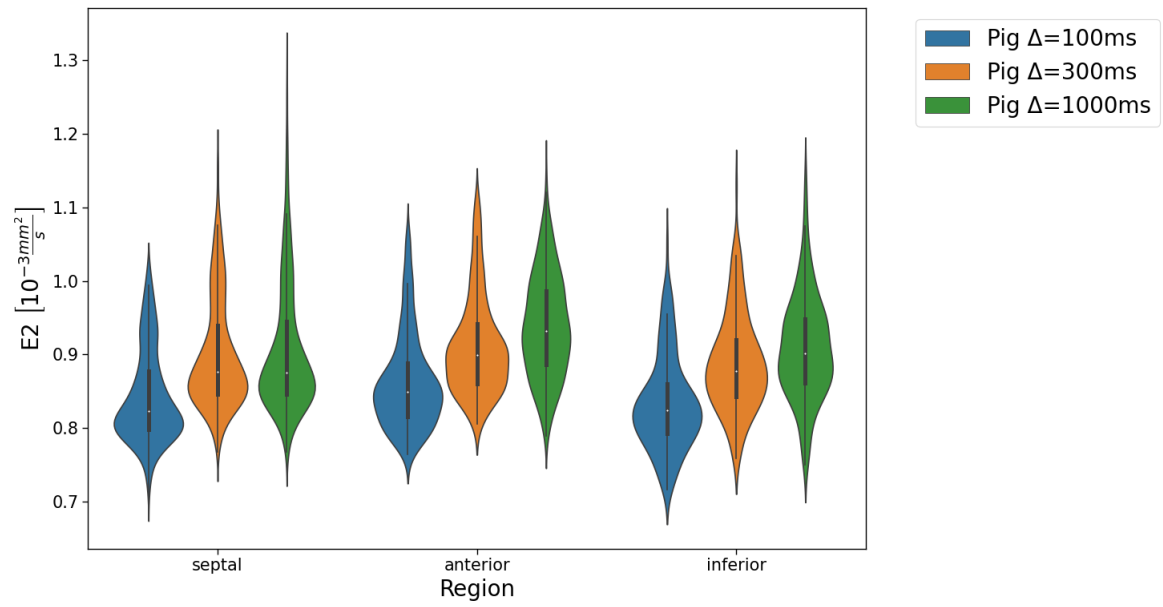
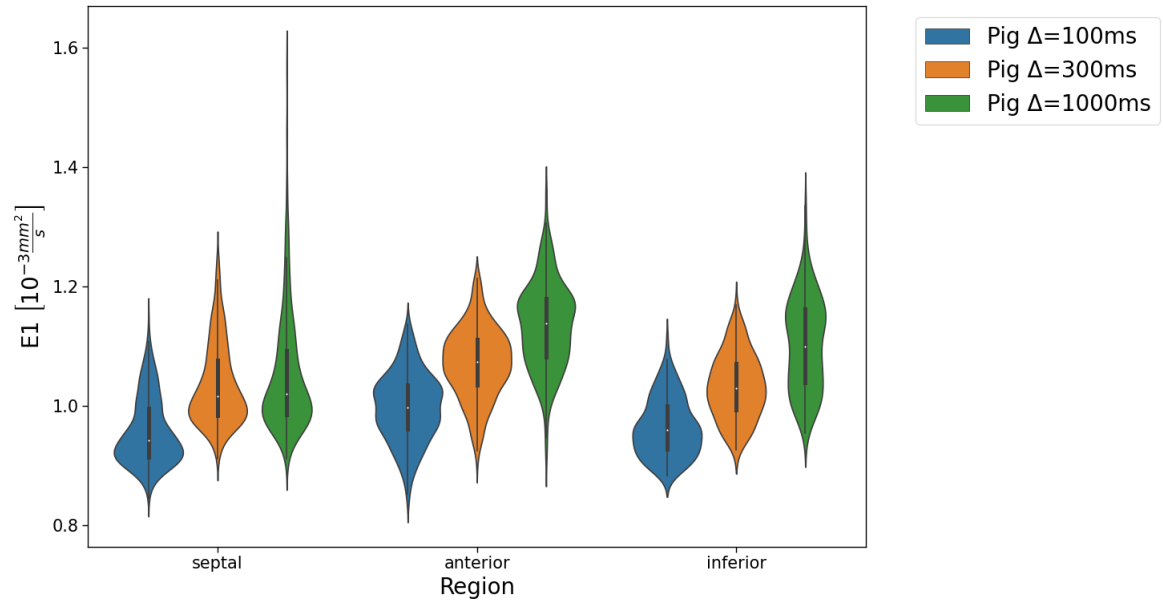
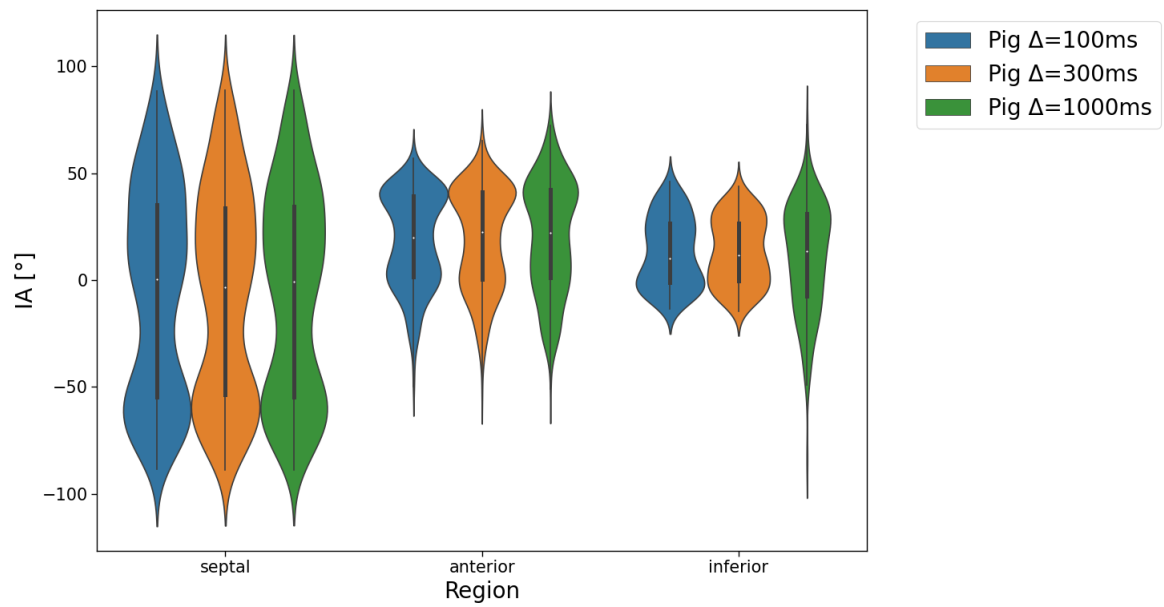
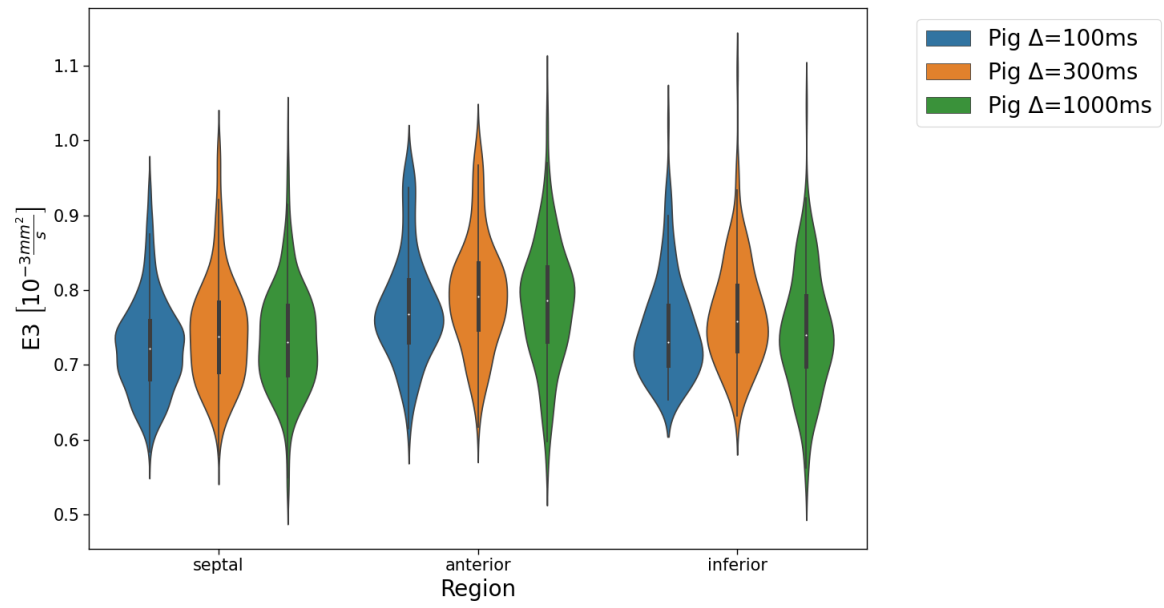
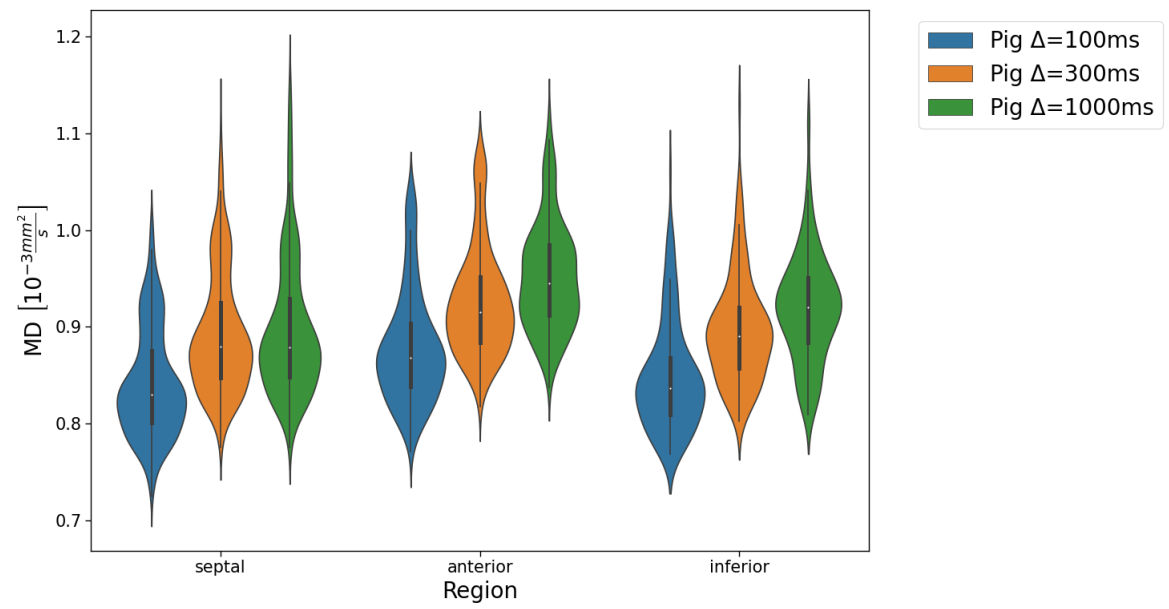
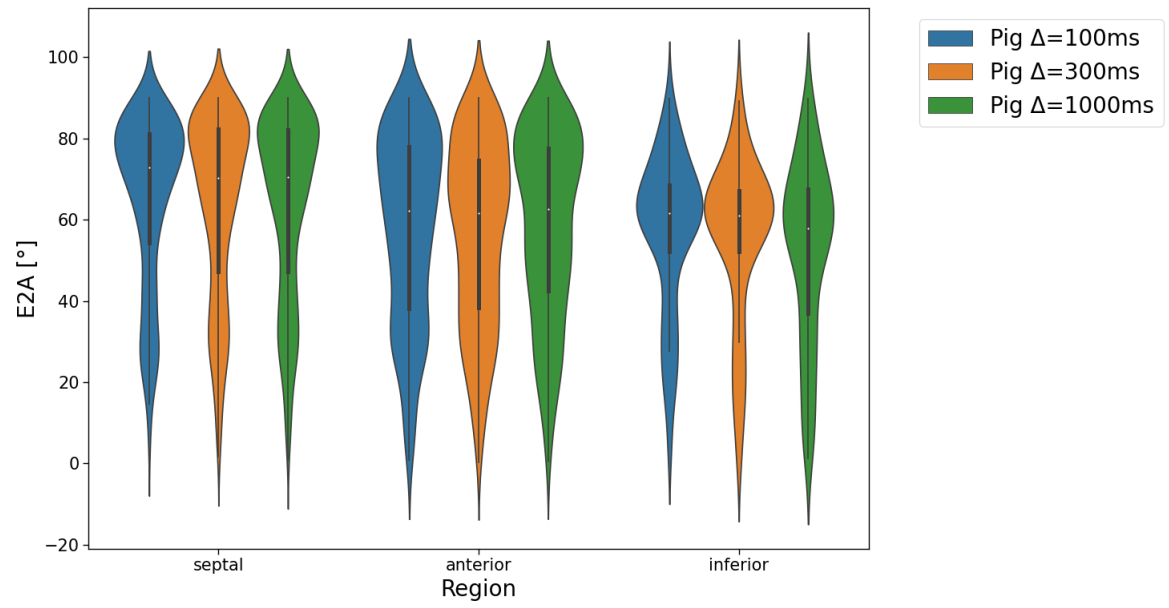


Figure 94: DT-CMR maps (IA [°], E2A[°], MD[$10^{-3} \text{ mm}^2/\text{s}$], FA[°]) for a range of Δ values (100, 200, 300, 500, 700, 1000) ms (Porcine heart).







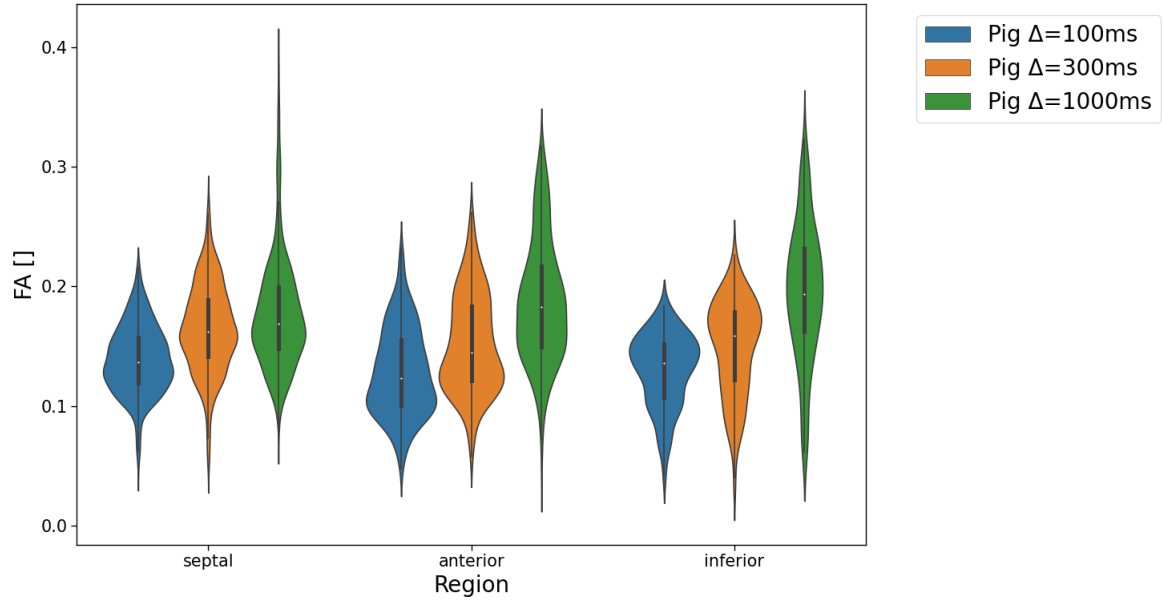


Figure 95: Violin plots of three different Δ (100 ms, 300 ms, 1000 ms) for the septal, inferior, and anterior RV regions (Porcine heart). Plots are shown for the following DT-CMR parameters E_1 [], E_2 [], E_3 [], IA [°], E_2A [°], MD [10^{-3} mm²/s], FA [].

In the SNR maps (Figure 96) it is visible that SNR values are highest for lower Δ values.

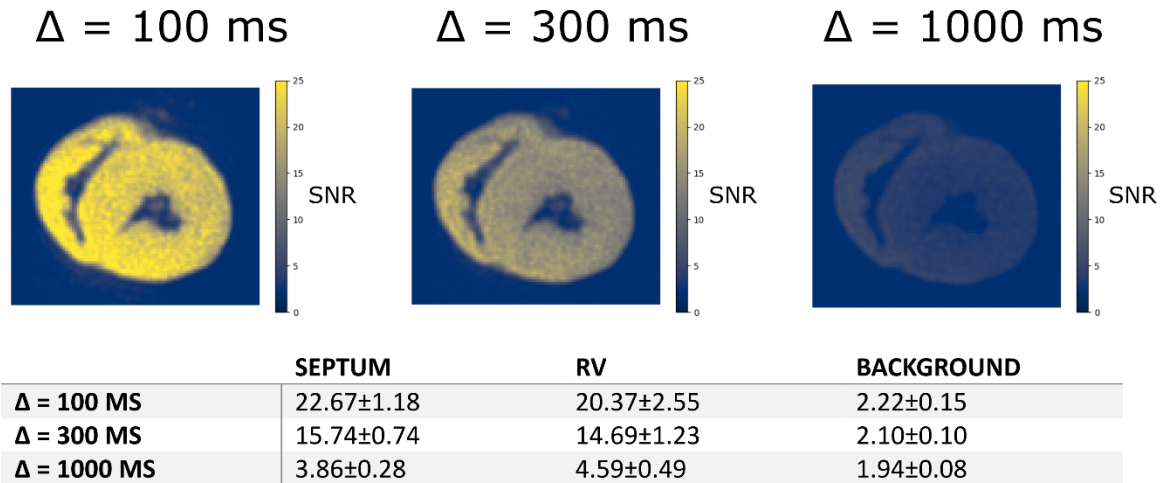


Figure 96: Porcine heart SNR maps of Δ values (100, 300, 1000) ms for $b=1250 \text{ s/mm}^2$ and accompanying regional measurements.

11.3.2 Healthy Human Heart

Figure 97 demonstrates the benefits of the high-resolution DT-CMR available with the interleaved spiral sequence. While for the same number of averages a higher resolution results in noisier DT-CMR maps (Figure 97), the $1\times1\text{mm}^2$ resolution provides additional detail, including in the IA in the anterior right ventricular free wall (red arrows Figure 97). Similar details are evident when the data is displayed as superquadric glyphs with additional detail visible at the higher resolution (Figure 98).

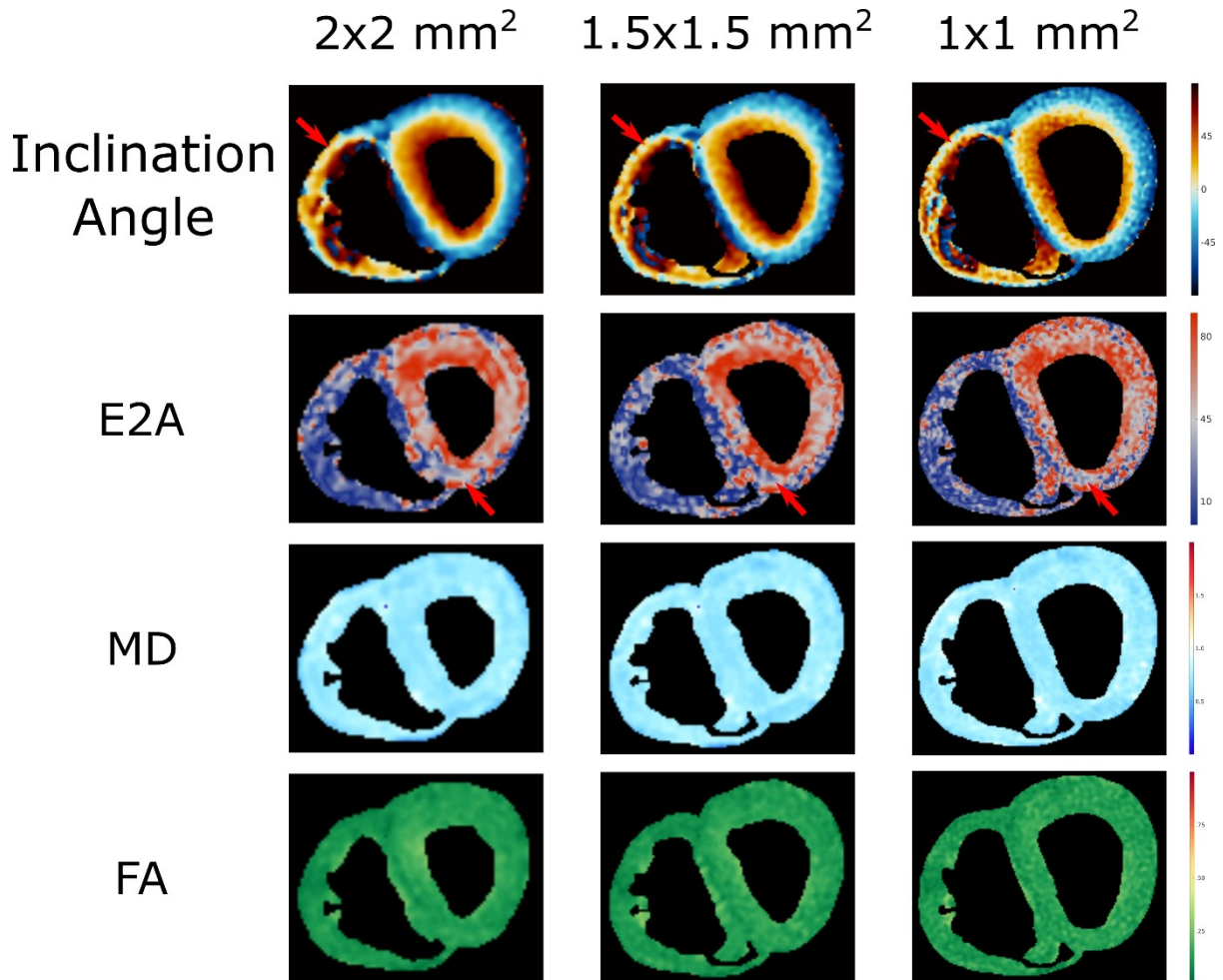
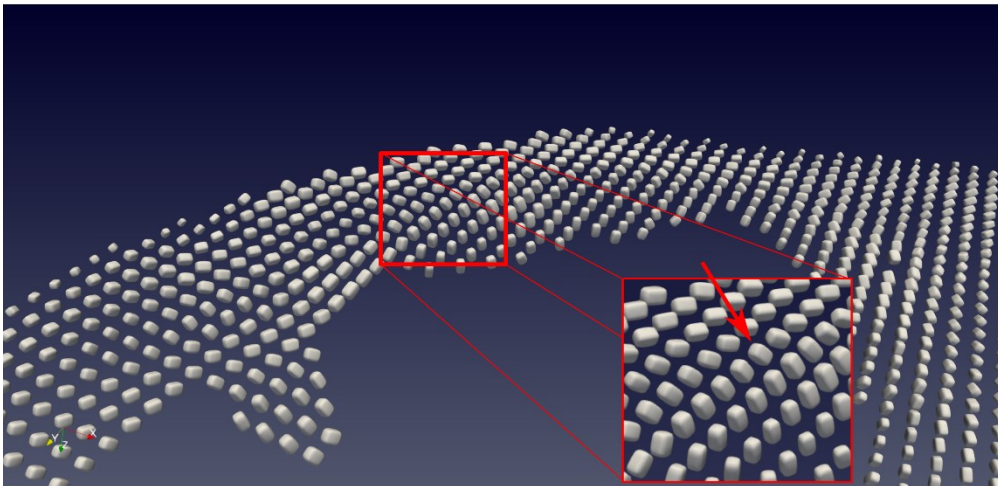
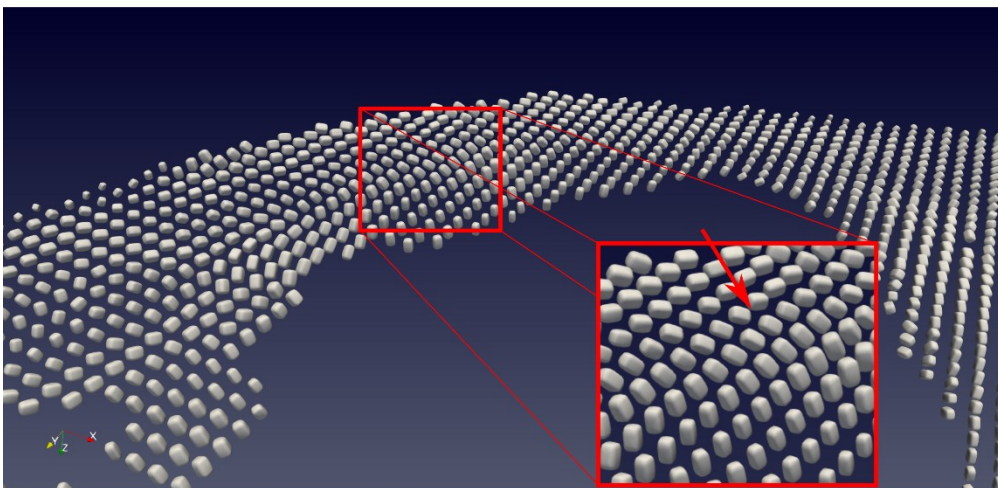


Figure 97: DT-CMR maps (IA [°], E2A[°], MD[$10^{-3}\text{ mm}^2/\text{s}$], FA[$\%$]) for the same midventricular slice in a healthy human ex vivo heart using 3 different in-plane resolutions ($2\times2\text{mm}^2$, $1.5\times1.5\text{mm}^2$, $1\times1\text{mm}^2$). All other sequence parameters are the same.

$2 \times 2 \text{ mm}^2$



$1.5 \times 1.5 \text{ mm}^2$



$1 \times 1 \text{ mm}^2$

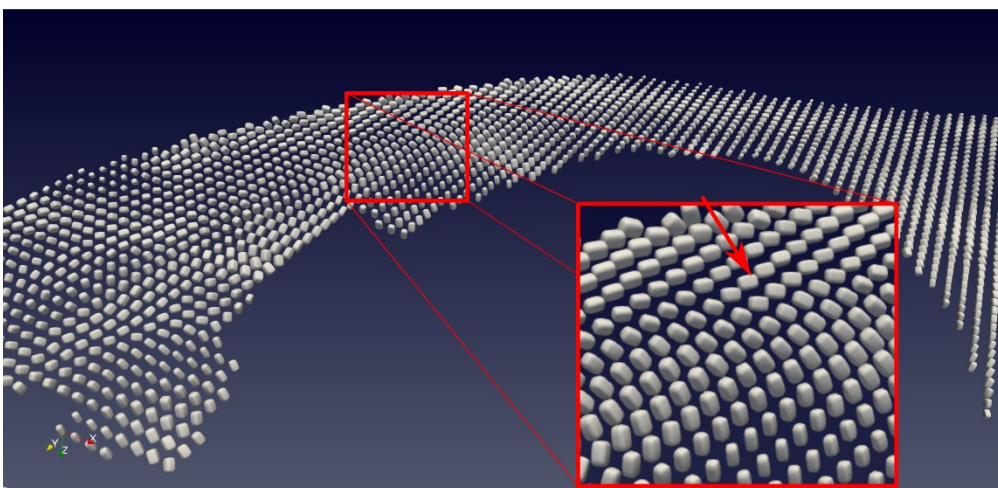


Figure 98: The diffusion tensor shown as glyphs for 3 different resolutions [$2 \times 2 \text{ mm}^2$, $1.5 \times 1.5 \text{ mm}^2$ and $1 \times 1 \text{ mm}^2$] of the same midventricular slice from a healthy human heart. The same region in the superior RV free wall is shown magnified in each image. The finer detail in transmural change is evident in the example with the higher resolution.

The IA and E2A obtained from data acquired in the two healthy human *ex vivo* specimens are shown in Figure 99.a. A T1 map and a T2 map for the mid slice in Heart 1 are also shown with a mean value of 149 ± 15 ms and 29 ± 5 ms respectively. Heart 1 has higher SNR when compared to the equivalent data acquired in healthy heart 2 (Figure 101). Further do all hearts have similar background SNR levels (Figure 101). In the LV, both hearts show similar patterns in IA and E2A. For the E2A both hearts also show similar patterns in the RV. However, in the IA Heart 2 shows more of a suggestion that there are two distinct cardiomyocyte orientations in the RV free wall (both positive angles shown in orange and negative angles shown in blue) compared to the healthy heart 1 where the data is more consistent with a uniform IA across the RV (Figure 99).

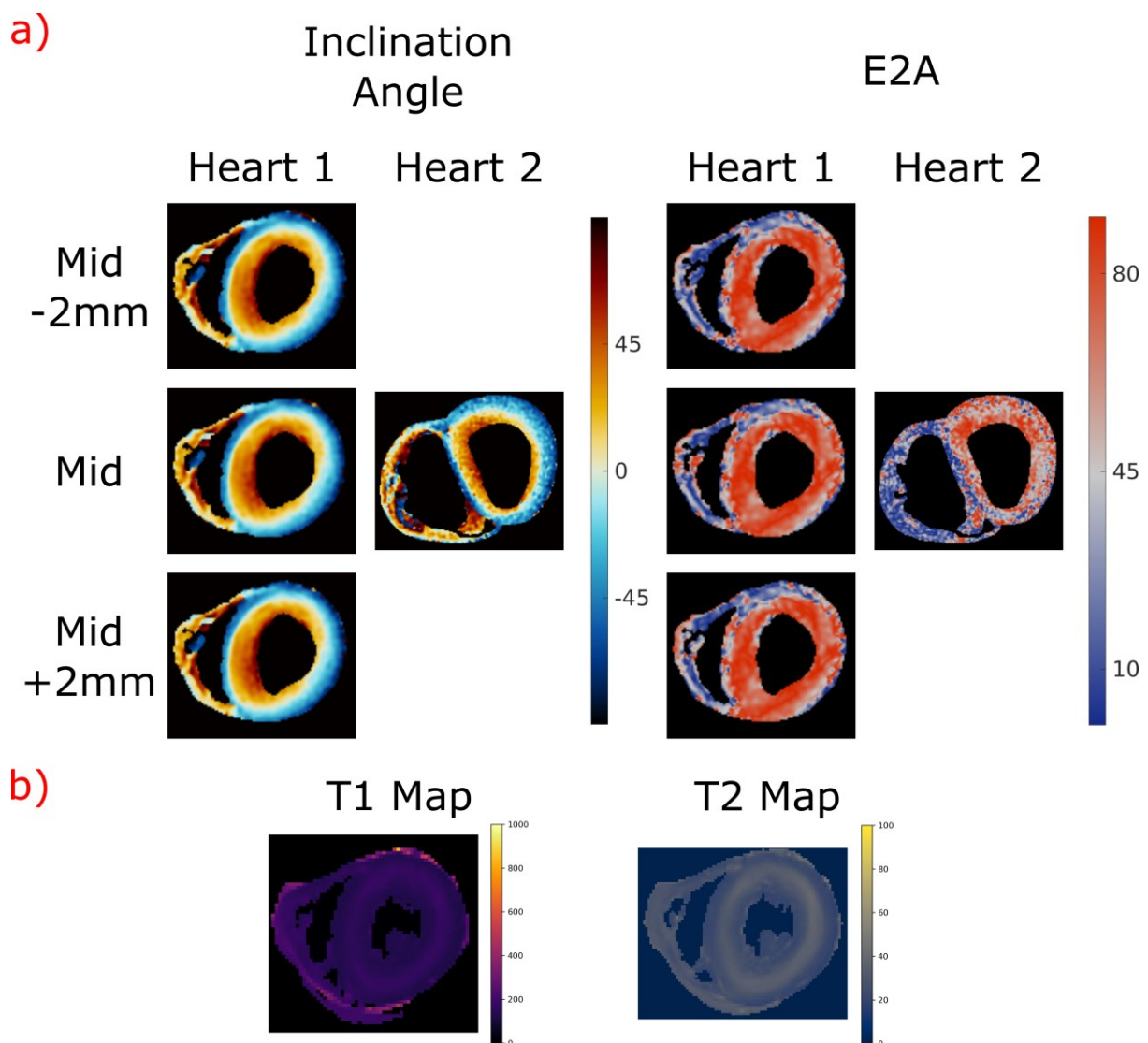
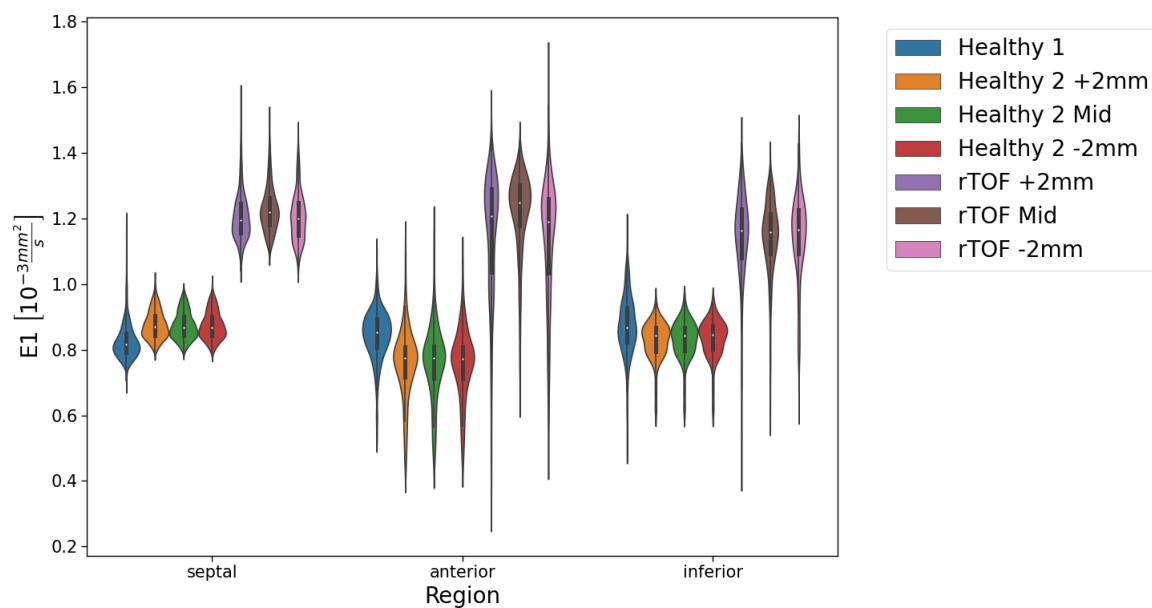
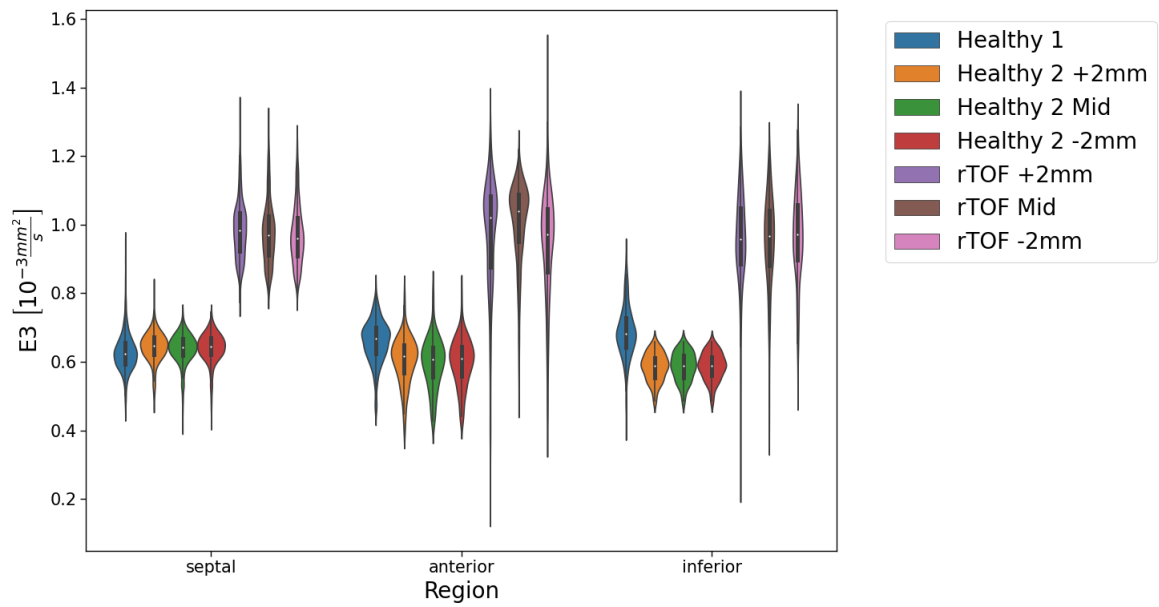
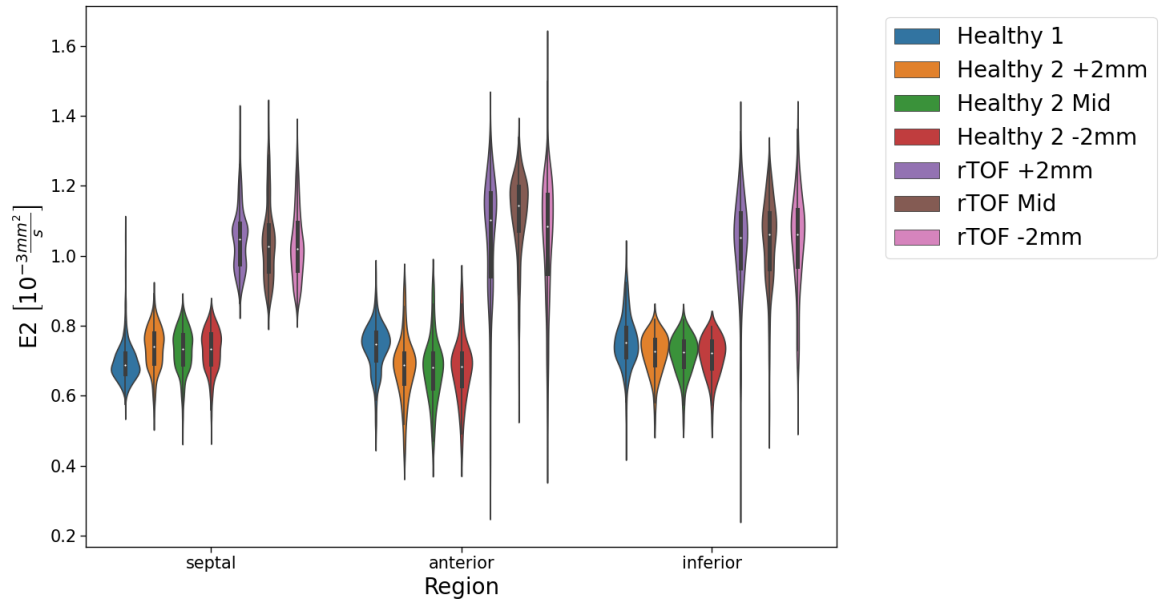


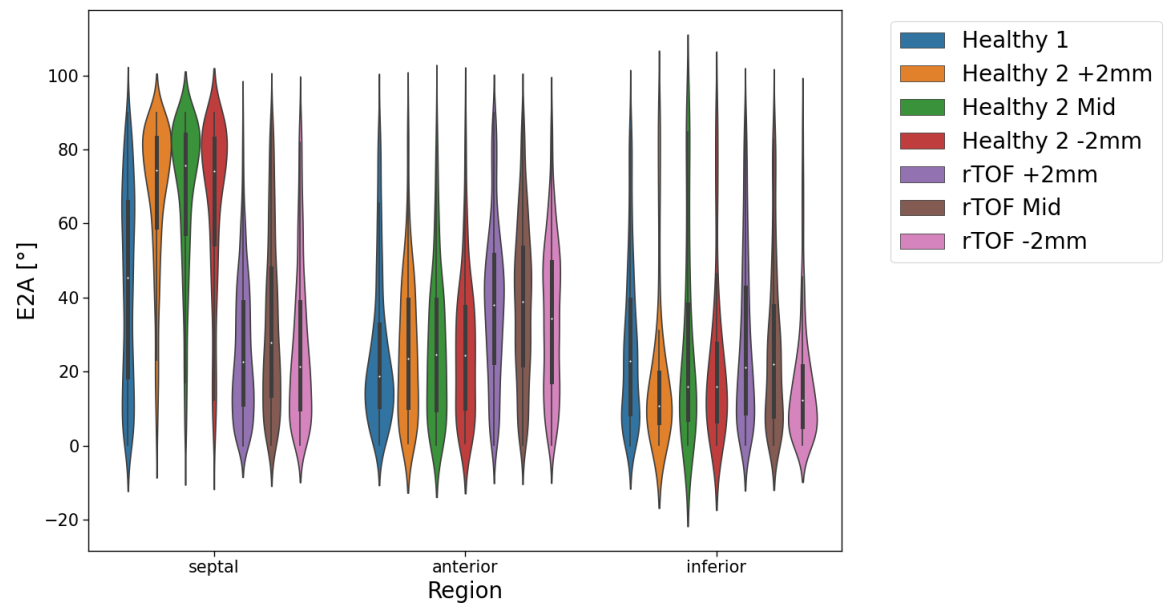
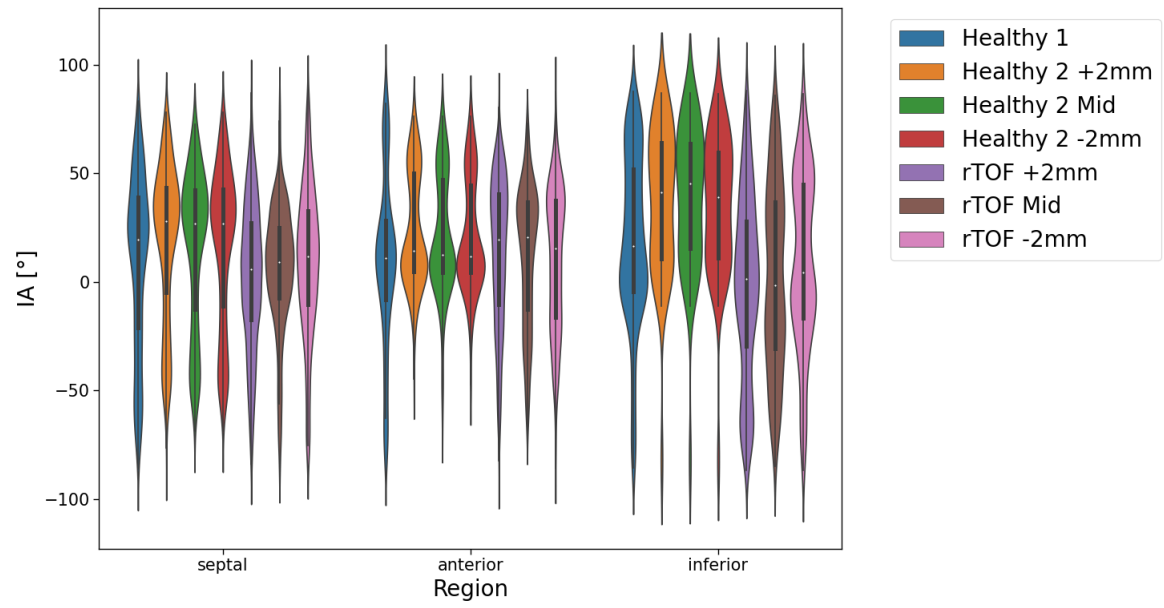
Figure 99: a) IA [°] and E2A[°] are shown for two different healthy human *ex vivo* hearts. Heart 1 is shown with 3 consecutive mid ventricular slices, while for Heart 2 only a single slice was imaged. b) T1 [ms] and T2 [ms] maps for the midventricular slice of Heart 1.

When displaying the DT-CMR results from the septum, inferior and anterior RV in a violin plot, the values of the consecutive slices match very closely in the healthy heart 2 (Figure 100). In general, the values and distribution of the various parameters match closely between both healthy hearts. When looking at the IA in the RV free wall, a difference between anterior and inferior wall can be observed. Further, differences in the E2A and increased eigenvalues (MD) in the rTOF heart are evident.

An exemplary set of the spiral diffusion weighted images ($b=100 \text{ s/mm}^2$ and $b=1250 \text{ s/mm}^2$, 6 directions in both cases, 120 averages per direction for the $b=1250 \text{ s/mm}^2$ and 15 averages per direction for the $b=100 \text{ s/mm}^2$) for the mid slice acquired in Heart 1 is shown in Figure 102. Image quality appears good and the higher signal intensity in the $b=100 \text{ s/mm}^2$ images is clearly visible compared to the $b=1250 \text{ s/mm}^2$ images (images are shown on the same greyscale). A region of high signal in the mesocardium is visible on the $b=100 \text{ s/mm}^2$ images which corresponds to the elevated T2 in this region, as shown by the T2 map in Figure 99.







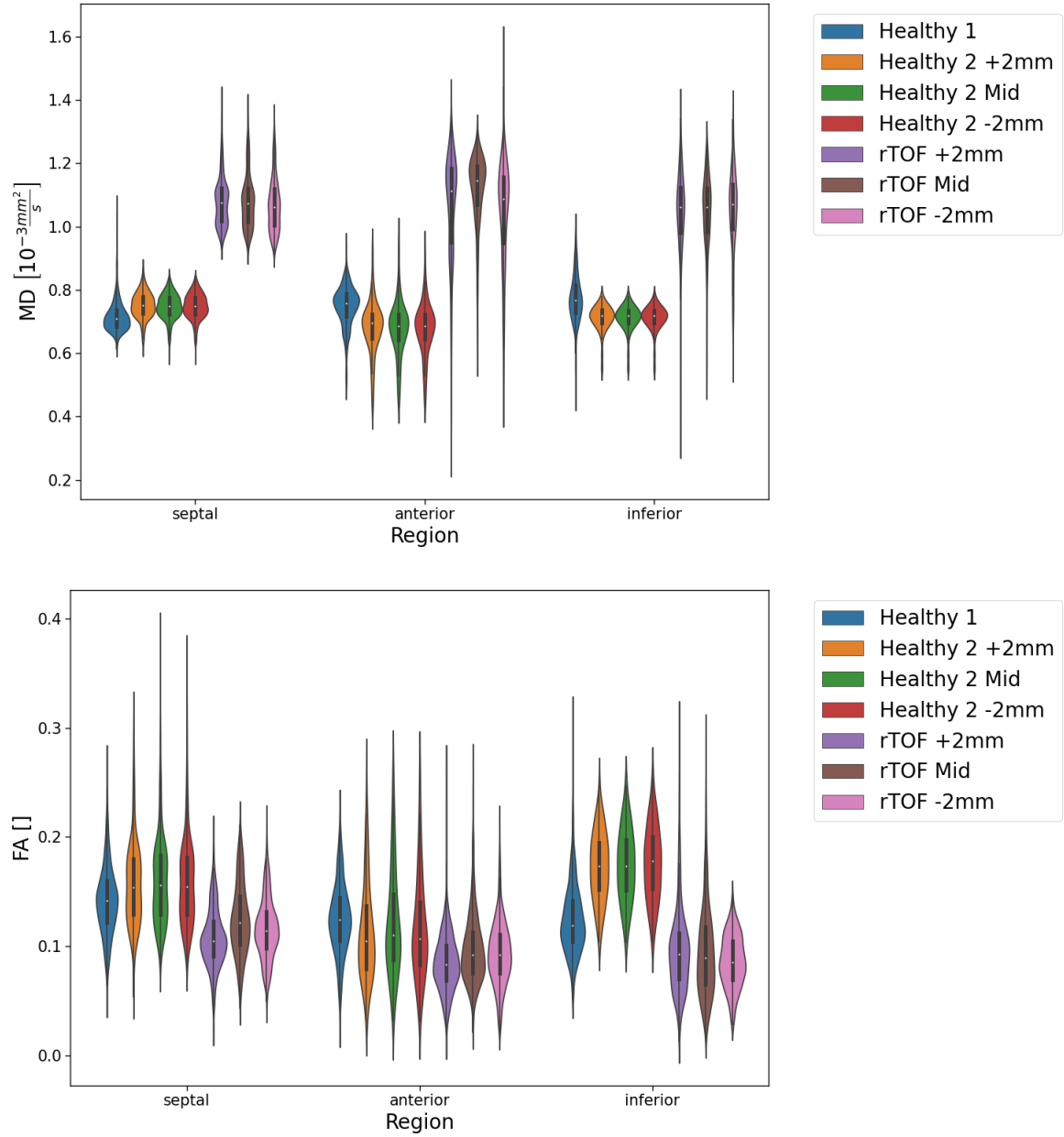


Figure 100: Violin plots of all healthy and diseased human hearts (Healthy₁, Healthy₂, rTOF) for the septal, inferior, and anterior RV regions. For Healthy₂ and rTOF hearts, data from 3 consecutive slices was available and is here denoted as -2 mm and +2 mm for the distance in mm from the mid slice. Plots are shown for the DT-CMR parameters: E_1 [°], E_2 [°], E_3 [°], IA [°], E_2A [°], MD [$10^{-3} \text{ mm}^2/\text{s}$], FA [°]. Inside the violin plots small boxplots show the median values of the distribution and the inter quartile range.

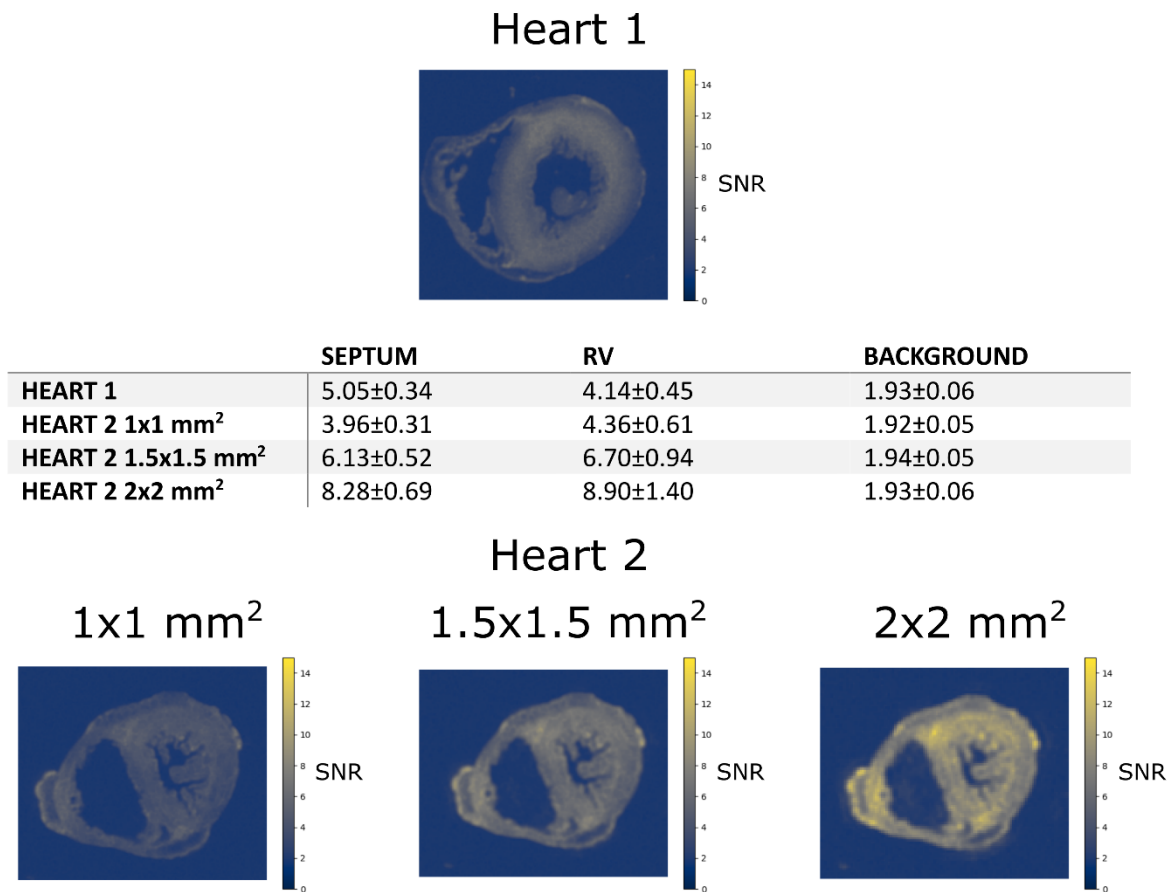


Figure 101: SNR maps from healthy human hearts (Heart 1 and Heart 2) and accompanying regional values.

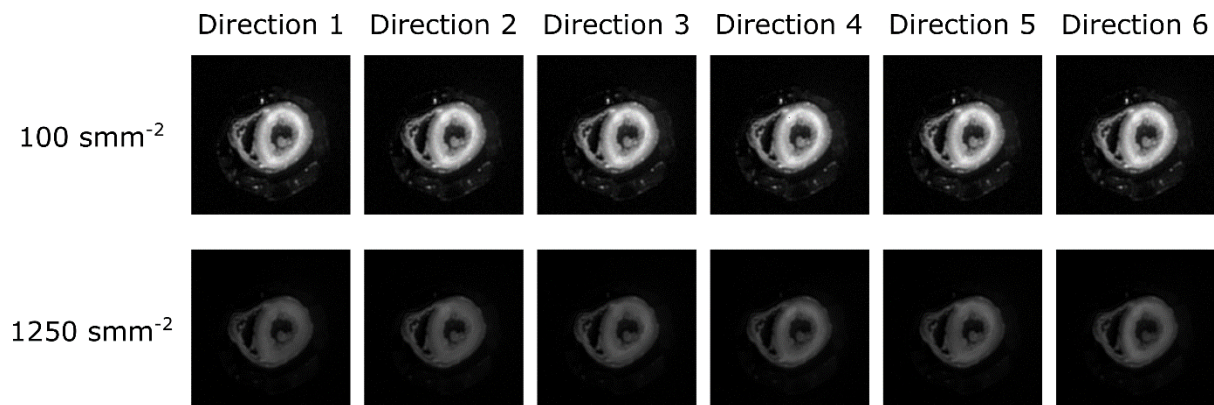


Figure 102: Diffusion weighted images after complex averaging the DT-CMR dataset for healthy Heart 1

11.3.3 rTOF Heart

The DWI for a midventricular slice acquired using the interleaved spiral STEAM sequence in the rTOF heart at $1 \times 1 \text{ mm}^2$ and 2 mm slice thickness is shown in Figure 103. A thick layer of epicardial fat is evident as low signal region outside the myocardium and the pericardium is visible as a layer of brighter signal outside the epicardial fat.

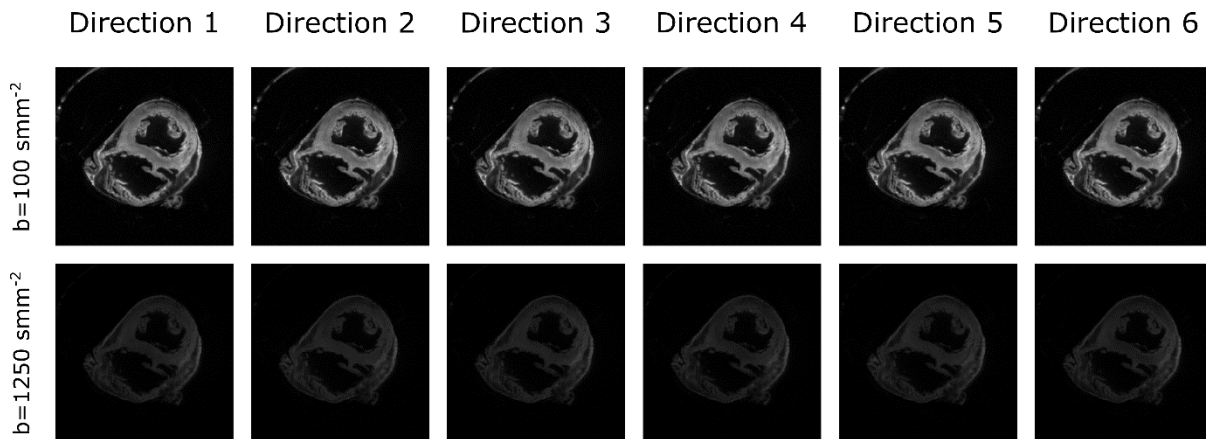


Figure 103: Diffusion weighted images acquired in the ex vivo rTOF heart. The images are all displayed on the same greyscale to highlight signal differences between the two b values. There is a large volume of epicardial fat (dark) surrounded by the pericardium (bright).

Figure 104 shows the DT-CMR maps of 3 contiguous slices from the rTOF heart in the mid-ventricle, with a turbo spin-echo image and T_1 and T_2 maps (mean LV values of $215 \pm 26 \text{ ms}$ and $34 \pm 4 \text{ ms}$ respectively). The LV IA corresponds to the expected change in cardiomyocyte orientation (helix angle) from epicardium to endocardium. The high proportion of negative IAs in the LV free wall and the high proportion of positive angles in the septum are consistent with the rotation of the imaging slice relative to a standard short axis orientation to orientate the slice perpendicular to the RV short axis (as described in Chapter 10.3). The E2A in the left ventricle is consistent with the heart being fixed in a systolic-like state which is similar to the results in the healthy human heart.

In the RV there are regions of both high and low MD, which correspond to apparently noisy regions (Figure 105) in the IA and E2A. Comparison with the anatomical image suggests that this region of noisy IA corresponds to a highly trabeculated region, where a large proportion of each voxel does not contain muscle tissue.

In some regions of the RV a transmural change in cardiomyocyte orientation is evident in the IA maps.

The lower E2A values in the RV of the rTOF heart than in the LV is similar to the pattern observed in the healthy human data in this chapter.

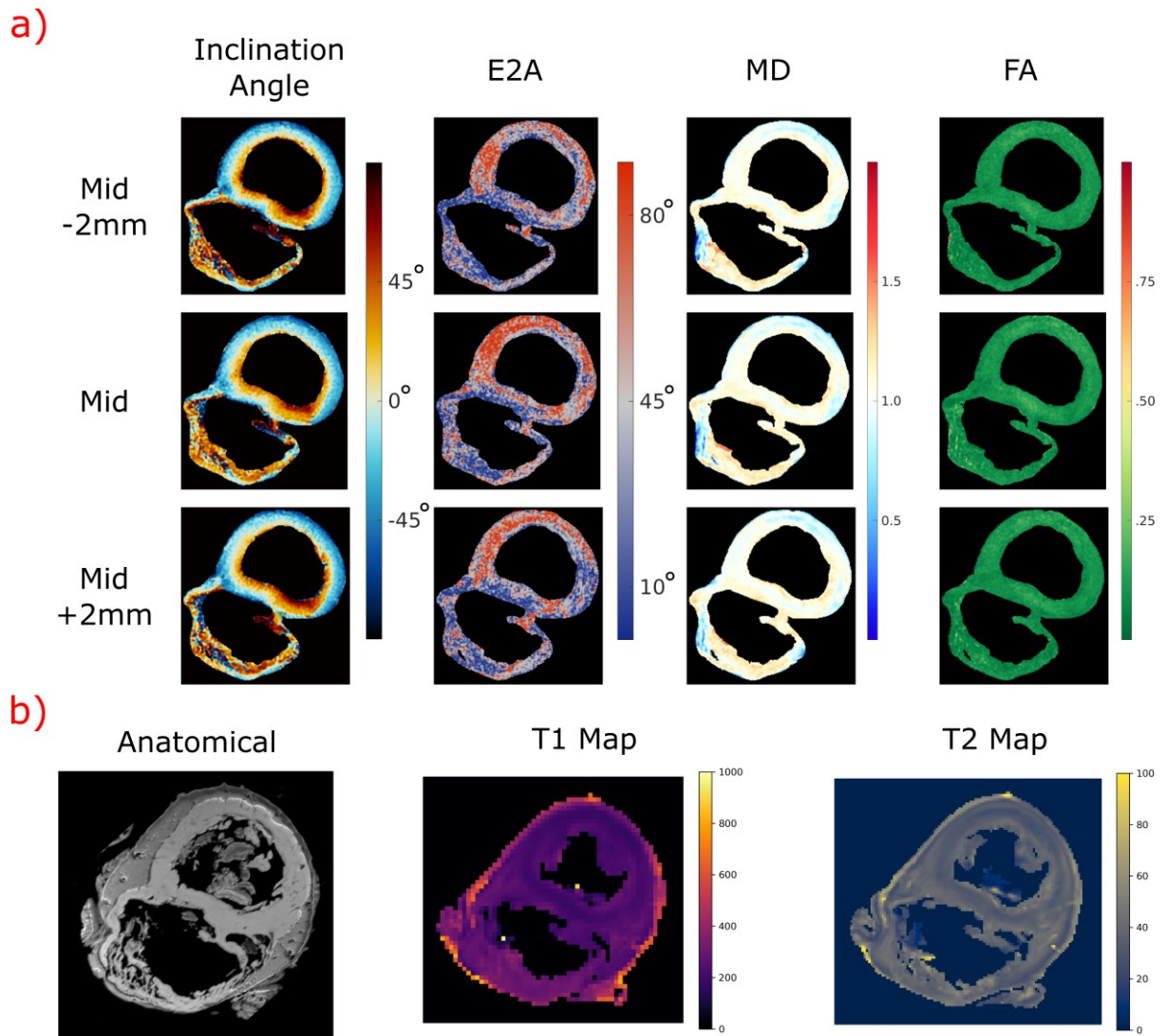


Figure 104: a) DT-CMR maps ($IA[^\circ]$, $E2A[^\circ]$, $MD[10^{-3} \text{ mm}^2/\text{s}]$, $FA[]$) for 3 contiguous mid ventricular slices acquired in an ex vivo rTOF human heart. b) Anatomical image of the mid ventricular slice, together with T_1 and T_2 maps for the same slice.

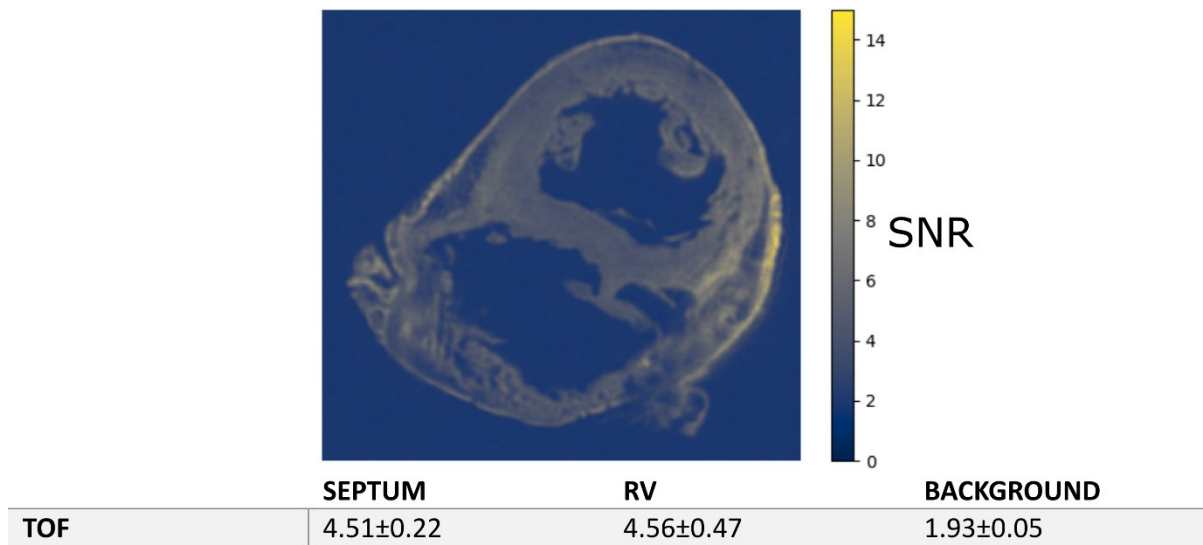


Figure 105: SNR map and corresponding regional SNR values for rTOF.

11.4 Discussion

We have demonstrated that an interleaved spiral STEAM sequence is able to provide high-resolution ($1 \times 1 \text{ mm}^2$ and 2 mm slice thickness) DT-CMR data.

11.4.1 Protocol Optimization

The acquisition used to produce CSM appears to make little difference to the quality of the DT-CMR data, although it is vital to use a coil sensitivity weighted reconstructed rather than SOS coil combination. Extracting the CSM directly from the main DT-CMR data avoids additional acquisitions and thus is preferential over the other methods tested in order to save time. Initial concern that the diffusion weighting in the images used to calculate the coil sensitivity maps could lead to artefacts in the sensitivity maps does not appear to be the case in any of the data shown here.

HA maps appear smoothest when $b=1000\text{--}1250 \text{ s/mm}^2$. This is in line with previous studies which suggested that a b -value of $1.1/\text{MD}$ is optimal for measuring diffusivity effects[181], which equates to $b=1337 \text{ s/mm}^2$ in this data ($\text{MD}=0.83 \times 10^{-3} \text{ mm}^2/\text{s}$). At lower b -values the image noise is a substantial proportion of the signal loss and at higher b -values the diffusion weighted signal may approach the noise floor [181], [196].

Longer spiral readouts result in more severe off-resonance artefacts (Figure 3), but more data can be acquired in each TR, increasing SNR efficiency. Our results suggest that increasing the number of averages is preferential to increasing the number of spiral interleaves for the range of parameters tested.

Based on these tests in the porcine heart, an optimal protocol was identified as follows: 40 averages of $b=1250$ s/mm², with 5 averages of $b=100$ s/mm², with the CSM calculated from the imaging data, 20 interleaves, $\Delta=300$ ms. Using this protocol, a single DT-CMR slice could be acquired within 2 hours.

However, initial acquisitions in a healthy human *ex vivo* heart demonstrated that the much longer preservation times of these hearts (heart 1 = 10 years, heart 2 = 10 years, rTOF = 8 years) resulted in reduced SNR when compared to the more freshly fixed pig hearts. This reduction in SNR compared to the freshly fixed hearts was believed to be caused by the dehydration of the tissue and as such a reduced available signal. Thus, to improve SNR the number of averages was increased to 120 resulting in acquisition durations of ~7 hours per slice. Furthermore, Δ was reduced to 100 ms for adequate SNR in the human *ex vivo* hearts. Additional tests with pig hearts demonstrated that DT-CMR parameters were only moderately affected by reducing Δ to 100 ms, while reducing signal decay due to T₁ and as such improving SNR.

An alternative method for increasing the SNR would have been to reduce the resolution as shown in Figure 101. However, the thin RV free wall means that high spatial resolution is vital and Figure 97 demonstrates the importance of using higher spatial resolution. Figure 97 demonstrates the transmural transition between the two cardiomyocyte populations in the RV that is not clearly evident in either of the 1.5×1.5 mm² or 2×2 mm² data, justifying the highest resolution acquisition used here.

Reduced available SNR, when comparing the freshly preserved pig to the human hearts impacts the DT-CMR parameter maps significantly. While for the spiral sequence a reduction in TM and an increase in averages was sufficient to allow imaging, the same approach was not sufficient for the EPI sequence.

11.4.2 Comparing Single-Shot EPI and Interleaved Spiral Sequences

In the comparisons of the interleaved spiral acquisitions and time matched single-shot EPI method the spiral acquisition resulted in superior image quality. This is due to the overall shorter readout length of the individual spiral trajectories (< 10 ms) when compared to the very long single-shot EPI readout (> 80 ms) required to match the spatial resolution and field of view. The longer TE required for the EPI sequence severely reduced the SNR of the EPI data compared to the interleaved spirals. Using this long EPI readout leads to T_2^* blurring and off-resonance artefacts in the EPI sequence. For the spatial resolution used in this study (1×1 mm²) and STEAM preparation, the single-shot EPI approach was not well suited. Single-shot EPI was used for comparison as it was the only other available DT-CMR sequence. While the EPI readout and reconstruction used were standard products provided by the scanner manufacturer (Siemens), the multiple signal averages were combined in complex image space to suppress the background noise (individual magnitude images often show no discernible signal at the higher b-value). Segmented, interleaved and readout segmented EPI methods have been demonstrated [262] and could provide a fairer comparison with the interleaved spiral methods in future investigations, but were not available for this study.

11.4.3 Healthy Human and rTOF Examples

While the data shown here were proof-of-concept examples and caution is required when deriving conclusions from the results, they provide initial insights and pilot data for future studies into the infrequently studied RV microstructure. The most notable observation was that the healthy human RV may consist of two distinct populations of the primary eigenvector orientation. This is in contrast to the more gradual change in cardiomyocyte orientation in the LV (Chapter 5.1.1). However, confounding factors such as partial volume effects due to resolution and the difficulty in identifying the compact myocardium in the RV make quantifying exact angles or distinguishing populations difficult. Their presence in layers that each appear to be approximately 2mm deep each transmurally with the relative high-resolution and SNR of the data acquired here, however, make a compelling case for the existence of two main orientations of cardiomyocytes in this region, and encourage further investigations.

11.5 Future Work

In this chapter, the sequences used were based on *in vivo* sequences. As a result, a number of methods were not available that could otherwise have been used to increase the efficiency of these *ex vivo* acquisitions. Interleaving slices within the TR is challenging for *in vivo* spiral STEAM acquisitions due to the in-plane orientation of the slice selection gradients used to reduce the stimulated echo field of view. These in-plane slice selective RF pulses also act on the magnetisation outside the imaging slice and, therefore, the SNR benefit of the usually increased longitudinal recovery provided by interleaved slice imaging is lost. However, the absence of a body around the *ex vivo* heart means that smaller fields of view can be imaged without in-plane slice selective RF pulses and the usual improved SNR of slice interleaved imaging could be realised. For the studies in this section, a TR=1500 ms was used; future studies with interleaved slice imaging could acquire 11 slices within the 1500 ms TR used in this work (assuming the sequence durations in Equation 62). Even without interleaved slice imaging, increases in imaging SNR efficiency could be achieved by optimising the TR. Given the assumption that the T₁ values is not higher than 300 ms (the maximum *ex vivo* T₁ measured in this thesis was 215±26 ms in the rTOF heart) it is reasonable to assume that at the timepoint TR_{max}

$$TR_{max} = T_1 \times 3 = 300ms \times 3 = 900ms \quad 61$$

95 % of M_z would be recovered, as such making TR_{max} the longest TR necessary. However, a shorter TR might still benefit the SNR by allowing more averages n which boost SNR by a factor of $\sqrt{n}$. To calculate how many averages fit into the optimal TR, it is necessary to know the duration T_{seq} of the spiral STEAM sequence which is approximately (not accounting for the time before the first RF peak(minimal)):

$$T_{seq} = TE + TM + T_{readout} = 21 ms + 100 ms + 9.5 ms = 130.5 ms \quad 62$$

With knowledge of T_{seq}, it is possible to define the number of averages that fit into TR_{max} as a function of the rest time ΔT_{wait} that describes the time after the readout to the start of the next sequence repeat:

$$n(\Delta T_{wait}) = floor\left(\frac{TR_{max}}{(T_{seq} + \Delta T_{wait})}\right) \quad 63$$

assuming that available SNR is dependent on the available M_z

$$M_z = 1 - e^{-t/T_1} = 1 - e^{-\Delta T_{wait}/300ms} \quad 64$$

It is now possible to define the following formula that describes the SNR factor achievable within $TR_{\max}$ for different ΔT_{wait} sequence repeat wait times

$$SNR \text{ Factor}(\Delta T_{\text{wait}}) = \sqrt{n(\Delta T_{\text{wait}})} \times \left(1 - e^{-\Delta T_{\text{wait}}/300\text{ms}}\right) \quad 65$$

In Figure 106, this relationship is plotted together with the potential number of averages used. Using two averages with a ΔT_{wait} time of 600ms ($TR=730.5$ ms) is the SNR optimal solution, achieving 1.2 times as much SNR as $TR_{\max}$ would achieve. Further, it would be possible to acquire 5 slices through interleaved slice imaging, increasing SNR efficiency further.

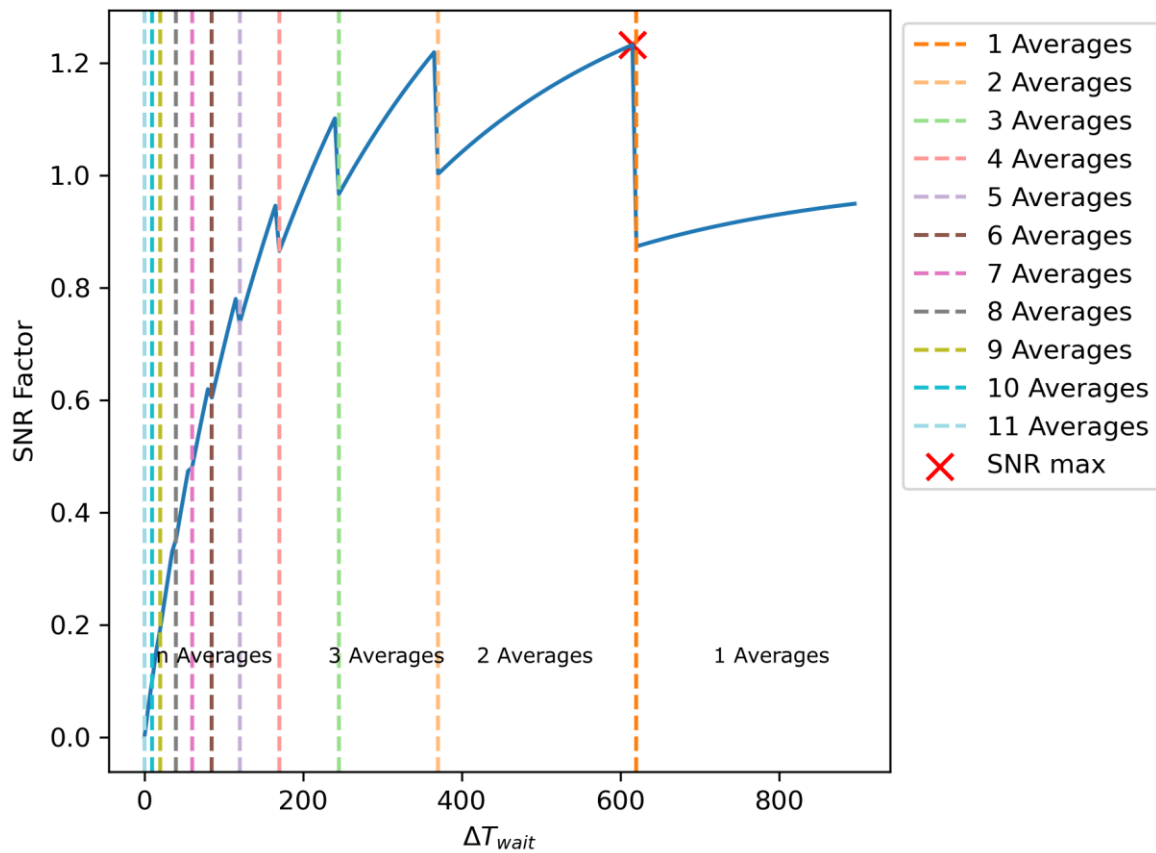


Figure 106: The relationship between SNR and the number (n) of averages and longitudinal signal recovery time (ΔT_{wait}). On the x axis the ΔT_{wait} is plotted, this time denotes the time from the end of the sequence readout to the start of a new sequence repeat. On the y-axis the SNR factor is plotted: it should be noted that a factor of 1 describes the use of $TR_{\max}$ for the sequence. The dotted lines denote the boundaries between averages. These have to be read from the right to the left.

In future, a comparison of interleaved EPI methods (either interleaved, segmented or readout segmented) with the interleaved spiral sequence is an important step in demonstrating which method is more effective *ex vivo*, but could also be an initial step towards the use of interleaved EPI for *in vivo* DT-CMR.

Here, the spiral readout trajectory was combined with the STEAM diffusion encoding, which was used for *in vivo* imaging in this thesis. While the STEAM sequence allows values of Δ similar to those used *in vivo*, and relatively short echo times, it does come with the disadvantage of a 50 % loss of signal due to the stimulated echo, and a further SNR loss due to longitudinal signal decay during TM. However, using Stejskal-Tanner like spin echo diffusion encoding [19] would provide additional SNR and may facilitate even higher resolution imaging. The reduction in Δ affects the scale of the microstructures probed [186], so it would be important to evaluate which sequence provides the most relevant information for the scientific questions being studied, similar to the diffusion time experiments shown here for the STEAM sequence.

Additionally to reduce the noise in the individual images, an AI-based denoising method such as recent work by Phipps et al. [324] or Deep Resolve [325] could be used in the future to reduce the number of averages and as such reduce scan time.

The current method takes about 7 h per slice on a 10-year-old heart, where 120 averages were used for the higher b-value. At 2mm slice thickness, to cover the heart's ventricles in about 10 cm, this would require total scan times of 350h. This time must be significantly decreased using the above-mentioned techniques to allow for realistic whole heart *ex vivo* imaging in the future. Alternatively, if it is possible to procure more recently preserved hearts, it should be possible to significantly decrease the number of averages required. This is due to the dehydration in older hearts which reduces the overall available signal and as such the SNR.

11.6 Conclusion

Interleaved spiral trajectories can be used to acquire high quality *ex vivo* DT-CMR data at high spatial resolution on a clinical 3 T scanner with the advantages of the long diffusion times of a STEAM sequence probing longer diffusion distances than spin-echo based methods. Acquisitions are, however, time consuming and in this work, we investigated the effects of the number of averages/interleaves, b-value and coil combination methods to provide an optimised protocol. This optimised protocol was demonstrated in *ex vivo* examples of fixed hearts from two healthy patients and from the heart of a rTOF patient. Initial insights into the arrangement of cardiomyocytes in the RV in normal and rTOF hearts were provided and warrant further investigation. Interleaved spiral methods will be valuable in providing high-resolution DT-CMR data for non-destructive microstructural assessment of *ex vivo* hearts, resulting in new understandings of the heart in health and disease and for validation of results obtained using lower resolution acquisitions performed *in vivo*.

The protocol optimisation on porcine hearts (11.3.1) was presented on the Annual Meeting of the International Society for Magnetic Resonance in Medicine 2021 with the Abstract No. 1326.

12 In Vivo DT-CMR

12.1 Introduction

DT-CMR has shown that it is a method capable of non-invasively investigating the left ventricular myocardial microstructure *in vivo* [50], [199], [206], [220]. While the method is still only available in a few centres for cardiac imaging [49], diffusion MRI is widely used in the brain and abdominal organs [326], [327]. There is a growing list of publications examining the left ventricular myocardium with DT-CMR, as discussed in Chapter 5.1, but the right ventricle has only been studied with DT-CMR *ex vivo* due to the much thinner myocardial wall.

The aim of this chapter is to evaluate high-resolution spiral readouts in application to DT-CMR in the RV myocardium with comparison to established EPI methods and determine how reproducible both techniques are in the RV.

12.2 Methods

All acquisitions in this chapter were performed on a clinical 3 T scanner (Siemens Vida). An 18-channel phased array chest coil in combination with typically 8 channels of the spine coil was used in all experiments. Ten healthy volunteers (4 female (26-36 years, mean 30 years), 6 male (24-56 years, mean 38 years)) were recruited in accordance with ethical approvals and provided informed consent. DT-CMR was performed in both the diastolic and peak systolic cardiac phases with the imaging plane aligned with the RV short axis, as described in Chapter 10.3, aiming to image a mid-ventricular slice. Each healthy volunteer was scanned twice with repositioning in-between the two studies to allow calculation of inter-study reproducibility measures. To replicate the same slice position between the two scans, the distance from the RV ventricular valve plane to the mid ventricular slice was measured in the first scan and the plane was shifted in the second scan to match. Volunteers were positioned to place the heart at iso-centre, moving the patient left-right on the examination table if necessary. The protocol for each scan consisted of localizers and bSSFP cine acquisitions for the image plane planning (Chapter 10.3) and identification of peak systole and diastasis, a STEAM EPI protocol [179], [196], [206] and an interleaved spiral STEAM protocol (Chapter 10.2.1). For both the EPI and the spiral scans, the adjustment volume was selected to contain only the heart and the scanner was forced to perform an additional shim to ensure the best possible B₀ homogeneity. The sequence parameters for both are shown in Table 9. For the spiral sequence the reconstruction methods described in Section 10.4 were used, while the EPI sequence employs the standard Siemens reconstruction pipeline.

	<i>EPI</i>	<i>Spiral</i>
<i>Resolution [mm²]</i>	2.8x2.8	2.0x2.0
<i>Slice Thickness [mm]</i>	8	8
<i>FOV [mm²]</i>	135(Phase) x 360(Frequency)	Central k-space = 190x190 → Edge = 110x110
<i>Excited FOV [mm²]</i>	110(Phase) x Full FOV (Frequency)	100x100
<i>Interleaves/shots</i>	1	2
<i>ADC sampling rate [μs]</i>	1.7	2.5
<i>Readout Duration [ms]</i>	23.0	14.6
<i>TE [ms]</i>	24	14
<i>TR [ms]</i>	2 RR Intervals	2 RR Intervals
<i>Parallel Imaging</i>	SENSE	-
<i>Diffusion Directions</i>	6	6
<i>b=150 s/mm² Averages</i>	2	2
<i>b=600 s/mm² Averages</i>	8	8
<i>Number of breath holds per slice and cardiac phase</i>	10	20
<i>Breath hold duration (RR-intervals)</i>	18	18

Table 9: Sequence parameters of both the single shot EPI sequence and the interleaved spiral sequence.

DT-CMR data was processed using the post-processing pipeline covered in Chapter 10.4.1.8. For the spiral data, the pipeline was modified to improve the performance of the image registration of the DWI as the standard methods were found to perform poorly due to spiral wrap artefacts in the area surrounding the RV. This modified image reconstruction was performed applying a non-local means filter (imnlnmfilt in MATLAB, with degree of smoothing 20x the MATLAB estimated value) to the current image and the reference image (first image in the set) and then manually masking both images to leave only a region around the RV. The filtered masked regions were then registered using a normalised cross-correlation based method including rigid translations with integer pixel shifts [315].

Due to the optimisation of the protocol to cover the RV, all DT-CMR maps presented in this chapter are cropped in the figures to include only the RV free wall and the septum (Figure 107). This crop was performed because often the LV is only partially contained within the spatially selective excitation FOV or includes artefact from being located at the edge of the spiral readout FOV.

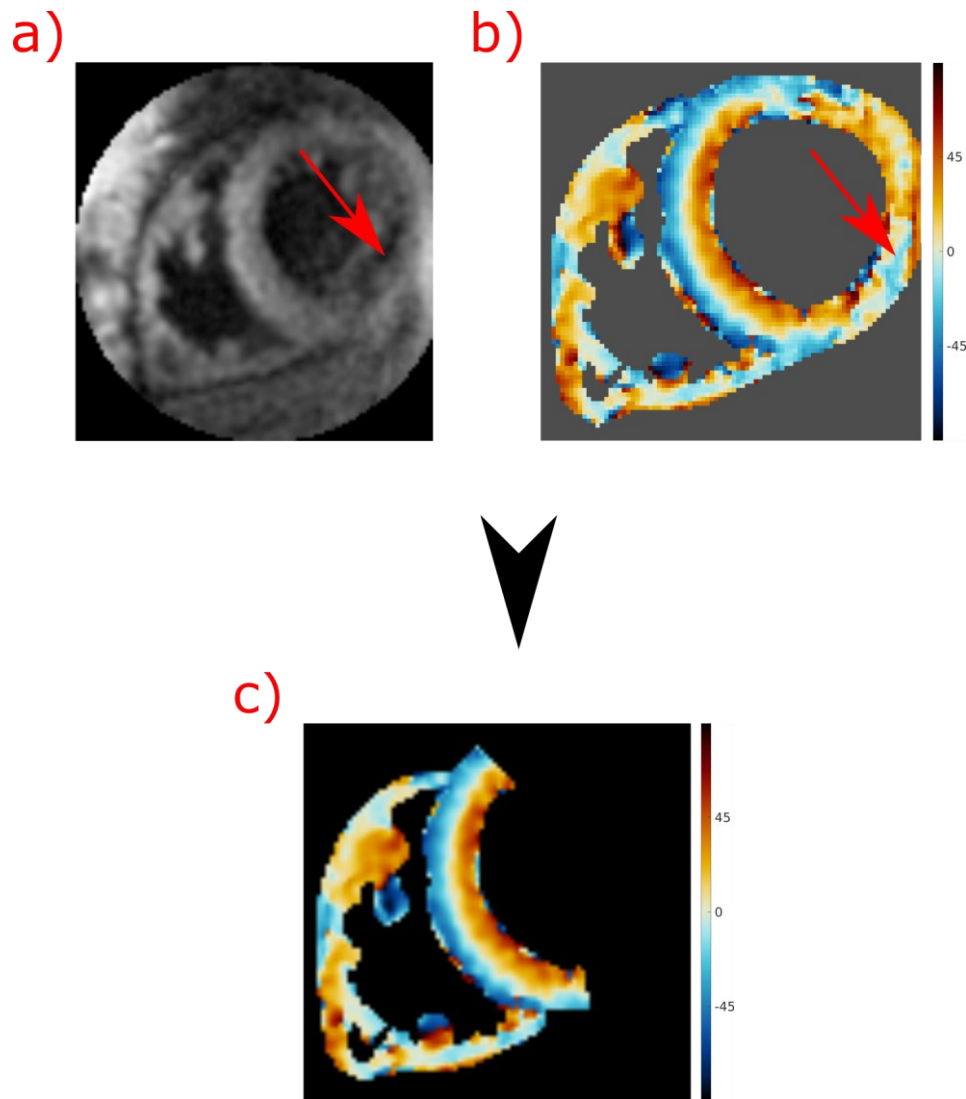


Figure 107: Figure explaining the cropping of the spiral DT-CMR parameter maps. a) shows a DWI in which the zonal selective FOV and readout FOV are chosen to image the RV (it should be noted that the presented images have already been cropped once as part of the DT-CMR processing, thus the FOV here appears offset). Thus, as shown by the red arrow, the LV free wall is only partially contained within the unaliased region and spiral wrap artefact is present on the LV free wall. b) shows the effect of the spiral wrap artefacts in the LV on the IA map in the same region. The red arrow shows clear artefact in the LV free wall. c) shows the IA after cropping the corrupted LV free wall from the image.

After processing all datasets, a visual inspection based on DT-CMR parameter map quality (Figure 108.a) and the quality of the image registration of the DWI (Figure 108.b) was conducted by two readers with DT-CMR experience. Datasets were rejected if the septum did not display the expected transmural rotation in IA, or there was drastically elevated MD over a large area of myocardium.

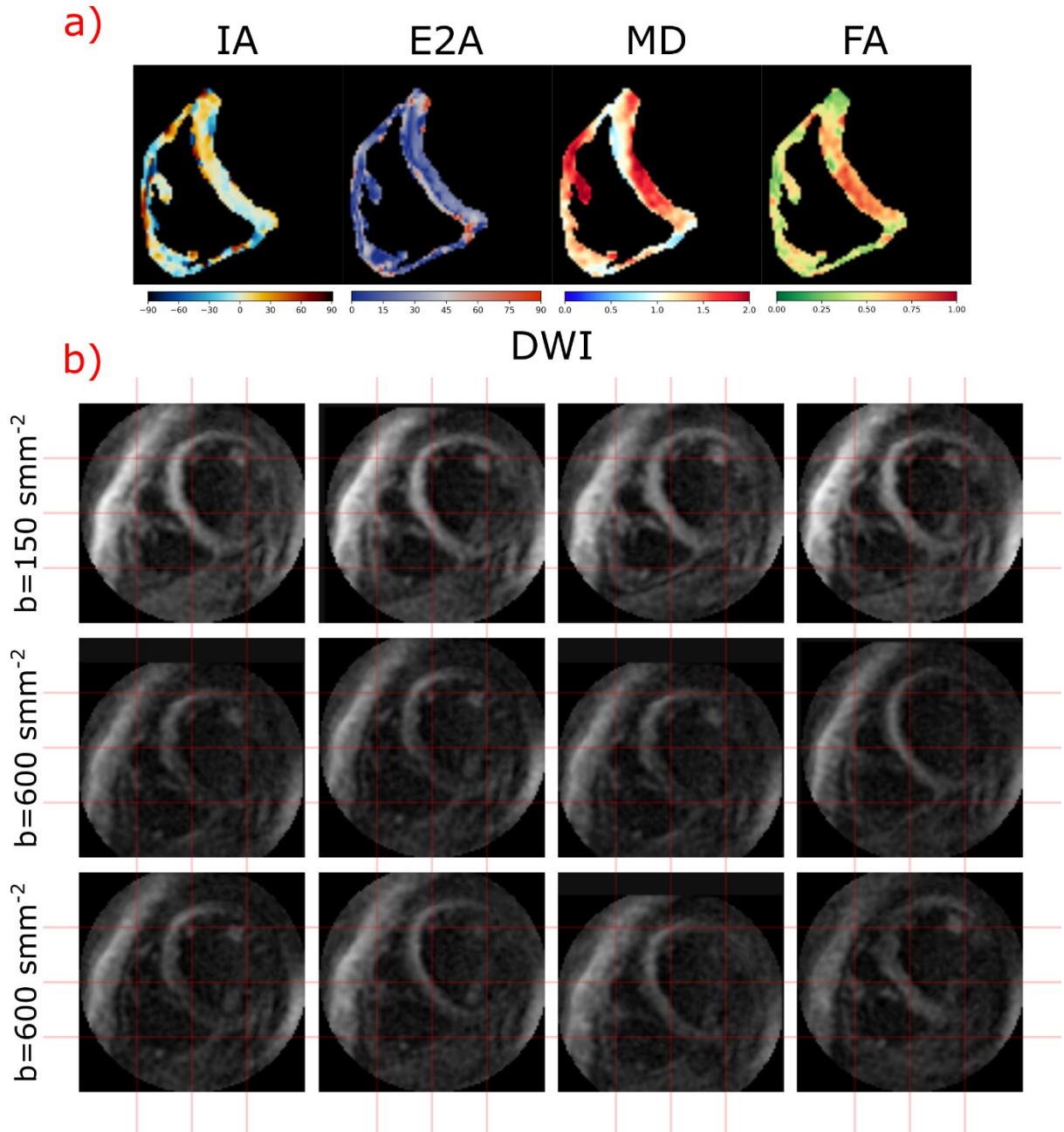


Figure 108: Example of a diastolic spiral dataset that was discarded. a) shows DT-CMR parameter maps (IA[°], E2A[°], MD[$10^{-3} \text{ mm}^2/\text{s}$], FA[]). b) shows a selection of the DWI (before averaging) from the associated dataset after registration. Even when the data was registered using the RV specific protocol described above, there is clear movement of the RV free wall between frames. Furthermore, in some images the inferior free wall and the liver are difficult to distinguish. The same is true for the anterior RV free wall and the anterior chest wall. As a result of the poor quality DWI, the septal IA did not demonstrate the expected transmural rotation and parts of the septum and RV show very high MD values ($\sim 2 \times 10^{-3} \text{ mm}^2/\text{s}$).

From the final DT-CMR maps three regions of interest: anterior RV, inferior RV, septum (Figure 109) were extracted by manual segmentation and used for the statistical analysis.



Figure 109: Example of the ROIs used to analyse the DT-CMR data presented in this chapter superimposed on a single $b=0$ image generated by the diffusion tensor calculation.

SNR was calculated for each dataset (systole and diastole, for spiral and EPI) of the first repeat using the same through-time method described in Chapter 11.2. Due to the number of averages used at the two b -values, the $b=600$ s/mm² data was used for SNR calculation, because 8 averages were acquired compared to 2 averages for $b=150$ s/mm². As in Chapter 11.2, the geometric mean of the pixelwise SNR over the 6 diffusion encoding directions was calculated before averaging pixel values over the ROIs shown in Figure 109.

SNR and DT-CMR results from the first repeat of each sequence in both cardiac phases were compared using a Wilcoxon signed rank-test. The second repeat was not compared between sequences to reduce the number of statistical tests performed and the risk of Type I errors.

To investigate the inter-study reproducibility of both sequences the Coefficient of Variation (COV) was calculated

$$COV = \frac{\sigma}{\mu} \times 100\% \quad 66$$

with σ the standard deviation and μ the mean and Bland-Altman analysis was performed for E_1 , E_2 , E_3 , MD, FA in each region and cardiac phase. Wilcoxon signed-rank tests were performed to compare results obtained in each myocardial region, for the initial and repeat studies and for the two sequences.

For statistical tests a value of $p < 0.05$ was considered to be significant. The choice of using the Wilcoxon signed-rank tests over the paired samples t-test was due to the relatively small sample size, which makes assessments of the normality of distributions difficult.

The definition of “fair” reproducibility can be ambiguous and even subjective if it is not defined clearly. Throughout this chapter the following definitions are used when describing test reproducibility based on COV (<5% very good; <10% good; <20% fair ; <30% poor).

12.3 Results

First, results are presented regarding the rejection of datasets considered unusable as described in the Methods above:

For all 80 datasets (10 subjects, 2 cardiac phases, 2 scan repeats, spiral + EPI data) Table 10 shows the frame rejection rate during DT-CMR processing as a percentage of the number of acquired images (8 completely rejected datasets as explained below are marked in red). In general, there were more rejected frames in the diastolic phase (1.37 ± 2.48 % EPI and 4.62 ± 5.81 % spiral) than in systole (0.55 ± 2.01 % EPI and 0.65 ± 1.04 % spiral). While EPI and spiral acquisitions had a similar proportion of rejected frames in systole, the spiral data had a much larger proportion of rejected frames in diastole than the EPI sequence.

The assessment based on the inspection of the processed DT-CMR maps as described in the Methods section, determined that 7/20 of the diastolic phase spiral datasets were unusable for further analysis and were discarded, whereas only one diastolic EPI dataset was found to be unusable. All of the systolic datasets showed sufficient data quality for inclusion in the quantitative analysis. A total of 32 datasets as shown in black in Table 10 were therefore in all the following results.

Volunteer	Scan Repeat	Scan Type	Cardiac Phase	Frame Rejection [%]	Volunteer	Scan Repeat	Scan Type	Cardiac Phase	Frame Rejection [%]
1	1	spiral	systole	2	6	1	spiral	systole	0
		EPI	systole	0			EPI	systole	0
		spiral	diastole	18			spiral	diastole	10
	2	EPI	diastole	0		2	EPI	diastole	0
		spiral	systole	2			spiral	systole	0
		EPI	systole	0			EPI	systole	0
2	1	spiral	diastole	13	7	1	spiral	diastole	3
		EPI	diastole	0			EPI	diastole	0
		spiral	systole	0			spiral	systole	0
	2	EPI	systole	0		2	EPI	systole	0
		spiral	diastole	9			spiral	diastole	0
		EPI	diastole	0			EPI	diastole	3
3	1	spiral	systole	0	8	1	spiral	systole	0
		EPI	systole	0			EPI	systole	1
		spiral	diastole	10			spiral	diastole	0
	2	EPI	diastole	1		2	EPI	diastole	0
		spiral	systole	0			spiral	systole	0
		EPI	systole	0			EPI	systole	0
4	1	spiral	diastole	8	9	1	spiral	diastole	0
		EPI	diastole	0			EPI	diastole	0
		spiral	systole	0			spiral	systole	3
	2	EPI	systole	0		2	EPI	systole	0
		spiral	diastole	2			spiral	diastole	10
		EPI	diastole	0			EPI	diastole	1
5	1	spiral	systole	0	10	1	spiral	systole	0
		EPI	systole	0			EPI	systole	1
		spiral	diastole	3			spiral	diastole	13
	2	EPI	diastole	1		2	EPI	diastole	10
		spiral	systole	2			spiral	systole	0
		EPI	systole	0			EPI	systole	0
Mean ± Standard Deviation			systole	spiral	0.65±1.04	EPI			0.55±2.01
			diastole		4.62±5.81				1.37±2.48

Table 10: Table showing the frame rejection rate for each subject. Scans that were excluded from the statistical analysis are marked in red. A summary of the table is provided at the bottom in terms of the Mean ± Standard Deviation number of rejected frames for each sequence type and cardiac phase (excluding the 8 discarded scans shown in red).

Figure 110 shows a selection of the healthy volunteer data ($b=0$ s/mm² images generated by the diffusion tensor calculation) acquired by both sequence repeats and for both cardiac phases. The RV anatomy in the selected short axis plane appears very different between subjects while the images show good reproducibility of the planning of the mid-ventricular SAX plane between scan repeats.

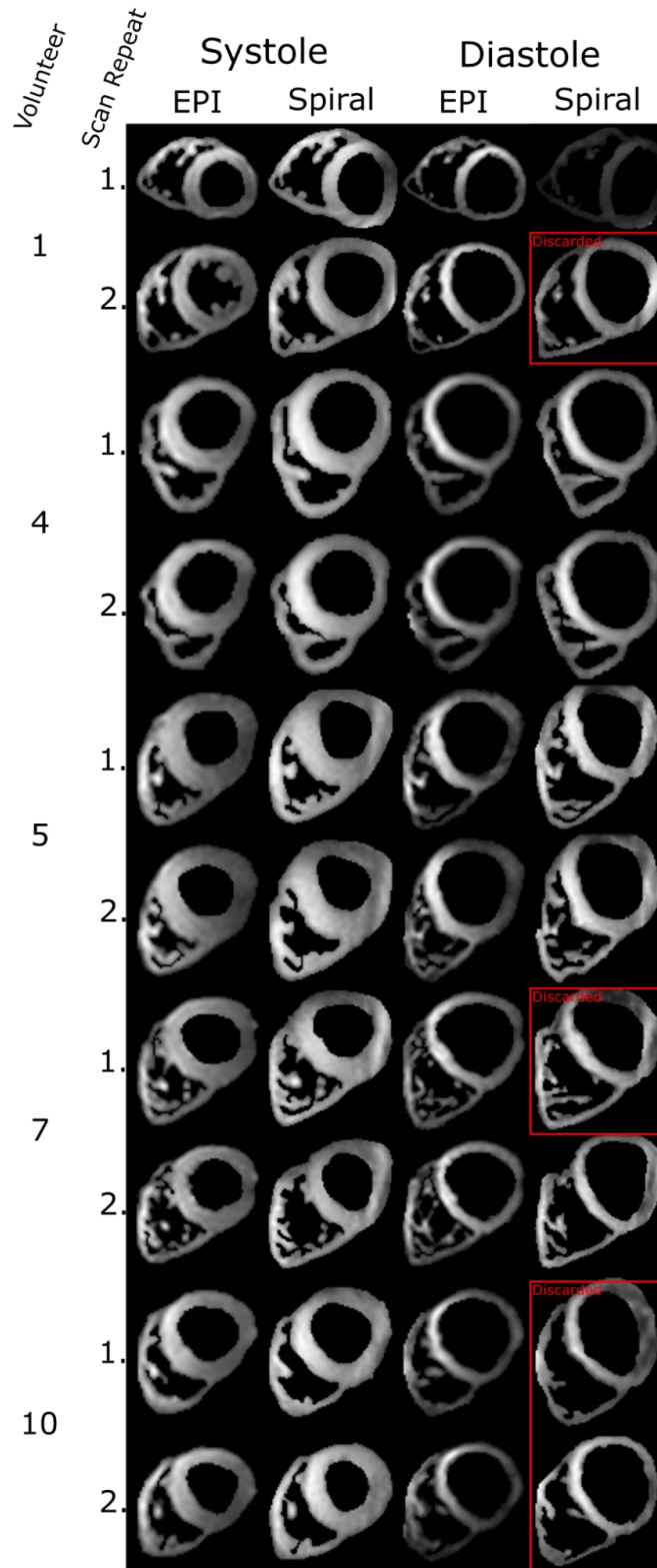


Figure 110: Figure showing 5 example datasets of masked $b=0$ s/mm^2 images generated by the diffusion tensor calculation, which are calculated using all the b -values, non-rejected averages and diffusion encoding directions. Images are shown for both scan repeats, cardiac phases and sequence types. Images from datasets that were completely discarded, as explained above (red in Table 10), are framed in red. Due to the DT-CMR processing software EPI and spiral acquisitions are cropped differently, thus appear in different sizes here (no effect on the acquired resolution).

12.3.1 Spiral Corrections

12.3.1.1 Field Map Correction

Figure III shows the impact of the off-resonance correction (described in Section 10.4.1.6). The increased sharpness of the DWI is visible when off-resonance correction is performed. While it was difficult to visually detect an increase in sharpness between 5-9 off-resonance bins, in all following results a bin number of 9 was used, in keeping with the results in Section 9.4.

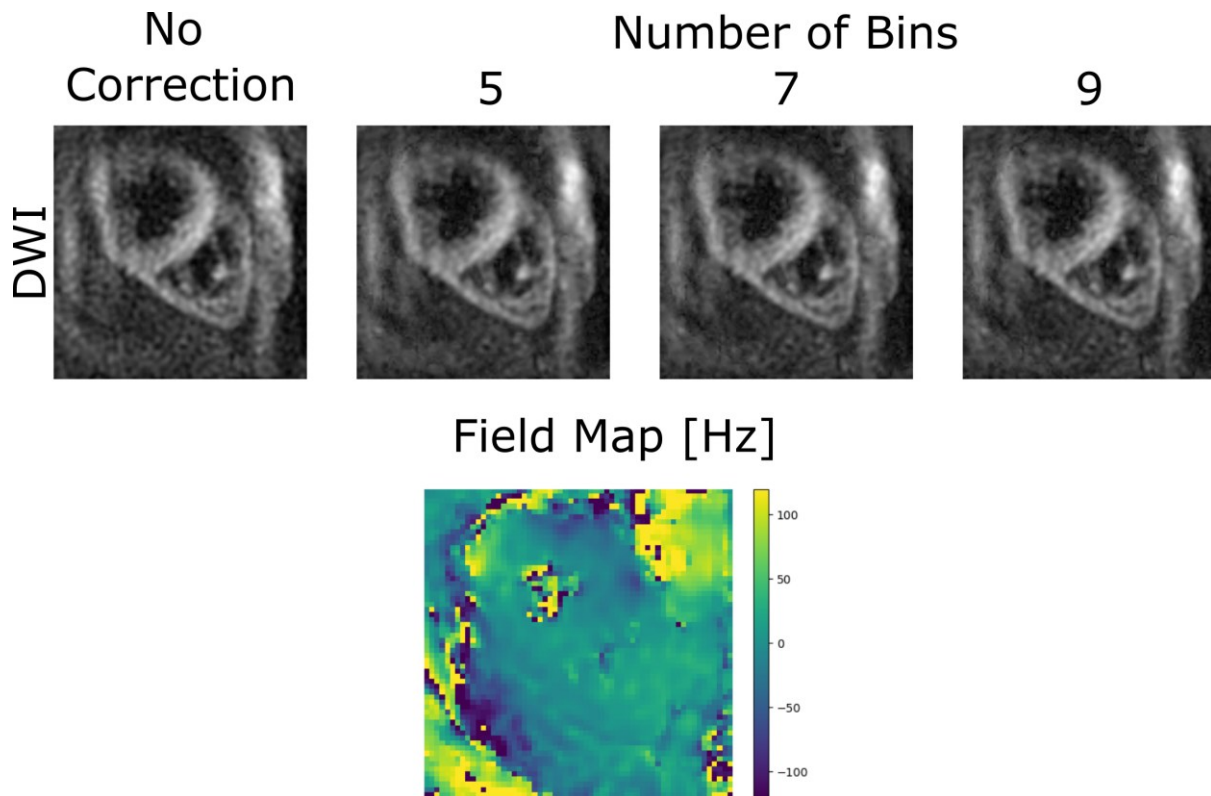


Figure III: The impact of the off-resonance correction on an in vivo spiral DWI. The first row shows the impact of different numbers of bins on the DWI, while the second row shows the field map governing this entire example.

12.3.1.2 *SNAILS Correction*

The SNAILS correction method was applied to all datasets as detailed in Section 10.4.1.5. The parameter for the kernel size (full width half max of 30 %) was used here for all subjects.

Figure 112 shows the results from SNAILS correction for DWI from an example subject imaged in a systolic and in a diastolic configuration. This example was selected for illustration, because the diastolic dataset was completely discarded from final analysis due to unphysiological MD in the RV free wall (one of the criteria for complete rejection specified earlier). It is visible from the data here that in both cardiac phases the SNAILS technique successfully corrects for motion-induced phase-cancellation. Small “inter-interleave” (*sic*) motion is visible based on the manually drawn contours shown and this observation, considered important, is discussed further in Section 12.4

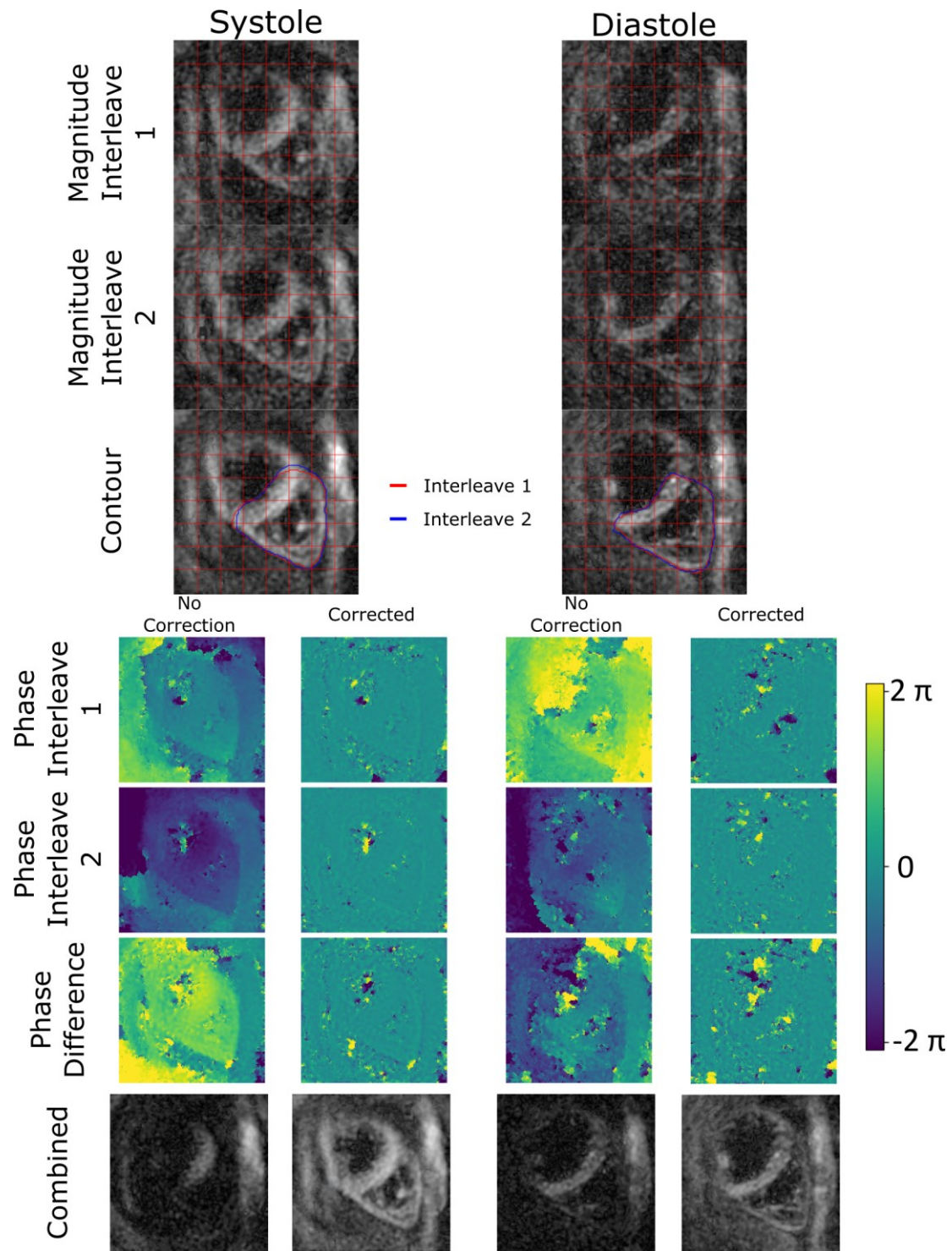


Figure 112: Example of corresponding pairs of interleaves and the performance of the SNAILS correction in a healthy subject for both cardiac phases. The dataset from the diastolic phase was discarded due to abnormally high MD values. The magnitude and phase of the two individual interleaves are shown from a single receive coil element, as well as the contour manually segmented for the individual interleaves. All phase maps are phase unwrapped to aid the display (unwrapping algorithm failing in diastole phase interleave 1 due to insufficient LV signal). The combined interleaved data after SNAILS correction and off-resonance correction using all coils combined is displayed. While the SNAILS correction provides good results in terms of removing motion induced phase error, the slight movement (visible here via the contour) between interleaves results in blurring.

12.3.2 Example DT-CMR Maps

Examples of the DT-CMR parameter maps and DWIs are shown as follows: To illustrate the range of data available, examples are shown for subjects with poor-quality data (Figure 113), typical-quality data (Figure 114), and high-quality data (Figure 115).

The poor-quality spiral example in both diastole and systole shows high MD ($\sim 2 \times 10^{-3} \text{mm}^2 \text{s}^{-1}$) in the RV free wall. In the second repeat of the diastolic data, this high MD is also present in the septal area and coincides with a region of artefactual IA in the spiral image. Visible from the figures is that areas that either display a thin wall or are closely bordering with the chest wall on the anterior and on the liver on the inferior are often affected. The spiral data in the RV free wall appears to be more affected by the proximity of the chest wall or liver when compared to the data from the EPI sequence.

For both the typical and high-quality examples, it is evident that the septum shows the same arrangement of cardiomyocyte organisation shown in other studies, with negative angles on the RV side, rotating smoothly through to positive angles on the LV endocardium (Chapter 5.1). It is also visible from the DWI that the delineation between the myocardium and neighbouring tissues is clearer in the typical and high-quality data than in the poor-quality example data.

The E2A in the septal area changes from the diastolic phase to the systolic phase from a lower angle to a higher angle. The same effect can be observed in the typical and high-quality data for the RV free wall regions, however patches of low E2A remain in certain areas of the systolic phase for these cases.

The IA shown in the septum here is in line with the HA confirmation found in past LV studies (Chapter 5.1). On the other hand, in the RV free wall the smooth transmural transition of angles is not observed. The IA patterns seen in the free wall are more consistent with two populations of cardiomyocytes with opposing signs of IA.

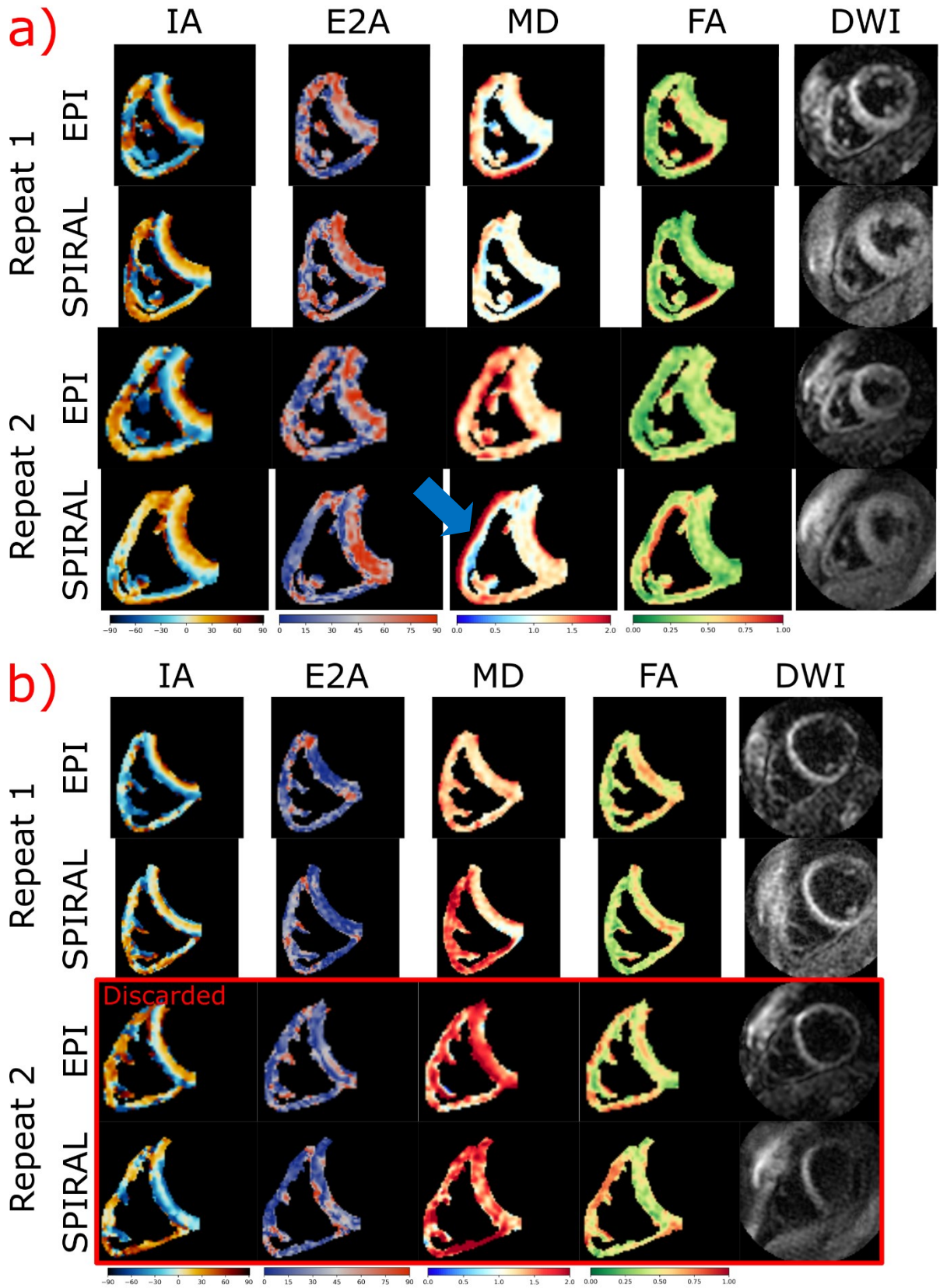


Figure 113: Example of DT-CMR parameter maps (IA[°], E2A[°], MD[10⁻³ mm²/s], FA[], DWI[]) from a subject with poor-quality from both sequences and scan repeats and cardiac phases. a) systole b) diastole. Arrow showing influence of misregistration on the tensor fitting process as discussed in section 12.4 .

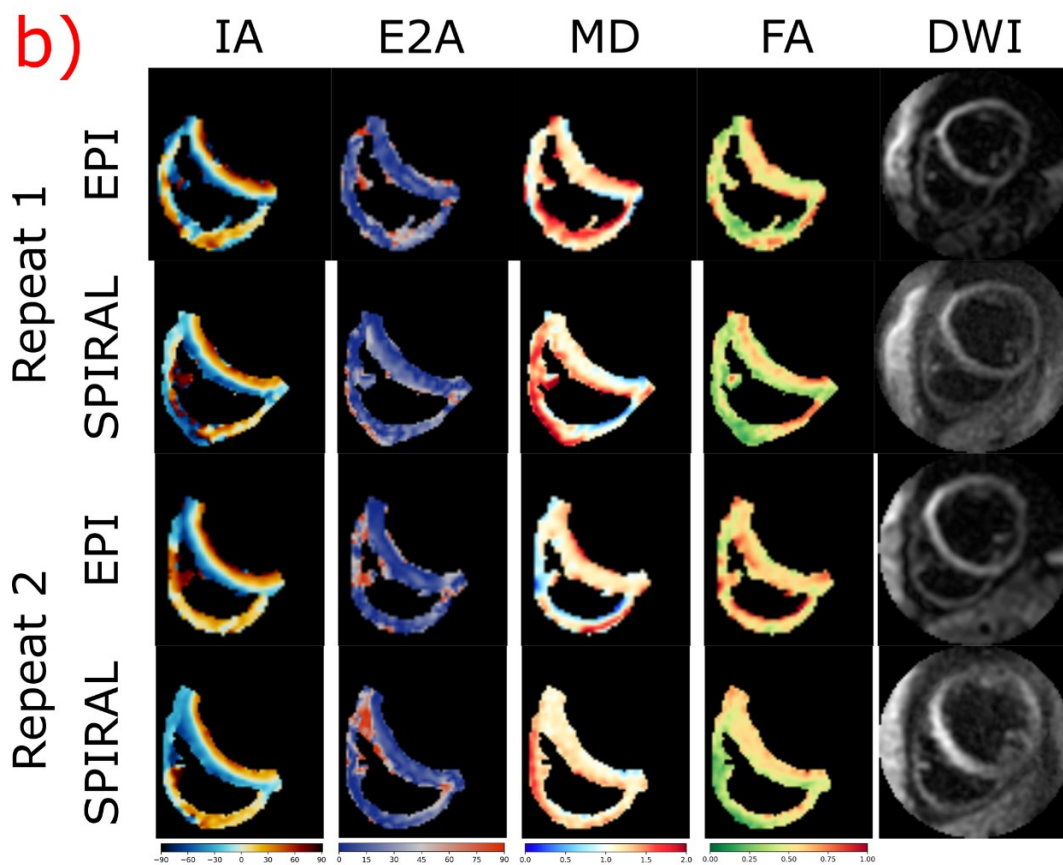
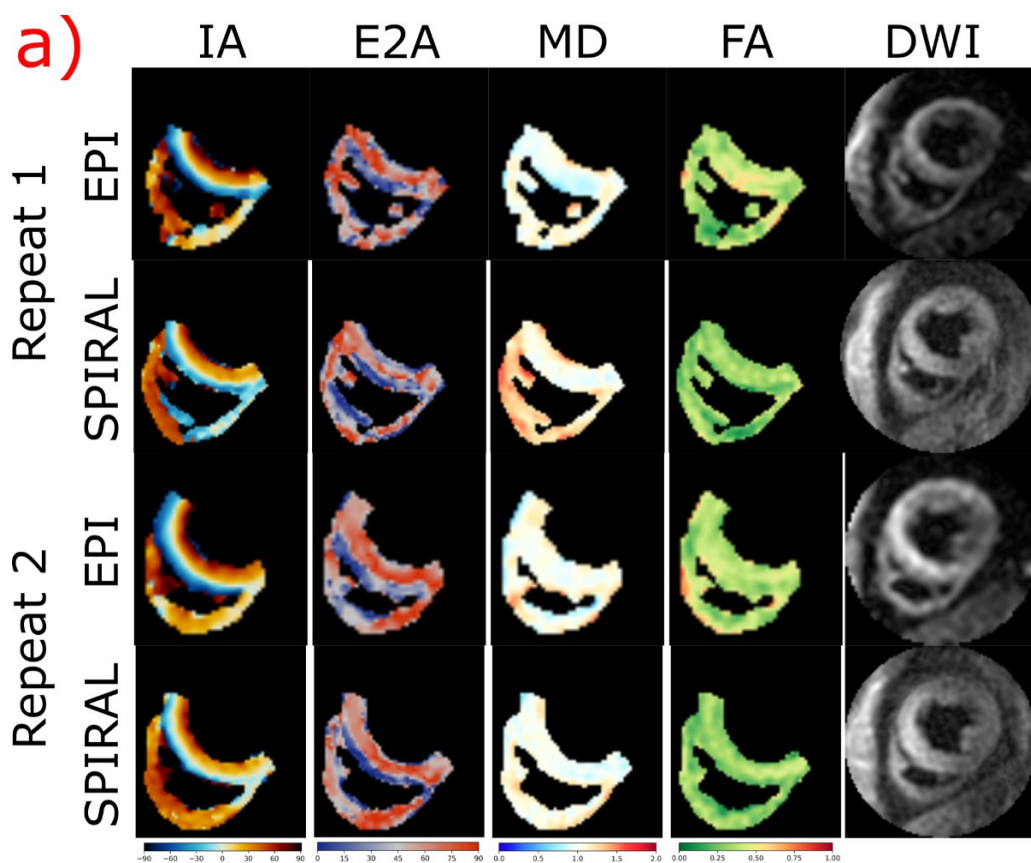


Figure 114: Example of DT-CMR parameter maps ($IA[^\circ]$, $E2A[^\circ]$, $MD[10^{-3} \text{ mm}^2/\text{s}]$, $FA[^\circ]$, $DWI[^\circ]$) for a typical-quality data subject in both sequences and scan repeats. a) systole b) diastole

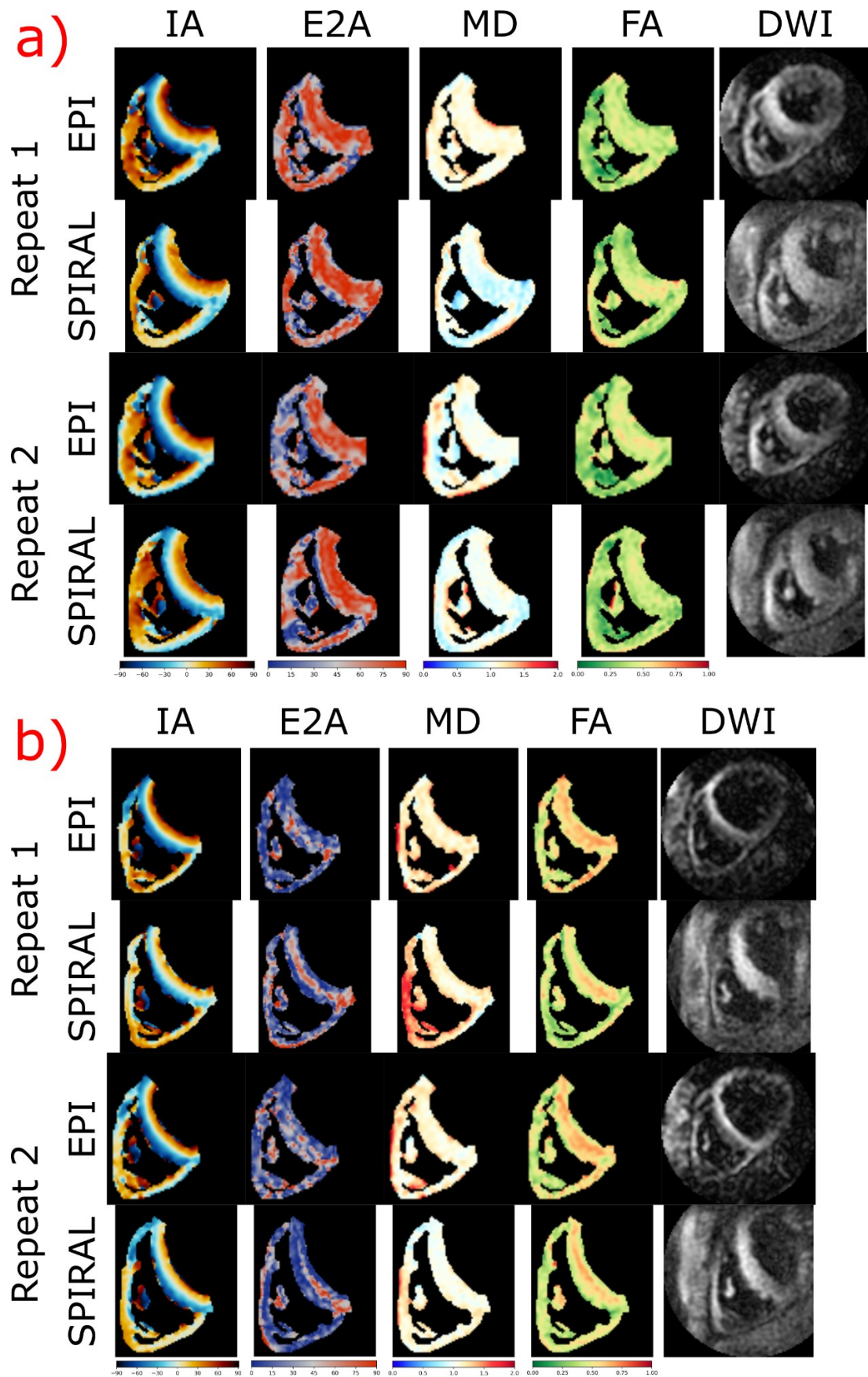


Figure 115: Example of DT-CMR parameter maps (IA[$^{\circ}$], E2A[$^{\circ}$], MD[10^{-3} mm 2 /s], FA[], DWI[]) for a high-quality data subject in both sequences and scan repeats. a) systole b) diastole

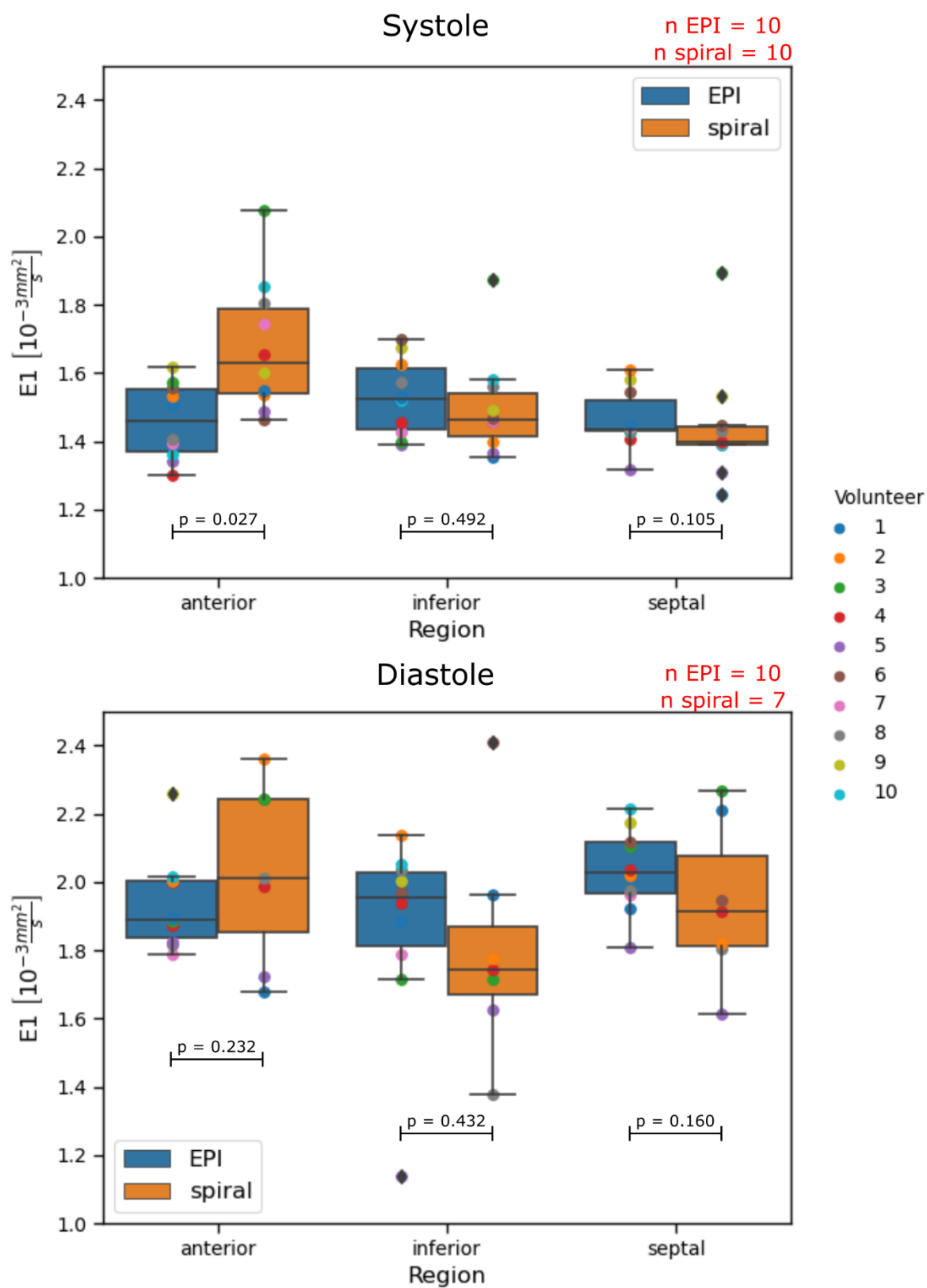
12.3.3 EPI vs Spiral

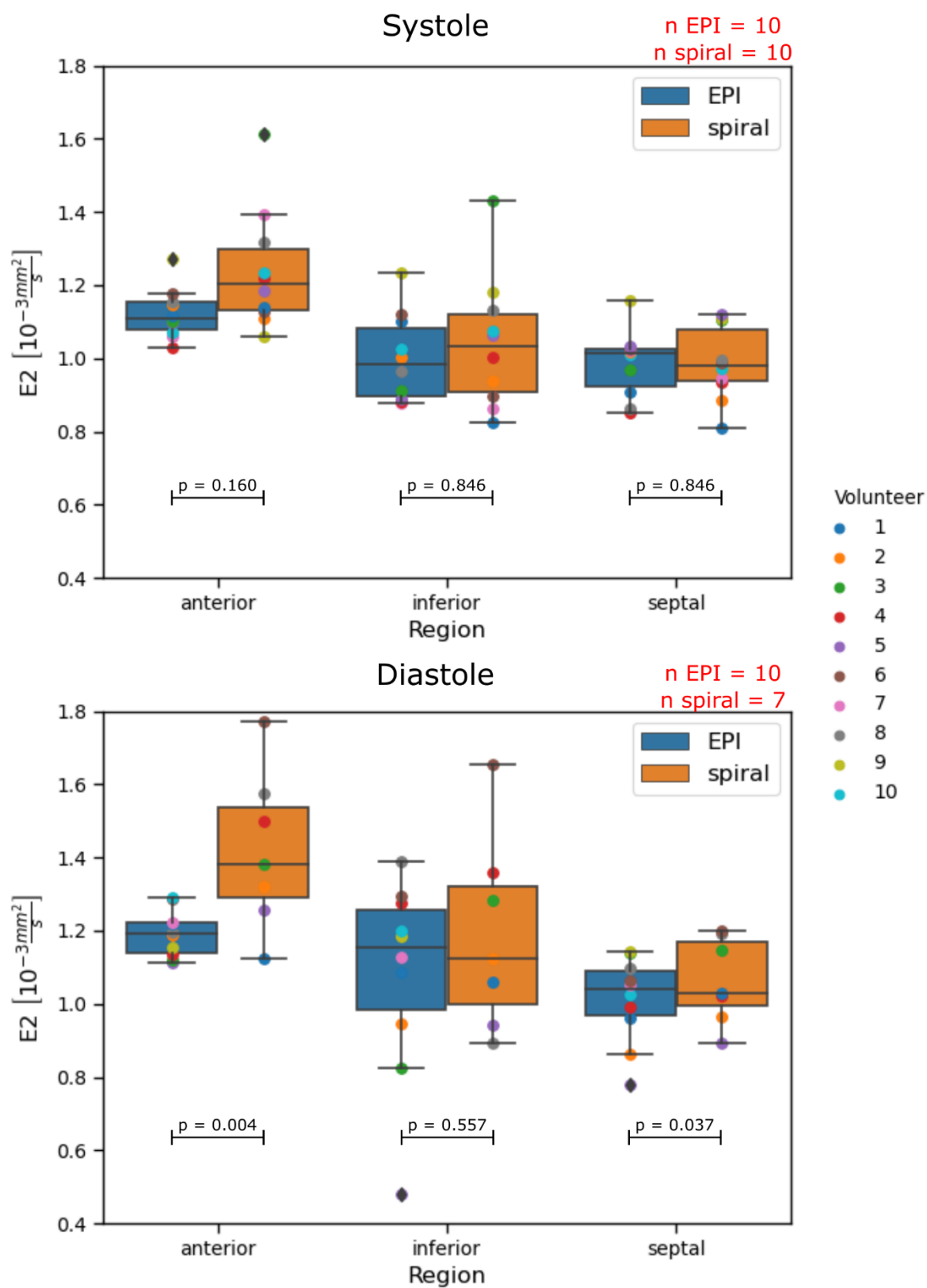
For repeat 1 only, the regional data for E1, E2, E3, MD, FA and SNR is displayed as boxplots for both cardiac phases and sequence types (Figure 116). Because only repeat 1 was used, discarded subjects are as shown in Table 10, the number of datapoints (n) is in systole n=10 for EPI and spiral, while in diastole n=10 for EPI and n=7 for spiral.

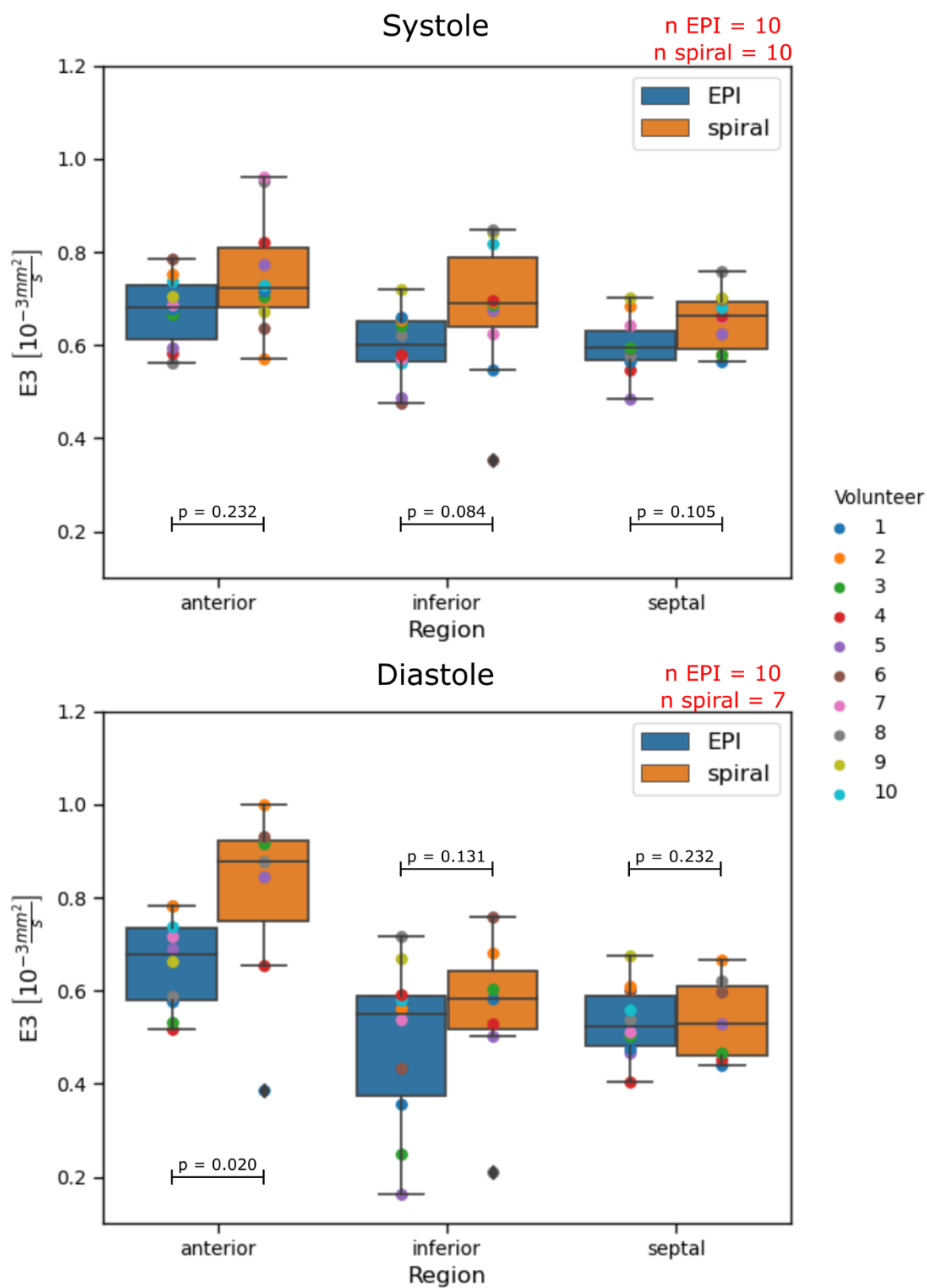
For the systolic DT-CMR parameters, the only significant difference between the sequences is found in E1 ($p=0.027$) in the anterior region, where spiral values are higher and in FA where values in the inferior region are borderline significantly lower in the spiral sequence ($p=0.049$).

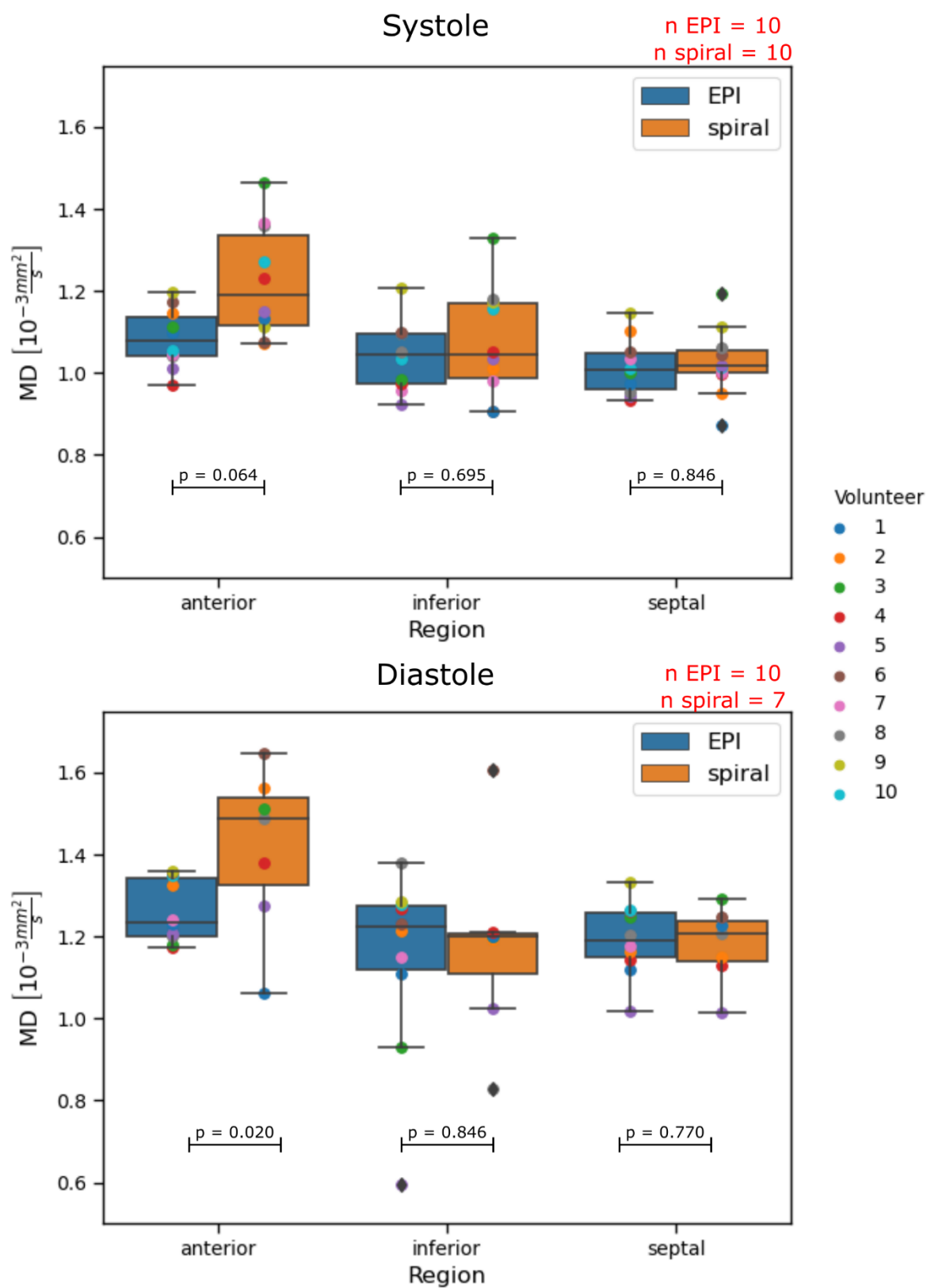
The diastolic phase shows significantly higher FA for the EPI sequence in all regions ($p=0.014$ (anterior), $p=0.037$ (inferior), $p=0.027$ (septal)). MD is significantly higher ($p=0.02$) using the spiral sequence in the anterior region. In the anterior region, E2 is higher in the spiral data in diastole ($p=0.004$) and for the septal region E2 is higher for the EPI sequence ($p=0.037$) in diastole. The E3 for the anterior region is higher for the spiral sequence ($p=0.02$) in diastole.

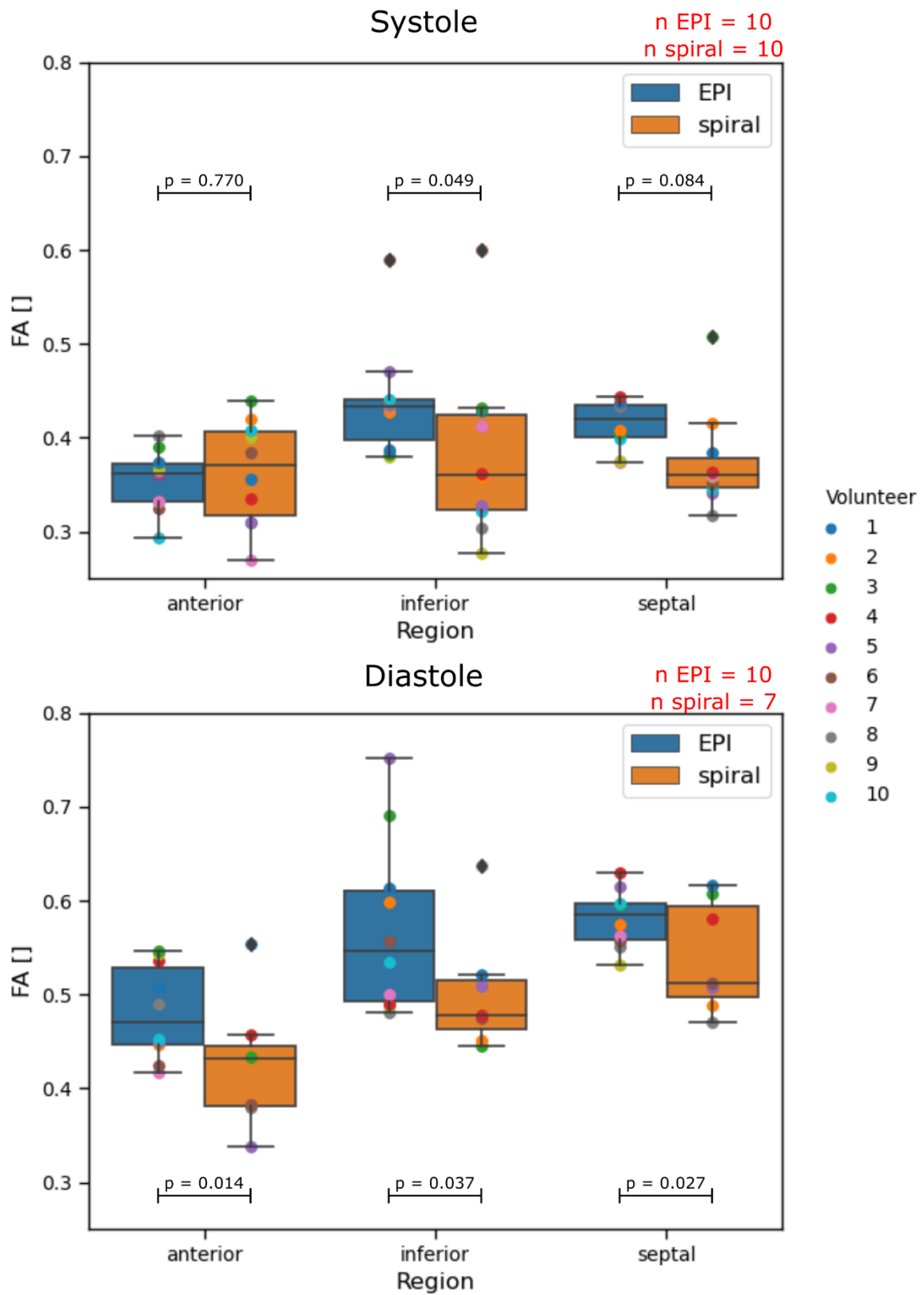
Again, for repeat 1 only, for the SNR measures in both cardiac phases, there are no significant differences between sequences in the inferior region ($p \geq 0.16$). In all other regions, the EPI sequence has higher SNR than the spiral sequence, with the anterior region in systole and the septal region in diastole showing the biggest changes ($p=0.004$ in both cases).











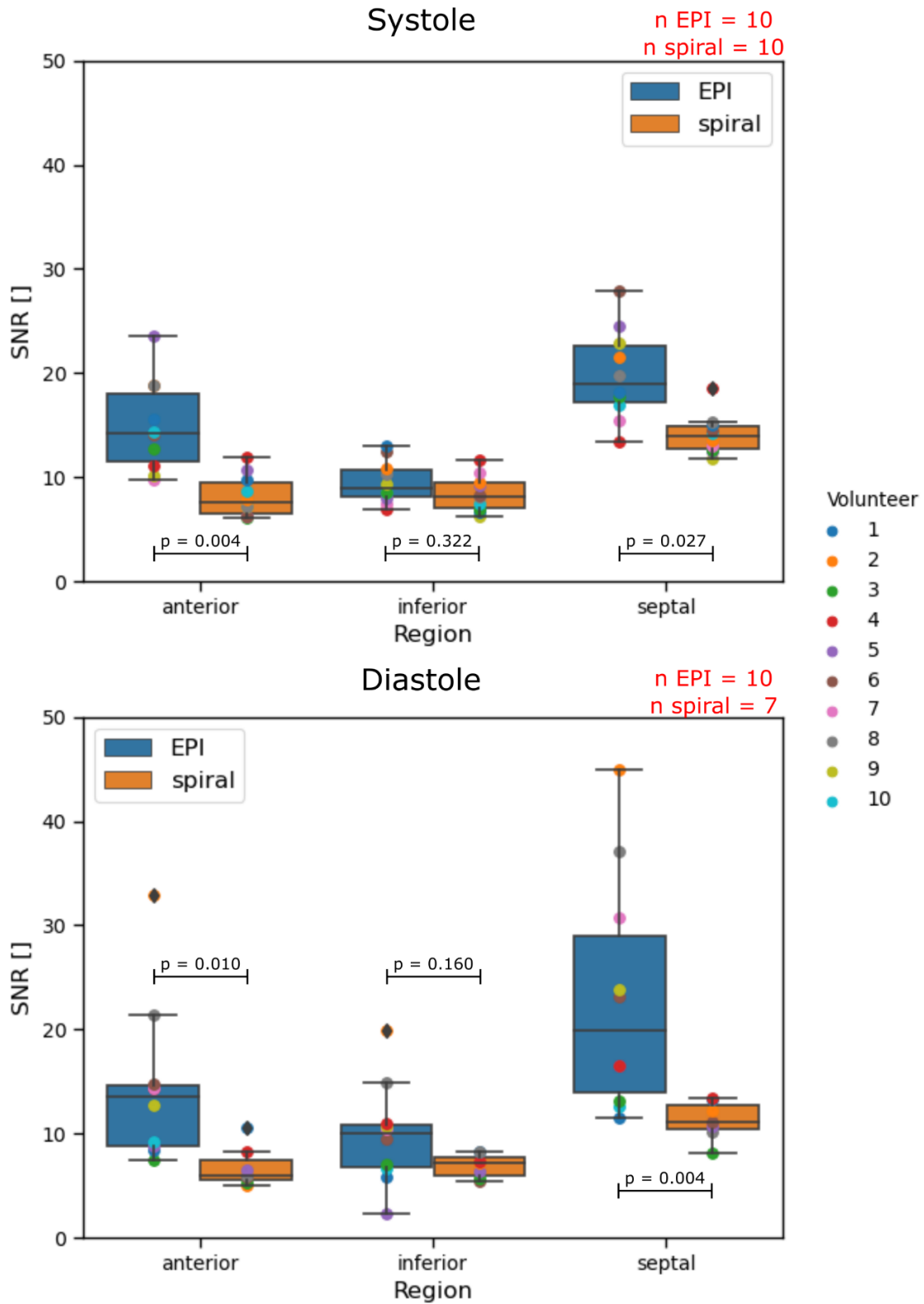
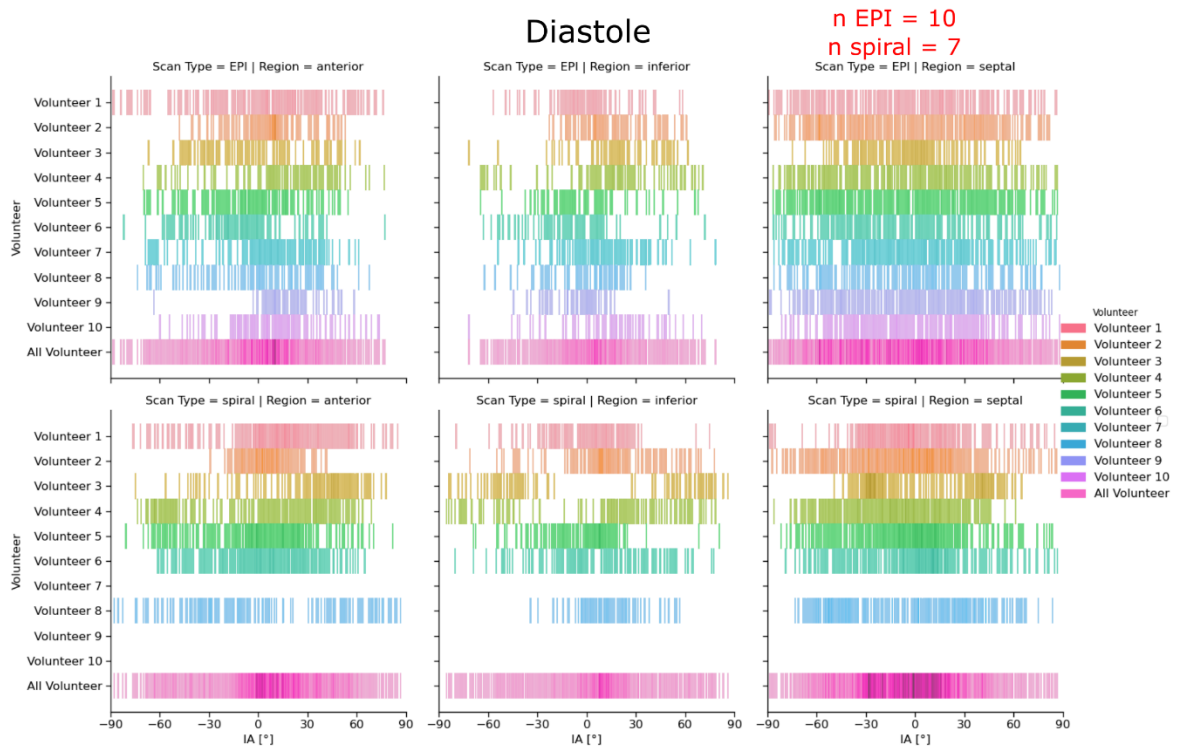
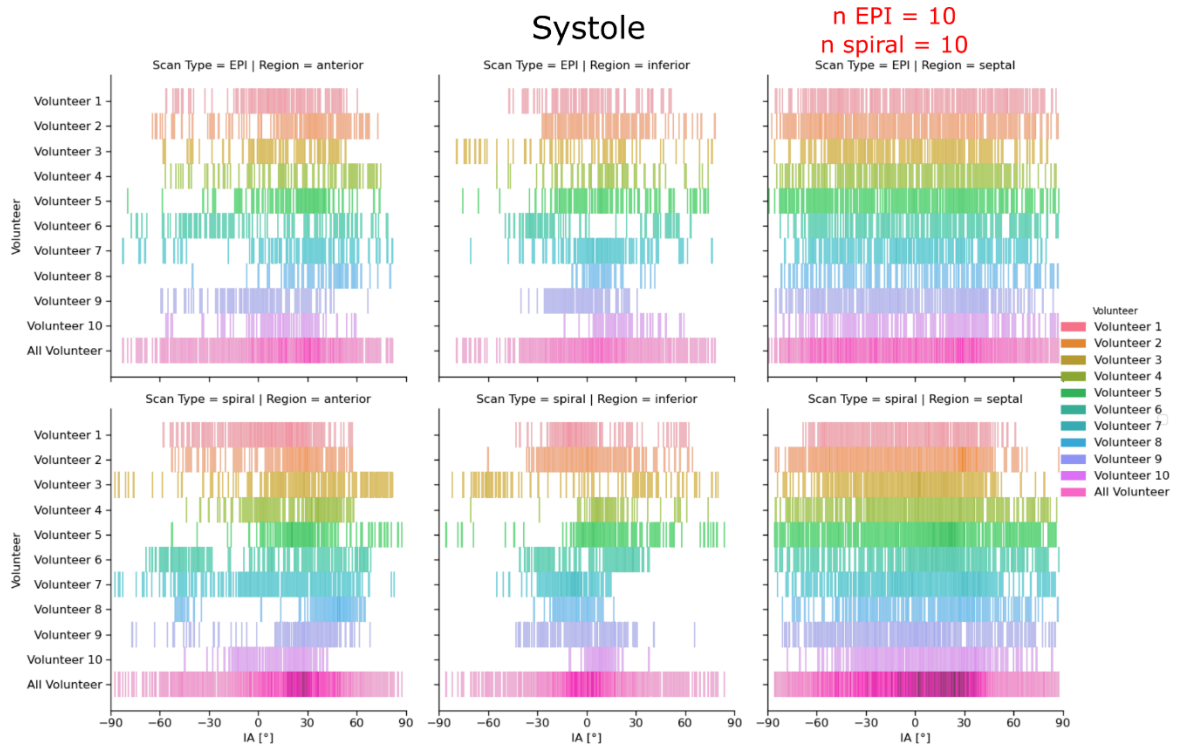


Figure 116: Boxplots of DT-CMR parameter maps (E_1 , E_2 , E_3 , MD, FA) and SNR measures for both sequence types. Results for both cardiac phases (systole, diastole) and the three regions (anterior, septal, inferior) are shown. For each volunteer, the mean regional value is plotted as an individual dot and boxplots present the data as quartiles and outliers (grey diamonds super-imposed). The p value of each Wilcoxon signed-rank test between sequence types is shown.

Figure 117 shows the pixelwise distribution of both IA and E2A for the data in the first scan repeat. It should be noted here that, due to the higher resolution of the spiral sequence, the histograms are more densely populated for the spiral sequence than for the EPI sequence. A good agreement is visible when comparing the population distributions (sum of all volunteers) between EPI and spiral datasets. In general, the E2A moves from values clustered around low angles to a more uniform distribution when moving from diastole to systole. The systolic anterior E2A shows a more visible clustering in the spiral sequence, with a peak at about 5° and a less dense peak at 30° . Further, the systolic septal spiral data shows a secondary peak at lower angles (primary peak $60-70^{\circ}$, secondary peak $0-20^{\circ}$) while in the EPI data only a peak at $60-70^{\circ}$ is visible.

The greater number of pixels makes identifying trends in IA between analysed regions more straightforward for the spiral sequence than for EPI. In systole the distribution of IA in the anterior region has a peak between $+25^{\circ}$ and $+30^{\circ}$, the peak of the septal data appears broader, somewhere between 0° and 30° and the peak in the inferior region is somewhere between -10° and $+10^{\circ}$. The patterns from the EPI data in systole are less clear, but consistent with the peaks found for spiral data in the same regions. In diastole, peaks in the summed distributions of IA are more identifiable in the EPI data. For both the EPI and spiral data, there is a peak in IA between 0 and $+20^{\circ}$ ($\sim 10^{\circ}$ for EPI) in the anterior region, while for the inferior region, there is a peak at $\sim +10^{\circ}$ for the spiral data and between 0° and $+10^{\circ}$ for the EPI data. For the septal IA in diastole, there is a less clear peak, with elevated values between -30° and $+20^{\circ}$ for spiral and a relatively uniform distribution for EPI data.



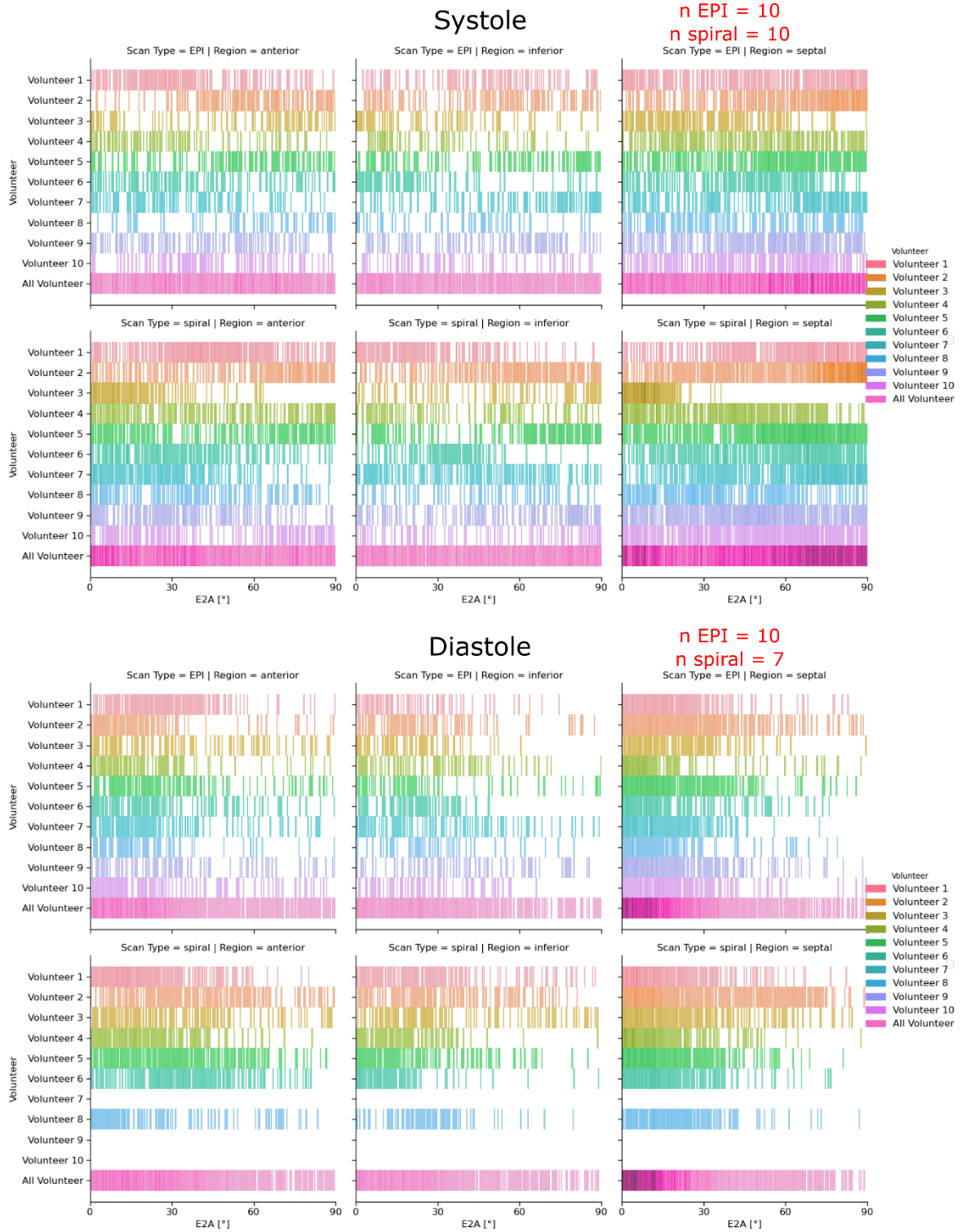


Figure 117: Histograms of the distribution of IA [°] and E2A [°] in every included volunteer, both cardiac phases and the three regions (anterior, inferior, septal) for the first scan repeat (n EPI = 10, n spiral = 7). For each cardiac phase and region, the individual volunteer values are combined to provide an overall population distribution (labelled All Volunteer). Darker shade of the colours corresponds to a higher density of values in the corresponding bin. Due to the higher number of pixels contained in the spiral data, the spiral plots tend to show darker values when compared to the EPI data.

Table 11 shows the results of the Wilcoxon signed-rank test between the EPI and the spiral sequence for median EzA in each region. There are no significant differences between sequences.

Map Type	Cardiac Phase	Region	p
E2A	systole	septal	1.000
		inferior	0.322
		anterior	0.232
	diastole	septal	0.375
		inferior	0.770
		anterior	0.322

Table 11: Results of paired Wilcoxon signed-rank test comparing EzA between the EPI and spiral sequence at both cardiac phases and in all three regions.

Table 12 compares septal data from scan repeat 1 with literature values [244] in the LV for a similar EPI and high-resolution spiral interleaved STEAM sequence. The data acquired in this thesis shows a general lower median E2A when compared to the literature values. For systole this equates to 48; 9(thesis) vs. 57; 15(literature) in EPI and 51; 19 vs 57; 7 in spiral (median; IQR). Similarly, the diastolic spiral values are lower here with 16; 4 vs 18; 6 (literature).

The MD values shown here show a marginally higher median with 1.01; 0.09 vs 0.99; 0.06 for systolic EPI, 1.02; 0.06 vs 1.00; 0.07 for systolic spiral and 1.21; 0.10 vs 1.14; 0.07 for diastolic spiral.

The FA values shown here show a slightly lower median with 0.42; 0.03 vs 0.48; 0.03 for systolic EPI, 0.36; 0.03 vs 0.46; 0.04 for systolic spiral and 0.51; 0.10 vs 0.59; 0.02 for diastolic spiral.

	<i>Data Scan Repeat 1</i>				<i>Gorodezky et al. [244]</i>		
	EPI		Spiral		EPI	Spiral	
	Systole	Diastole	Systole	Diastole	Systole	Systole	Diastole
<i>E2A [°]</i>	48; 9	18; 2	51; 19	16; 4	57; 15	57; 7	18; 6
<i>MD</i> [$10^{-3} \frac{mm^2}{s}$]	1.01; 0.09	1.19; 0.11	1.02; 0.06	1.21; 0.10	0.99; 0.06	1.00; 0.07	1.14; 0.07
<i>FA</i> [°]	0.42; 0.03	0.58; 0.04	0.36; 0.03	0.51; 0.10	0.48; 0.03	0.46; 0.04	0.59; 0.02

Table 12: Comparing median; IQR results for E2A, MD and FA from the septal area of the first scan repeat with results obtained in the LV by Gorodezky et al. [244].

12.3.4 Reproducibility

In Figure 118, the CoV [%], between the two repeats, for each sequence and cardiac phase, is calculated for the eigenvalues (E_1 , E_2 , E_3), FA and MD. Except for the diastolic E_3 (inferior EPI [23.2%], anterior spiral [20.8%]) all derived diffusion properties show good reproducibility with CoV under 20%.

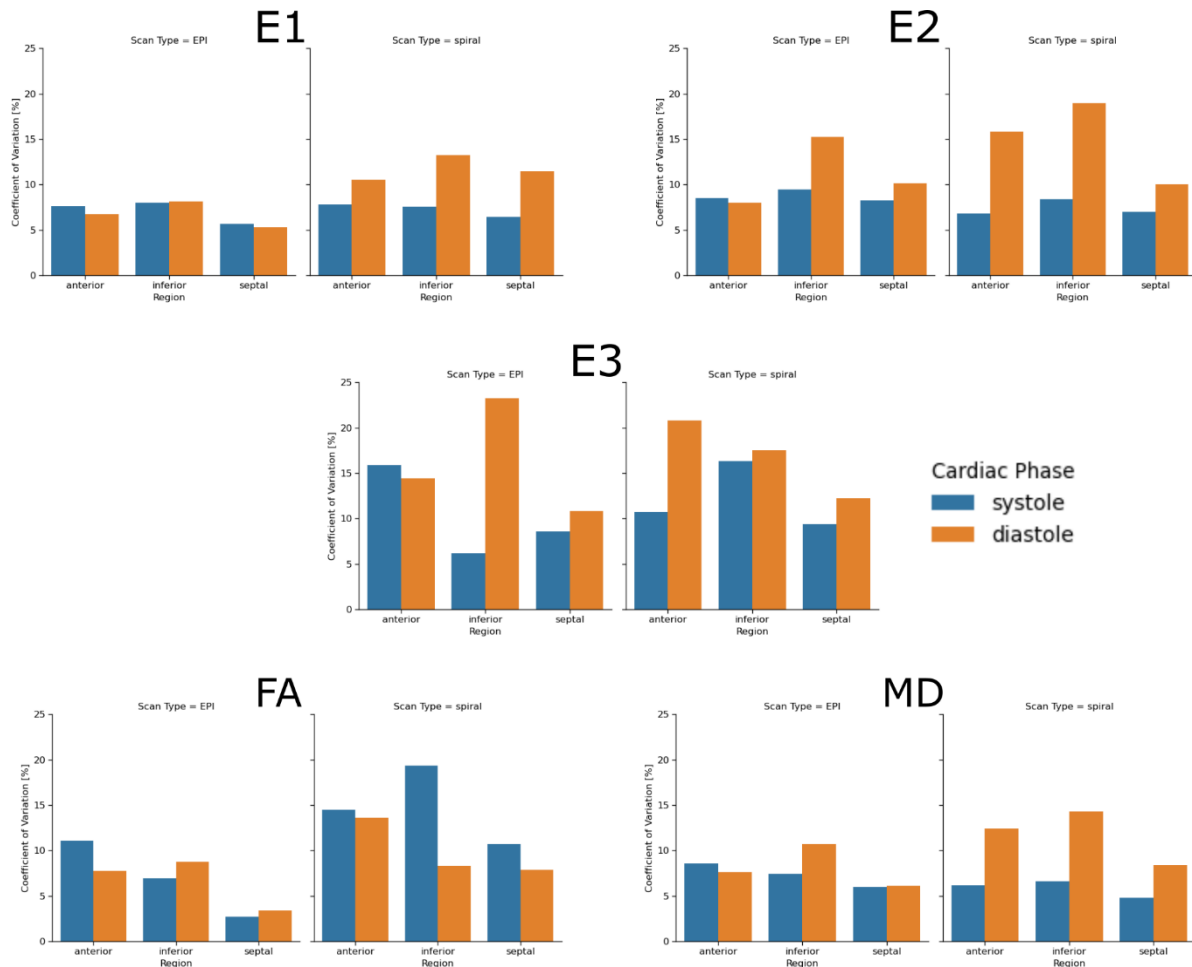
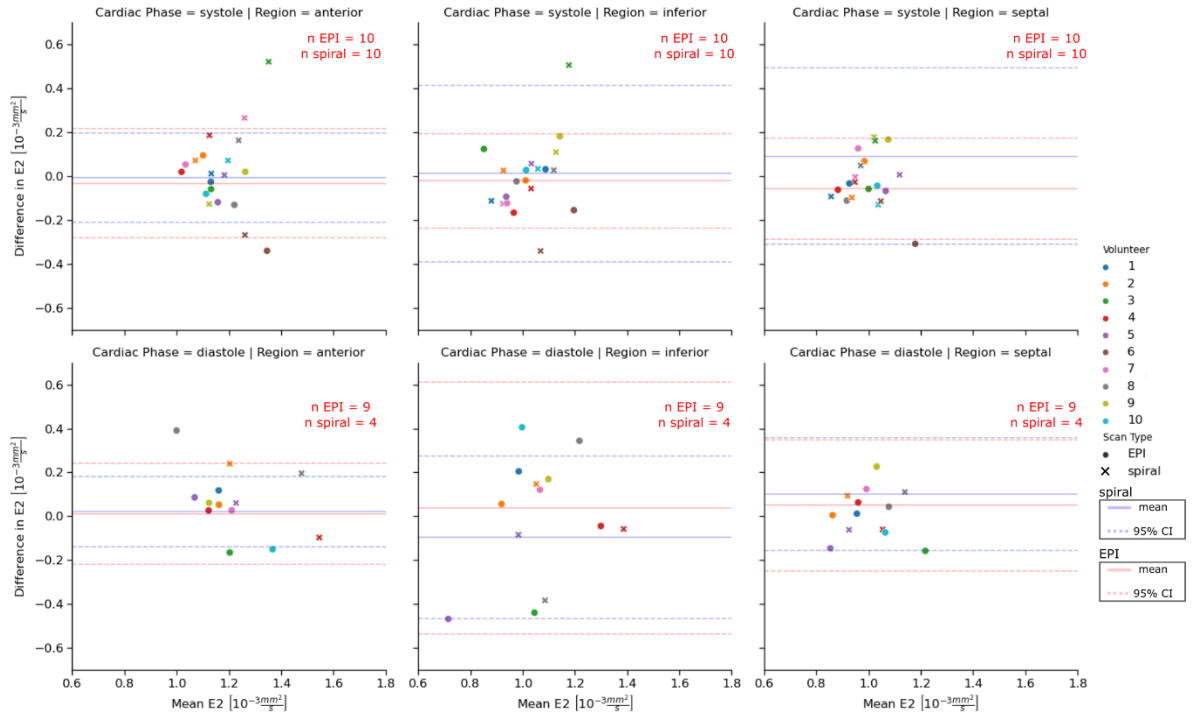
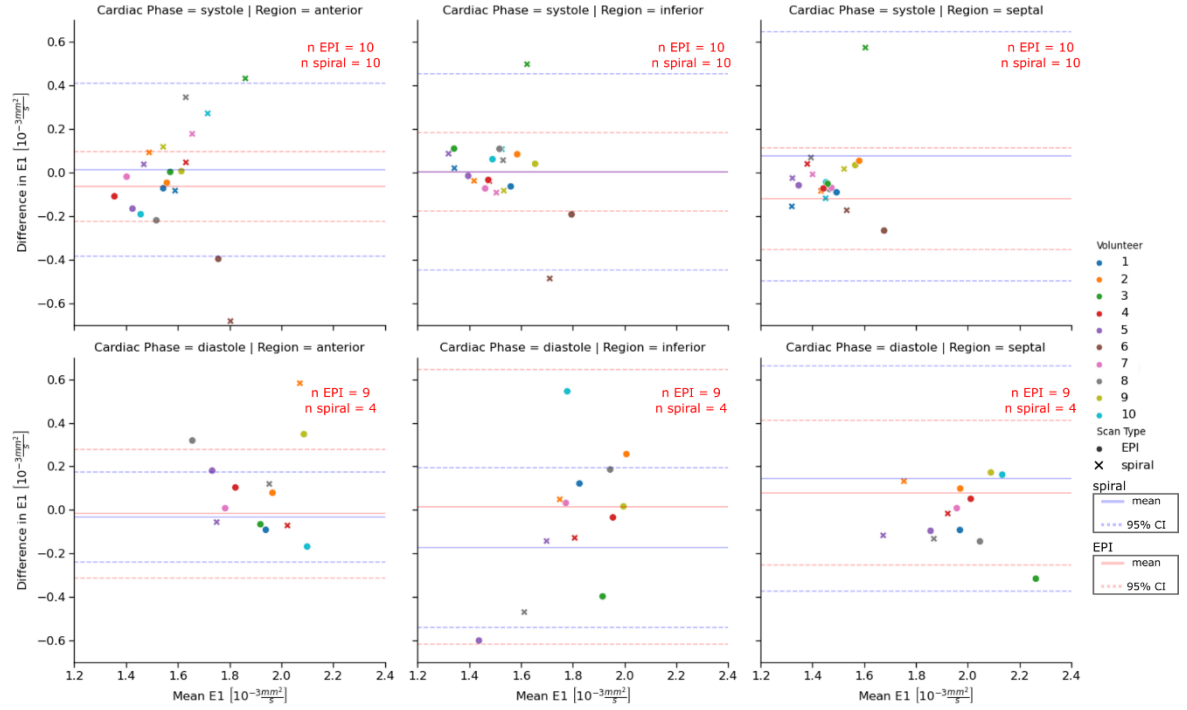
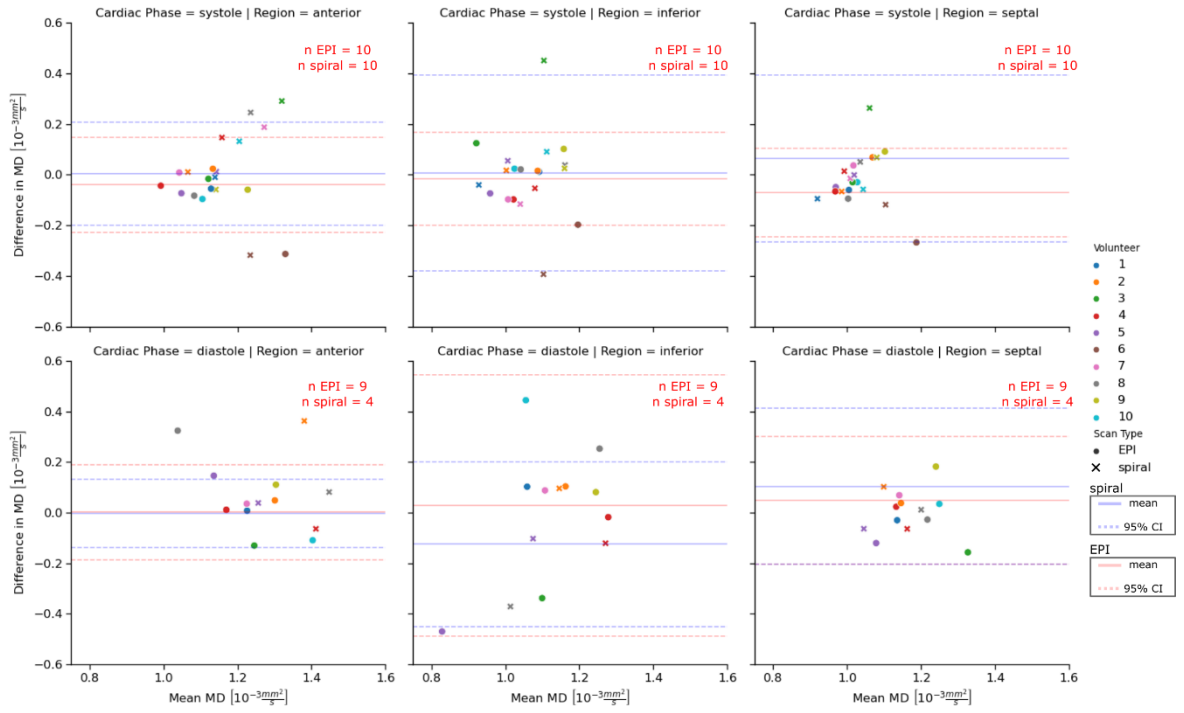
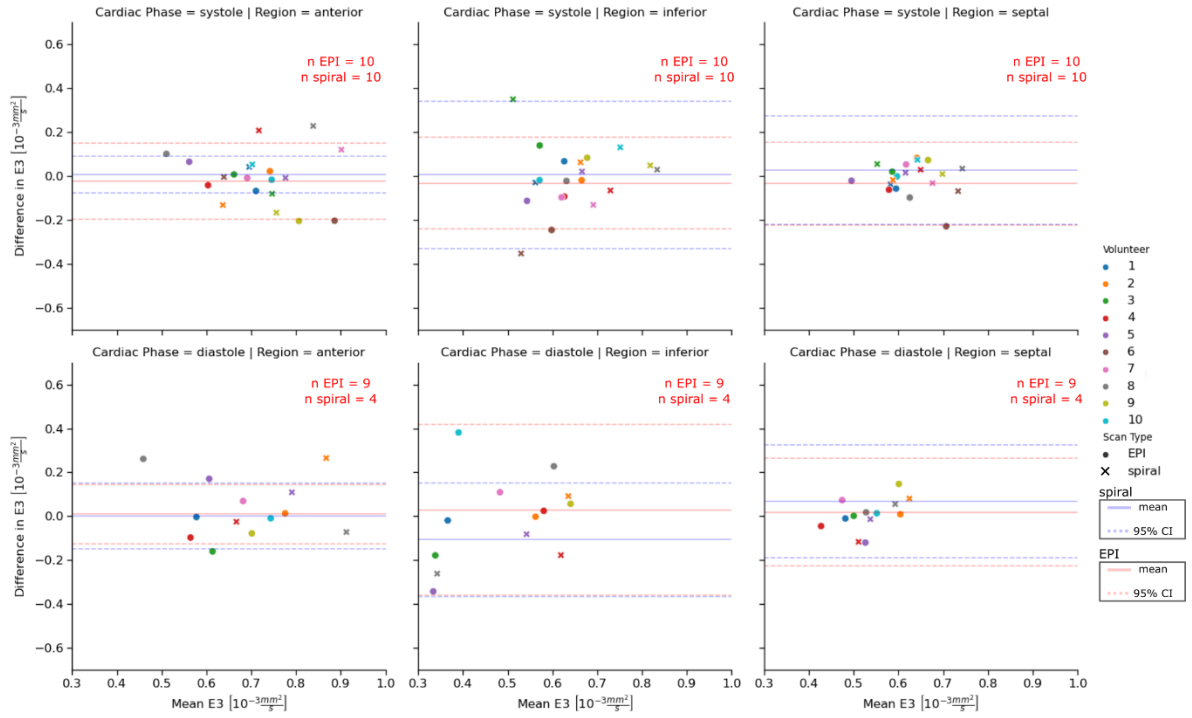


Figure 118: The Coefficient of Variation in % for E_1 , E_2 , E_3 , FA, MD for both EPI and spiral acquisitions. The results are further divided into cardiac phase and myocardial region.

In Figure 119, Bland-Altman plots are provided for the DT-CMR parameters (eigenvalues E_1 - E_3 , MD, FA, E_2 A). No substantial inter-study bias is present for either sequence in any region or cardiac phase. It is possible to see that the septal region in both cardiac phases and sequence types is the most reproducible region (smallest difference and narrowest spread in the Bland-Altman plots).





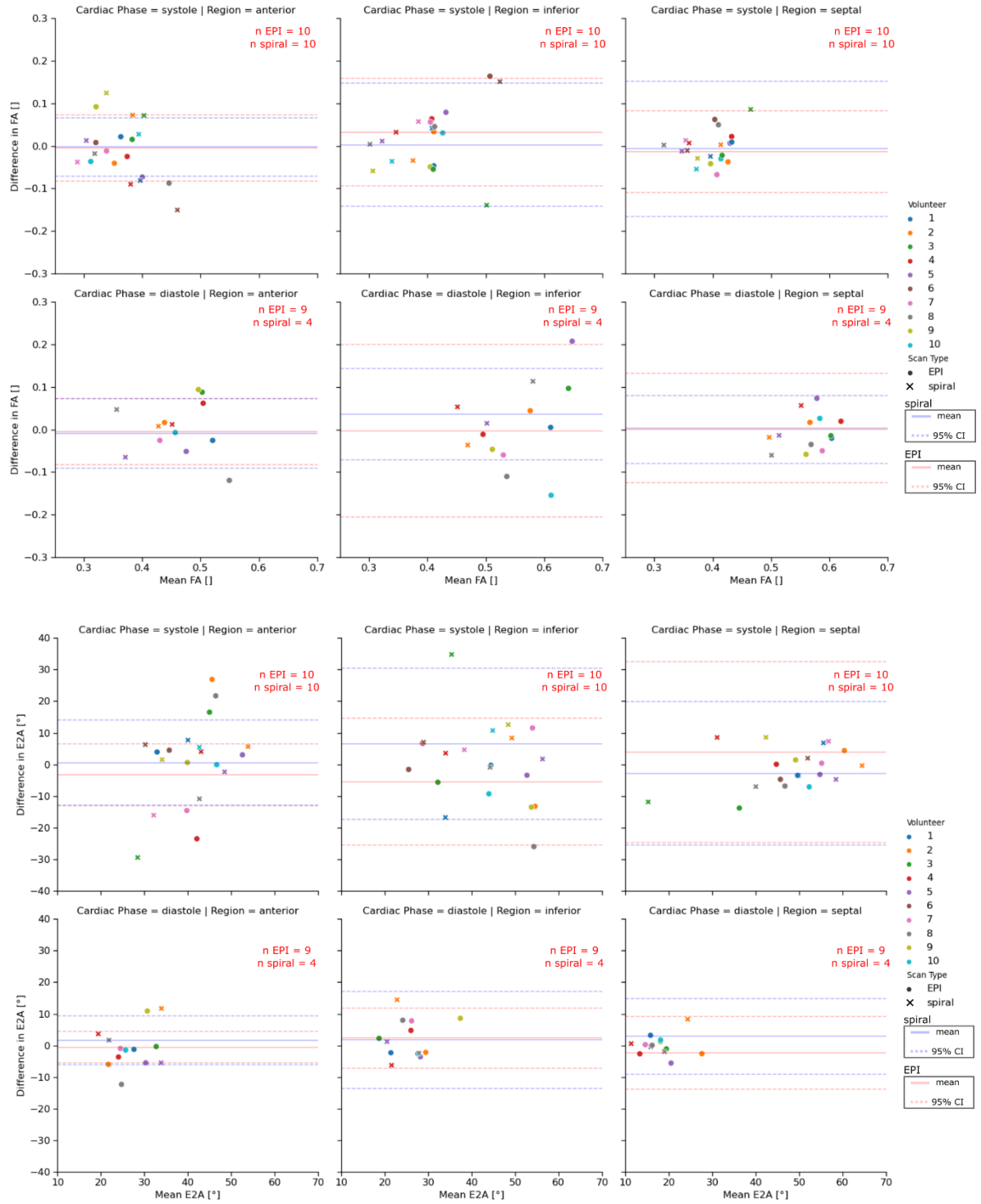
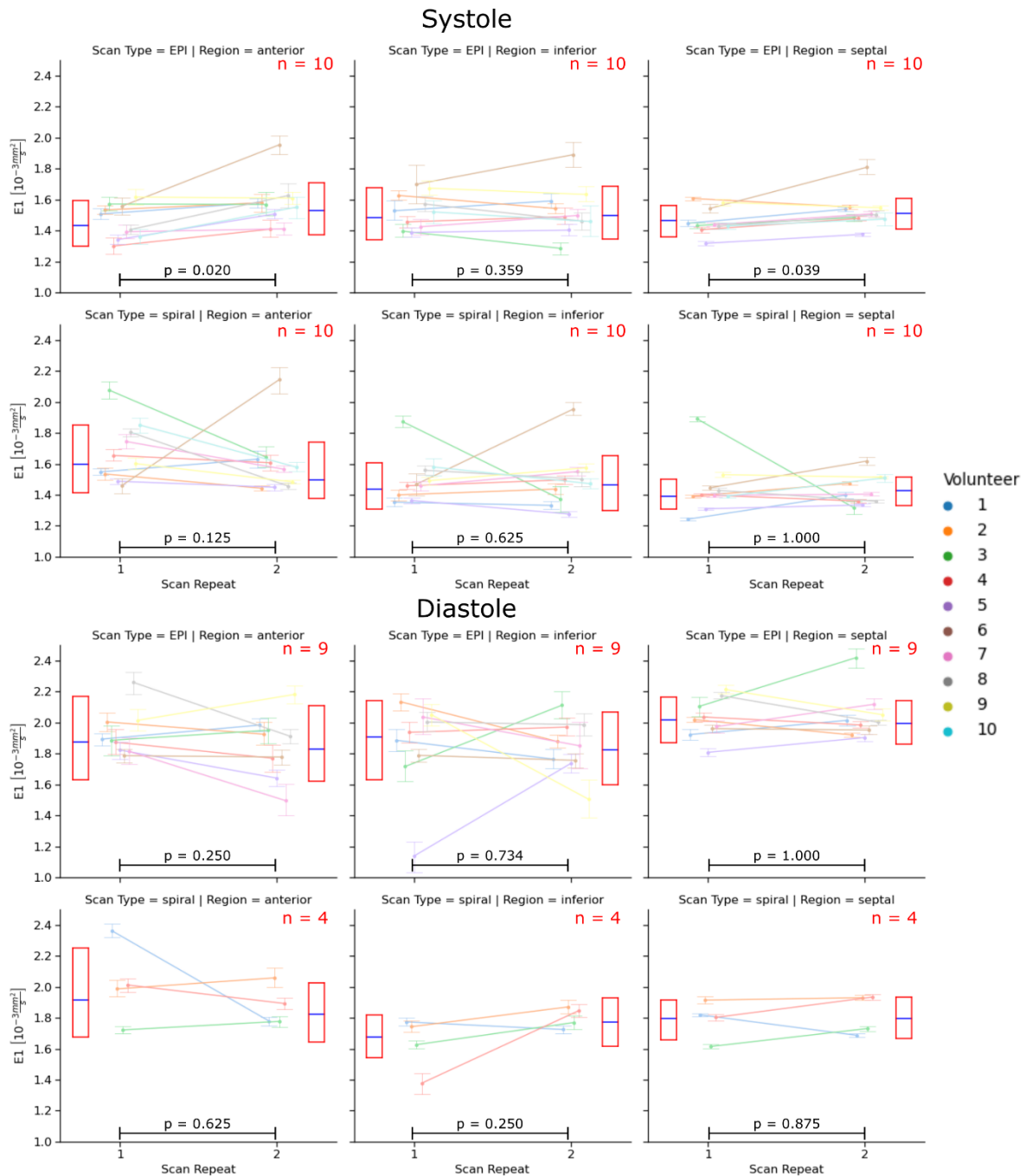
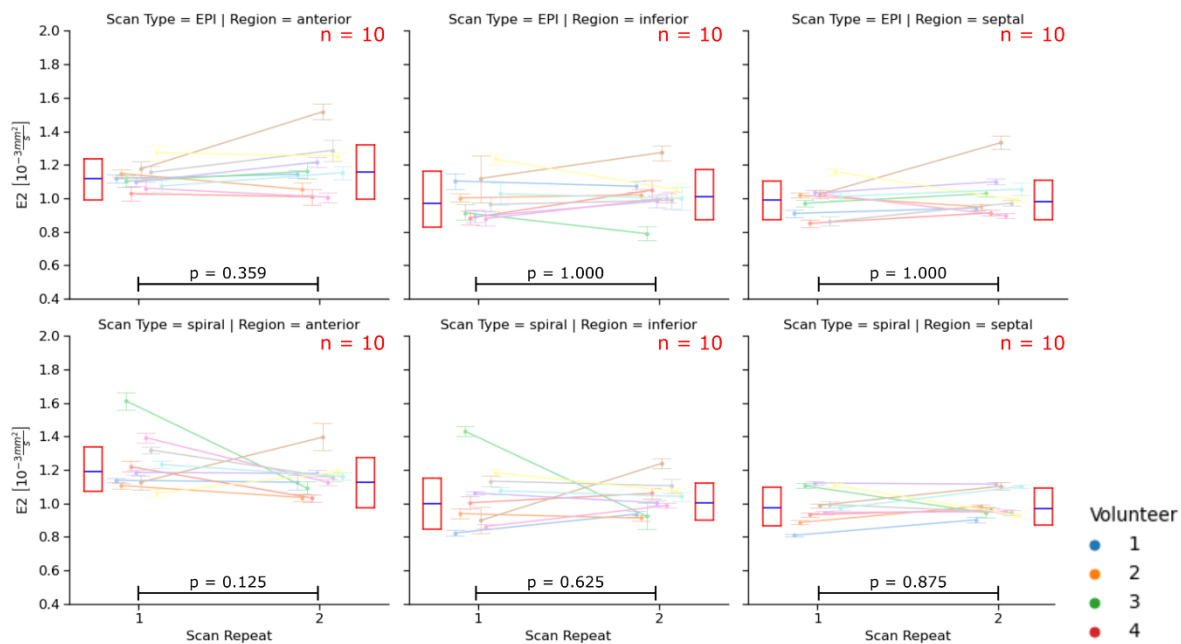


Figure 119: Inter-study Bland-Altman plots of EPI (dots) and spiral (crosses) DT-CMR parameters (E_1 [], E_2 [], E_3 [], $MD[10^{-3} \text{ mm}^2/\text{s}]$, FA [], E_2A [°]) data in systolic and diastolic cardiac phases for the three regions (anterior, inferior, septal). The mean and 95%CI for the EPI data is displayed as red lines, while the spiral ones are shown in blue. For each plot the number of completed repeatability tests by each sequence is shown as n (derived from Table 10). Further, the individual healthy volunteers are shown through the range of colours indexed on the right

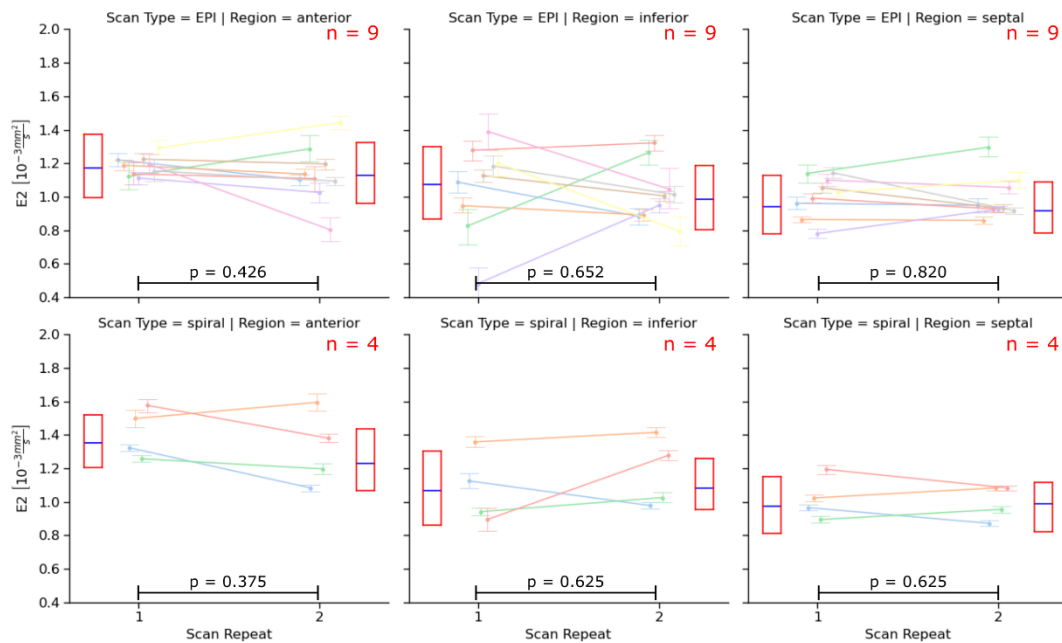
The paired point plot of the two repeated DT-CMR scans shown in Figure 120 provide an evaluation of differences in any region or sequence. The mean and standard deviation of each ROI in each subject, as well as the median, 25 and 75% quartiles over all subjects is plotted and the p-value of the paired Wilcoxon signed-rank test is displayed.

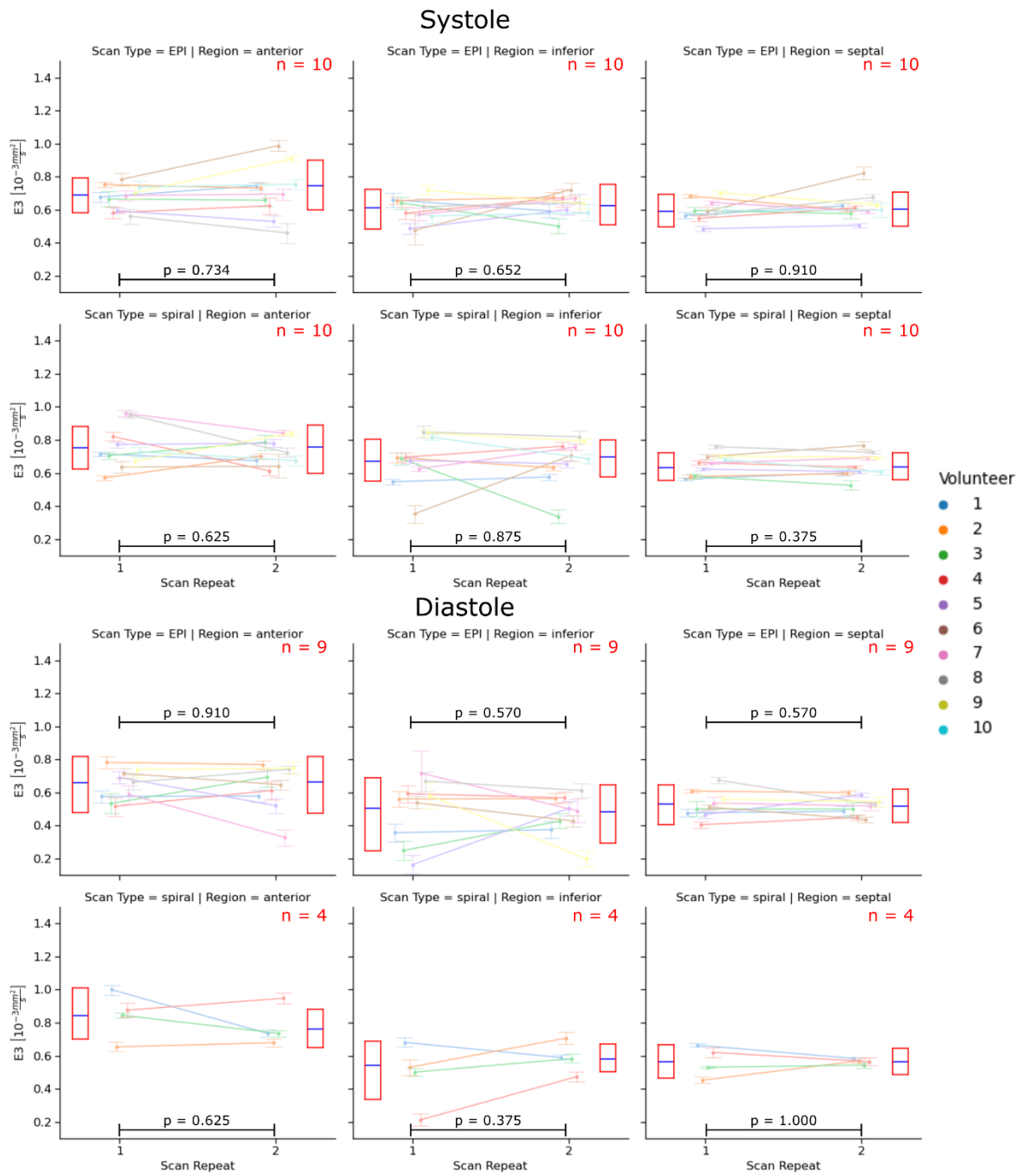


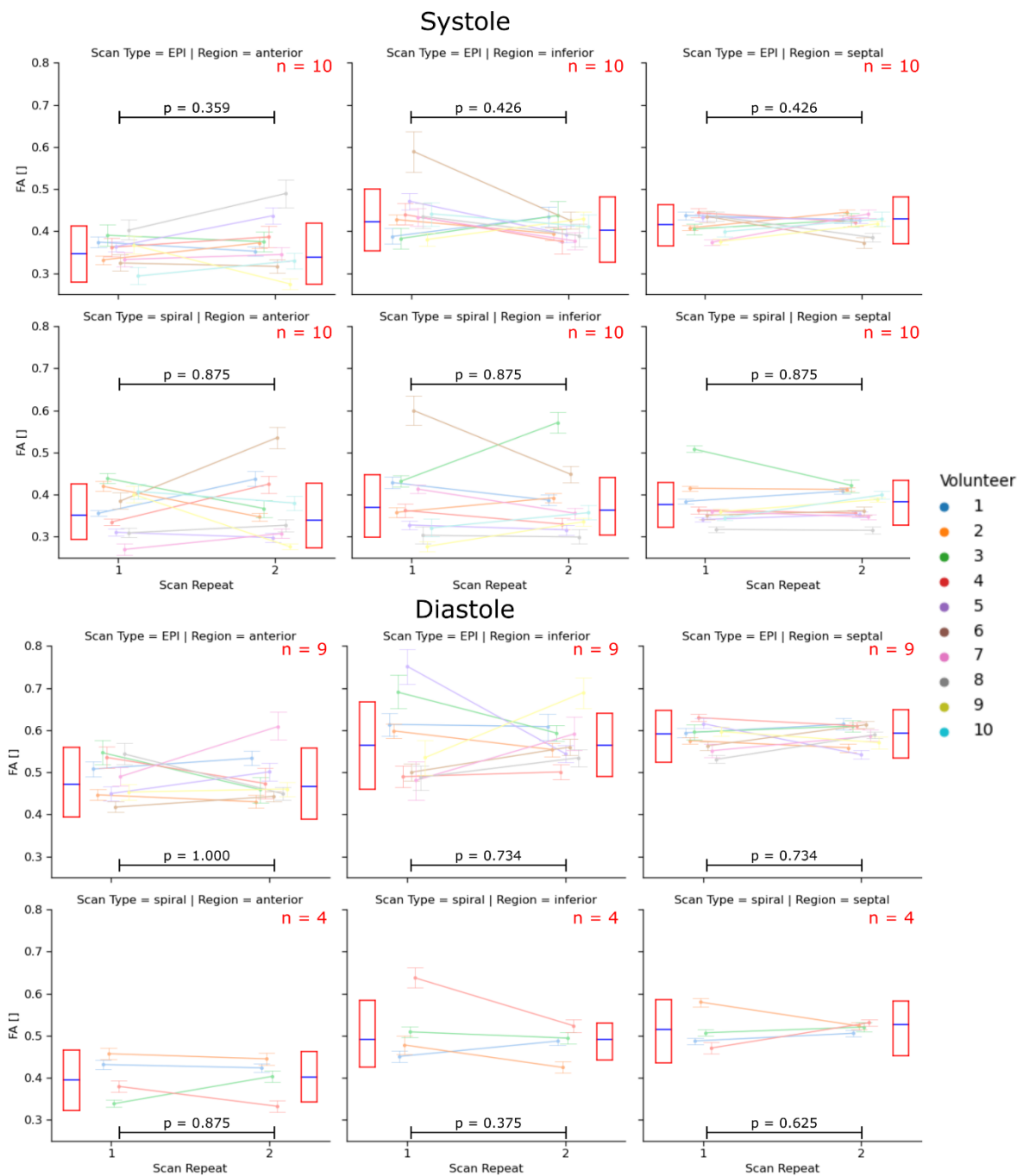
Systole



Diastole







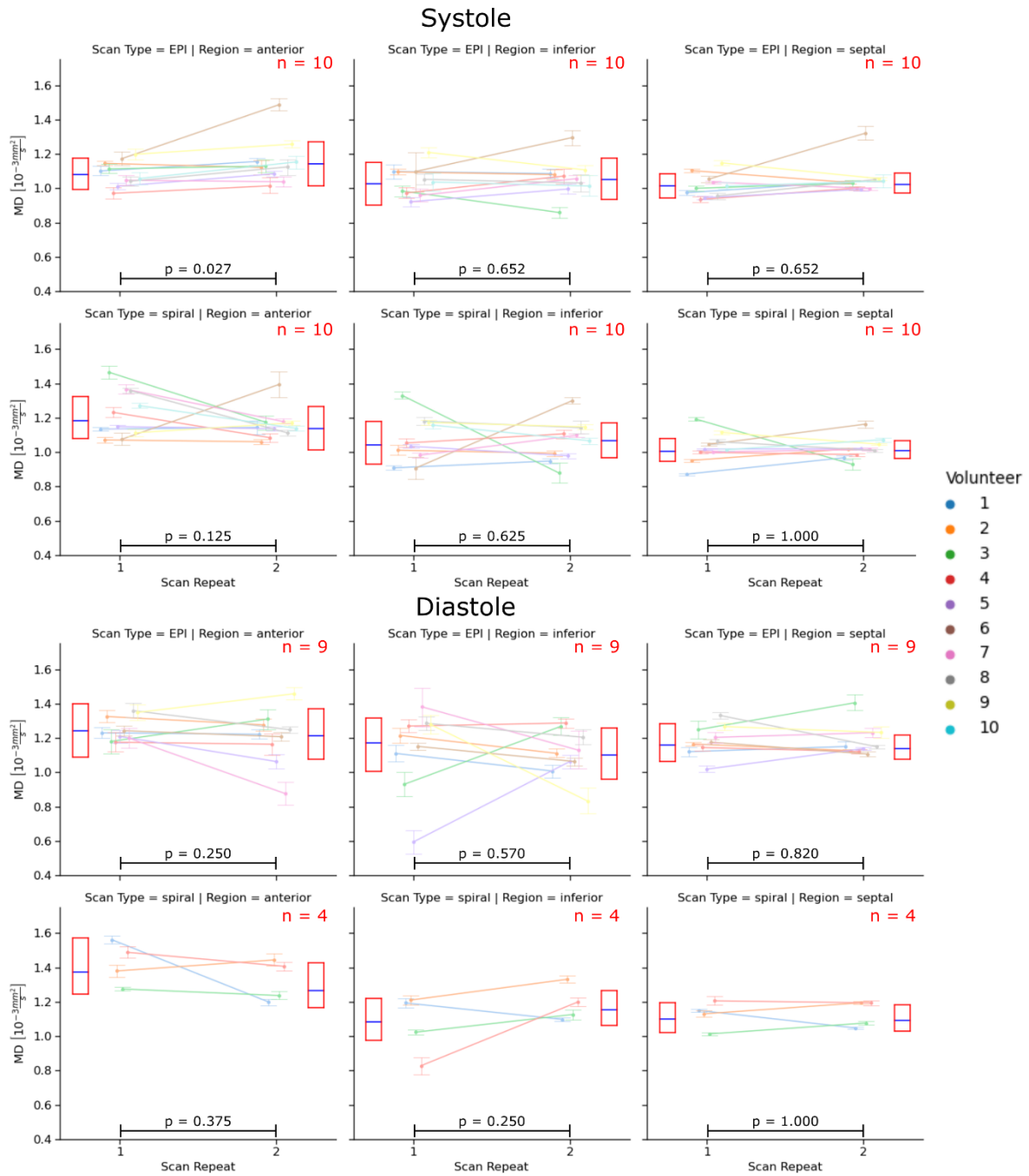


Figure 120: Paired point plots of the two repeated DT-CMR parameter maps ($E1[]$, $E2[]$, $E3[]$, $FA[]$, $MD[10^{-3} \text{ mm}^2/\text{s}]$). Shown are both cardiac phases (systole, diastole) and the three myocardial regions (anterior, inferior, septal). For each volunteer, the mean and standard deviation in the region is plotted as an individual whisker plot, while the red box with the blue line displays the median and 25-75 % IQR for all volunteers. Further, the p value of each Wilcoxon signed-rank test is shown. (The discretized p -values such as $p=1.000$ arise for the small $n=4$ pairs of diastolic spiral data).

The spiral and EPI methods provided similar reproducibility for MD in systole, with minimal bias in both cases (Bland Altman mean difference for [anterior, inferior, septal] [10^{-3} mm²/s], [0.06, 0.007, 0.004] for spiral, [-0.07, -0.02, -0.04] for EPI) and limits of agreement ($1.96 \times$ SD [10^{-3} mm²/s], [0.33, 0.39, 0.2] for spiral, [0.17, 0.18, 0.19] for EPI). The COV is suggestive of slightly less reproducible results in the three regions in systole using EPI (8.5, 7.4, 5.9 %) vs spirals (6.1, 6.6, 4.8 %), although all results were “very good” (see definitions). In the anterior region, the EPI sequence showed a significant difference in MD between scans in the paired test ($p=0.027$), which originated from a significant difference in E1 in the same region ($p=0.020$). A significant difference was also present in E1 in the septal region ($p=0.039$).

For FA on the other hand, EPI provided more reproducible results in systole. There was minimal FA bias between sequence repeats for both sequences (Bland Altman mean difference [-0.002, 0.003, -0.007] for spiral, [-0.005, 0.03, -0.01] for EPI) and limits of agreement are small in both cases ([0.16, 0.15, 0.07] for spiral, [0.10, 0.13, 0.08] for EPI). The COV was lower in all three regions for EPI (11.0, 6.9, 2.7 %) when compared to spiral (14.5, 19.3, 10.6%).

Both sequences showed little bias in diastolic MD (Bland Altman mean difference, [0.100, -0.120, -0.003] for spiral, [0.049, 0.027, 0.001] for EPI) and limits of agreement ([0.31, 0.32, 0.13] for spiral, [0.25, 0.52, 0.19] for EPI). The COV was elevated in the inferior region in diastole compared to the systolic data for the EPI sequence (10.7 % in diastole vs. 7.4 % in systole) and elevated at diastole compared to systole in all three regions for the spiral data (12.4 vs. 6.1, 14.3 vs. 6.6, 8.4 vs. 4.8 %).

The diastolic FA too showed reproducible results with very small biases (Bland Altman mean difference, [-0.001, 0.036, -0.009] for spiral, [0.006, -0.003, -0.005] for EPI) and limits of agreement ([0.08, 0.11, 0.08] for spiral, [0.13, 0.2, 0.08] for EPI). The diastolic COV values for FA showed elevated variability in the inferior and septal regions compared to the systolic data for EPI (7.8 vs 11.0, 8.8 vs 6.9, 3.4 vs 2.7%) and lower variability compared to systole in the spiral sequence (13.6 vs 14.5, 8.3 vs 19.3, 7.9 vs 10.6 %).

12.4 Discussion

To the best knowledge of the author, this was the first study quantifying *in vivo* DT-CMR results for the RV free wall by any technique, in this work using either a single shot EPI or an interleaved spiral DT-CMR sequence. One of the reasons for this novelty is the focus of DT-CMR on LV pathologies in previous studies. The other reason for the prior LV focus is that imaging the RV free wall is more challenging in CMR generally. Five key reasons can be identified that make this imaging target challenging, particularly for DT-CMR:

- **Thinner Myocardial Wall:** As is visible from Figure 4 and Figure 110, the RV free wall is substantially thinner when compared to the LV. This results in more severe partial volume effects due to the slice thickness. A smaller partial-volume effect occurs in-plane at lower spatial resolutions.
- **Increased Subject Heterogeneity:** Compared to the LV, the RV shape is more complex and heterogeneous between subjects. This was demonstrated in Figure 110 and further in the examples of the DT-CMR maps in Figure 113, Figure 114, Figure 115. Thus, not only is the drawing of ROIs more difficult in the RV, but also the orientation of the measured tensor will vary depending on the orientation of the free wall compared to the image plane. The more complex shape of the RV makes reproducible planning of the imaging plane more difficult in the RV. Small differences in angulation of the imaging plane normal to the RV wall, could therefore result in uncontrolled erroneous variations in the measured IA and E2A.
- **Anatomical Surroundings:** As visible in Figure 4 and Figure 113 the anterior RV borders the chest wall and the inferior RV is adjacent to the liver. Both neighbouring organs can generate bright signal patterns in the DWIs with similar signal strength to the myocardium. The chest wall includes muscle tissue with relatively similar relaxation times to myocardium, while the liver signal has T₁ values close to myocardial T₁ values at 3T with approx. 780 ms [328] compared to approx. 1192 ms in myocardium [329], but much shorter T₂ values approx. 15 ms [330] in liver compared to approx. 55 ms in myocardium [330]. The short T₂ values in the liver result in higher signal intensities from this organ in the spiral sequence than the EPI sequence, due to the shorter TE times with spirals (14 ms vs EPI 24 ms). These bright signals adjacent to the RV free wall can not only result in partial volume effects, but also complicate post-processing steps such as image registration and the drawing of ROIs when it is not easily visible where myocardium begins and other anatomy ends.

- **Inter shot motion:** In many DT-CMR studies breath hold-based approaches are applied to reduce inter-shot motion and build up sufficient averages and diffusion directions for the tensor calculation[185], [226], [244]. However, inter-shot motion is still of concern and most approaches deploy a rigid motion registration as a data pre-processing step [50]. This is of particular interest for the interleaved spiral sequence, which uses two shots to generate a single image. While it was shown that the SNAILS algorithm (Figure 112) sufficiently corrects for motion induced phase variation between the shots, even in challenging diastolic acquisitions, displacements between the interleaves will still result in image blurring. The lower pressure in the RV chamber, changes in pressure and reduced stiffness potentially also result in a less reproducible RV shape between cardiac cycles.

Residual motion between individual images in a DTI experiment can have a range of effects on the tensor fitting process. While experimental data and an extensive literature review is out of the scope of this thesis, some basic principles can be used to infer the likely effects of inter-image motion. Shear, stretch and rotation of the tissue modify the effective diffusion encoding [331]. Rigid translations between images in DTI datasets can have a number of effects. Within a relatively homogeneous region of tissue, they will have a blurring effect on the final DT-CMR parameter maps. Conceptually this originates in shifts between the individual frames resulting in the final calculated tensor at each pixel being calculated from data in region around this pixel instead of the exact same location. A direct result from this blurring effect is that that small features will be masked similar to partial volume effects in other MRI methods. However, unique to the DTI process is that this averaging effect can have different results on the parameter maps depending on the location of the pixel within the myocardium. If the pixel in question is located away from the borders of the myocardium so that all pixels in the tensor calculation originate from within the myocardium, angular measures and mean diffusivity will be blurred (averaged), while the increased range of microstructural orientations contained within each voxel are likely to result in a reduced FA and a reduced precision in the fitted tensor. However, if the pixels are located near the border and data from pixels containing little signal (outside the myocardium) are introduced into the tensor calculation by the residual motion, then MD and FA values are often substantially over or under-estimated. For example, if the high b-value data is replaced by data from the blood pool (very low

signal), the artefactually high MD would be calculated. The effects of this can be seen in Figure 113.

- **Cardiac Phase:** The RV often does not display such a clear global RV end-systolic pause and diastasis as the LV does. In some subjects it may be difficult to find such quiescent periods optimised for imaging of the entire RV wall.

12.4.1 EPI vs Spiral

One notable and unique problem of the spiral sequence when compared to the EPI is the inevitable geometric difference between the square zonal excited FOV and the circular spiral readout FOV. Due to the focus on the RV in this thesis, the centroids of both the excite and readout FOVs were positioned at the centre of the RV blood pool and, due to the small FOVs used, they generally only partially covered the LV. Thus, to maximise the coverage of LV free wall, the zonal excited FOV was chosen to be only 10mm smaller than the spiral readout FOV (100x100mm² zonal excited FOV vs. 110x110mm² edge of spiral readout k-space). However, since the spiral FOV is a circle and the zonal FOV is a square, the corners of the zonal excite FOV are outside the outer spiral readout FOV of the variable-density design (Table 9). The diagonal of the square excitation FOV was 141 mm ($\sqrt{2} \cdot 100 \text{ mm}$), which means that while the central spiral k-space data (190 mm FOV) fully samples over the excited FOV, only 61 % of the spiral k-space diameter covers the corners of the excited FOV. For the outer 39 % of the variable-density k-space spiral coverage, the sampled FOV as it falls towards 110mm, is less than the excited 141mm diagonal. This as shown in Figure 107, caused “high-spatial-frequency” FOV wrapping artefacts, as well as reduced performance of rigid motion correction methods. In future this cannot be recommended and instead a smaller zonal FOV (i.e., within the 110 mm complete spiral FOV) should be selected, at the expense of LV coverage. Alternatively, a 2D RF pulse design could be used to generate a circular zonal excited FOV.

The EPI and spiral sequences both showed acceptable single average SNR levels. The EPI sequence produced higher SNR when compared to the interleaved spiral approach. However, a direct comparison between these sequences is of course limited because the spiral sequence has a higher spatial resolution, although a shorter TE and longer total acquisition duration. In future, an interleaved EPI method for *in vivo* imaging could be implemented with similar resolution to the interleaved spiral method, making more direct comparisons possible, (facing the increased challenge of inter-interleave motion for EPI compared to spirals)

Turning to discussion of the results, most significant differences in DT-CMR parameters between the sequences were found in the diastolic phase as shown in Figure 116. The increase

in anterior E2 and E3 in the spiral caused the significant increase in MD when compared to EPI, while the increase in septal E2 caused the significant increase of FA in the EPI sequence. One likely reason for these differences is poor registration performance for the spiral data.

For IA and E2A, a visual improvement in DT-CMR map quality was evident using the higher resolution spirals for some acquisitions. One such example is visible in the septal E2A of the diastolic data shown in Figure 115. Here the higher resolution spiral resolved a band of higher E2A which was not sufficiently resolved in the EPI sequence. Further evidence of improved delineation of structures was shown for the IA in the first systolic repetition of Figure 114, here the inferior free RV wall in the spiral example showed a much clearer “two angle” structure when compared to the EPI data. In contrast, the corresponding EPI data showed a small reduction in IA in the same area but did not resolve the pattern due to the loss of fidelity relative to the spiral sequence. This improvement in resolution, however, comes at the expense of increased total acquisition time, with the spiral sequence taking double the amount of breath holds. In future, this drawback might be overcome by implementing a parallel imaging method to the spiral sequence, giving a fairer comparison to the EPI sequence, which already leverages parallel imaging.

For the moment, the interleaved spiral method has proven to be less reliable in the diastolic phase, causing more rejected frames and completely discarded datasets. This is most likely due to the image registration algorithms available, as shown in Figure 108, and also the problems described above due to the outer k-space spiral path’s FOV wrap.

While this was a small initial development study and describing the structure of the normal RV was not the primary aim of this work, in both the spiral and EPI data it was observed that the microstructural conformation in the RV wall is different from those found in the LV free wall or the septum. In the majority of datasets, two discrete angles appear to be present in the RV, rather than the continuous change in angle transmurally from EPI epicardium to endocardium seen in the LV wall. It also appears that MD values are higher and FA values are lower in the free RV wall sections than in the septum, although this would require further investigation as registration was more difficult in the RV. However, an interesting result was that the E2A showed a similar behaviour to the LV data in changing from a low angle in diastole to a higher angle in systole (Chapter 5.1).

12.4.2 Reproducibility

Given the challenge of acquiring DT-CMR data in the RV, the reproducibility of DT-CMR measures in the RV is highly relevant for future studies. Establishing that reproducibility was a key aim of this chapter.

Both sequences tested have shown to be reproducible in the systolic cardiac phase. This text is based on the definitions of the terms ‘good’ etc. given in Section 12.2. Despite the good performance of both methods, the EPI sequence was shown to be slightly more reproducible than the interleaved spiral sequence. This was likely due to the better motion registration performance of the post processing in the EPI case and because it is a single shot method it is less subject than the interleaved spiral to “inter-interleave” motion.

In the diastolic cardiac phase, the EPI sequence has shown good reproducibility. On the other hand, the spiral sequence has shown good reproducibility but poor reliability as in this phase 7/20 scans had to be discarded. However, when assessing the paired plots in Figure 120 it is evident that the accepted datasets showed a fair reproducibility. The reason for the generally more reliable performance of the EPI sequence was likely to be the underperforming motion correction algorithms and the increased wrapping artefact caused by the size of the square zonal excited FOV in relation to the circular spiral readout FOV discussed above

In both sequence types, the septal region has shown to be the most reproducible of the three areas analysed. Not only was the septal wall substantially thicker than the RV free wall and so less affected by partial volume effects, but it was also located away from other organs containing bright signal and was usually located close to the centre of the FOV where there are few wrap artefacts.

12.4.3 Other Studies

To the best knowledge of the author, no other study has investigated *in vivo* DT-CMR in application to the healthy human RV. As such, it is only possible to place the work performed here in the context of human LV studies that include septal values.

Gorodezky et al. [244]

The work presented here was the second iteration of high-resolution interleaved spirals for use in STEAM DT-CMR. Gorodezky et al. [244] performed the initial demonstration of the method with a focus on LV imaging and without assessing reproducibility.

Gorodezky et al. [244] found the spiral SNR in systole to be similar to the SNR of the EPI sequence. Their findings do not agree with the data shown here, where the SNR of the EPI was in general slightly higher than the SNR of the spiral. One reason for this was likely to be the reduced performance of the motion correction in the RV for the spiral data. Due to misregistration, the through-time SNR measures may have measured more noise (because of through-time partial voluming) in the thin and mobile walls and thus reduced SNR in the spiral methods here. Furthermore, the study by Gorodezky et al. [244] focussed on the LV, with less of the spiral wrapping problems encountered (also use of slightly smaller zonal excitation FOV at 96x96mm²). Gorodezky et al. [244] also calculated the SNR of the whole LV myocardium, while the SNR measures here were only performed in the septum. This difference in method might be expected to introduce a bias when comparing the SNR.

In Table 12 the E2A, MD and FA findings of Gorodezky et al. [244] are shown in comparison to the data acquired in this thesis during the first scan repeat. There is good agreement between the results in both sequences in comparison to the findings of Gorodezky et al. [244].

Scott et al. 2018 JCMR [186]

Scott et al. [186] compared the LV in M2-SE EPI to STEAM EPI at three cardiac phases in a single repetition study (n=15, healthy subjects). The STEAM EPI protocol used was similar to the protocol used in this thesis, and post-processing was performed using similar software.

The septal DT-CMR values shown in both sequences (spiral, EPI) in this thesis are in good agreement with the STEAM LV values shown by Scott et al. [186] in the diastolic and systolic phase. This includes the increase in MD and FA and further the change of E2A from approx. 55° to 15° for systole and diastole respectively. In the work by Scott et al. [186], the systolic phase was also shown to be more reliable than the diastolic phase.

Khalique et al. 2019 MAGMA [332]

Khalique et al. [332] used a similar approach to the study by Scott et al. [186] with both the same sequences and processing steps used for DT-CMR. Only systolic and diastolic data was acquired and instead of healthy volunteers this study assessed 10 HCM patients.

Reproducibility was not assessed in ref 20. The pattern that the systolic phase is more reliable when compared to the diastolic phase was again observed by Khalique et al., and agrees with the observations shown in this thesis and Scott et al.'s [186] work.

McGill et al. 2012 JCMR [333]

McGill et al. [333] assessed the inter-study reproducibility of a somewhat different STEAM EPI protocol to that of this thesis and the above references. The main differences from the EPI presented in this thesis and refs 19,20 were the use of “b=0” s/mm² and b=350 s/mm² for the low and high b values, and also the use of GRAPPA instead of SENSE for the parallel imaging). McGill et al. used this earlier version of the EPI DT-CMR to evaluate 10 HCM patients at systole only. For MD, the COV was found to be 22.2 % for the slice of LV in a mid-ventricular SAX slice, and 30.9 % for a septal region combined across basal, mid and apical LV short-axis slices.

Compared to the results of McGill et al. [333], the systolic septal data shown in this thesis was substantially more reproducible, with a Coefficient of Variation of 6 % (EPI) and 5 % (spiral). The increased reproducibility is likely to have arisen from improvements in scanner hardware, sequence design and post-processing methods during the decade since the McGill et al. [333] study. Furthermore, the McGill's work was conducted with a more challenging HCM patient cohort, in comparison to the healthy volunteers studied here. Also, the values from McGill et al. [333] are again quoted as either an average over the whole SAX mid-slice LV myocardium, or an average over the septal area in basal, mid and apical slices, and as such are not directly comparable to the septal mid-slice region measured in this thesis.

Tunnicliffe et al. 2014 JCMR [204]

Tunnicliffe et al. [204] conducted an inter-centre reproducibility study of 10 healthy volunteers in mid-SAX LV slices at systole and diastole using a STEAM EPI DT-CMR sequence. The main differences to the EPI presented in this thesis were the use of $b=15 \text{ s/mm}^2$ and $b=350 \text{ s/mm}^2$ as the low and high b values, and the use of GRAPPA instead of SENSE for the parallel imaging. The COV for the systolic phase was shown to be 7 %(MD), 6 %(FA) and for diastole 7 %(MD), 3 %(FA), calculated from a single ROI covering the LV myocardial ring in the SAX slice (excluding papillary muscles) [204].

The reproducibility shown by Tunnicliffe et al. [204] showed good agreement with the reproducibility results shown in this thesis. Only the systolic FA results using the EPI methods were more reproducible in this thesis than in Tunnicliffe et al. [204]. It should be noted that Tunnicliffe et al. [204] analysed the SAX slice-averaged LV, while only septal values were analysed in this thesis.

12.5 Future work

The most important improvement that must be made in future studies is to the in-plane image-registration of the RV free wall. The current rigid correction algorithms have clear shortcomings when applied to RV spiral DT-CMR data. Non-rigid deformation approaches could potentially yield significantly more accurate results. DT-CMR relies on intensity ratios, so care has to be taken when the registration algorithm alters pixel intensity. A potential solution would be to set limits for the changes in pixel intensity during registration, limits that would not lead to substantial errors in the final DT-CMR fitting, or enable some form of correction after tensor fitting that might take these intensity changes into account. Alternatively, a neural network could be trained to perform the registration step.

For future variable-density spiral STEAM DT-CMR studies, it will be important to suitably reduce the zonal excited FOV. This would reduce spiral wrap artefact at the high spiral readout spatial frequencies observed in this thesis, and could potentially benefit the registration algorithm, at the expense of a reduction in the extent of the imaged anatomy. Alternatively, a larger spiral readout FOV could be obtained by an associated increase in spiral duration, although the duration (14.4 ms) used was considered to the longest reasonably reliable for routine use and probably a parallel-imaging method would be more routinely practicable (discussed further below).

Like in the *ex vivo* work of this thesis, an improved SNR would benefit the SNR constraints of the data from the STEAM sequence. Thus, a deep-learning denoising network [324], [325] could be implemented to improve SNR levels in the DWI data.

While, as described in Chapter 10.4.1, the reconstruction of the spiral data included corrections for gradient timing errors with respect to the timing of the sampled k-space path, the addition of a more complete k-space trajectory correction method should improve the general data quality. After a very long history of such methods, the Gradient Impulse Response Function (GIRF) approach as used by Campbell-Washburn et al. [334] has been shown to sharpen spiral imaging acquisitions and might be strongly beneficial for the narrow RV free wall.

The EPI sequence used in this chapter utilised parallel imaging methods, while the spiral acquisition did not. An important future study would evaluate if a parallel imaging approach could improve the SNR efficiency by enabling the acquisition of more averages when under sampling along the spiral interleave dimension. The trade-off between the inherent and partially spatially-dependent (g-factor) SNR loss of parallel-imaging versus the potential SNR gain of enabling more averages has not yet been investigated. The data presented here could be used as an initial dataset for testing, because it was fully sampled and included separate coil sensitivity data.

Free breathing protocols are often associated with the ability to scan challenging patient groups. Here, a free breathing approach could be used to acquire additional raw data for high SNR, and high spatial resolution data without the need for extensive and exhausting breath holding. STEAM imaging during free-breathing is, however, difficult [49] due to the requirement for the heart to remain in the same position over two cardiac cycles.

Finally, the improved high-resolution spiral method will need to be clinically evaluated to see if it could provide any new insights in the detection of RV diffuse fibrosis in rTOF patients.

12.6 Conclusion

Both EPI and spiral sequences have been shown to provide reproducible DT-CMR parameters in the RV. Without further improvements, the use of the higher resolution interleaved spiral method cannot be recommended for diastolic imaging, when it has been shown to be insufficiently reliable. In systole, the benefit of higher resolution from the interleaved spiral method may justify the slight reduction in reproducibility and also its longer total acquisition duration. Finally, both methods in this thesis have shown microstructural measures consistent with other DT-CMR studies in the septum and have provided initial *in vivo* DT-CMR data in the RV.

13 RV T1 Mapping

13.1 Introduction

As discussed throughout this thesis a substantial clinical interest in T₁ mapping exists to detect and quantify changes in the Extra Cellular Matrix (ECM). The main aim is to detect diffuse fibrosis at a stage most relevant for clinical decision making. In the case of rTOF this would be to assist in assessing the ideal timepoint for pulmonary valve replacement [67]. However, despite promising progress towards clinical application of T₁ mapping in the LV [69], the investigation of feasibility of T₁ mapping in the RV (for applications as rTOF) is in its infancy [335]–[337]. One key reason for this is the general lack of focus of cardiac MR on RV pathologies. Many RV studies are focussed on the CHD pathologies where RV function is of greater interest. The more complex macroscopic structure and often thinner free wall of the RV make RV T₁ mapping challenging.

One of the biggest problems with current T₁ acquisition methods is caused by partial volume effects [69]. Signal from the blood pool and epicardial fat frequently contaminates the myocardial signal using both saturation and IR-based methods, which is particularly problematic in the thin RV. The high mobility of the RV, particularly in anterior regions also make imaging more challenging. Thus, current T₁ sequences designed for the LV do not provide adequate quality data in the RV and may fail to provide answers to the research questions, even if the sequence parameters are optimised for targeted RV imaging [335]–[337].

To reduce these partial volume effects two obvious paths can be taken from the sequence development point of view, either reduce the voxel size so that different myocardial tissue groups can sufficiently be resolved or employ signal suppression methods to filter out only the signal of interest (myocardial muscle). Here we focus on the latter approach, as substantial effort [335]–[337] has already been made in improving resolution and without prolonged scanning protocols there is little room for further substantial improvements.

To suppress both the fat and the blood we propose a modified STEAM sequence to facilitate dark blood fat-suppressed saturation recovery based (SASHA) single-shot T_1 mapping (STEAM-SASHA). In the following this sequence is validated in phantoms and tested in *in vivo* subjects with comparison to a standard MOLLI sequence. The performance of two designs of saturation pulse is compared and the effect of the number of averages used for the STEAM-SASHA method is evaluated. Inter-study, inter-observer and intra-observer variability are measured for both STEAM-SASHA and MOLLI sequences in a range of myocardial regions. Finally, data is presented from the application of the STEAM-SASHA method in one example rTOF patient as a demonstration.

13.2 Methods

To validate the T_1 measures obtained using both the MOLLI and STEAM-SASHA sequences the TiMES [338] phantom was imaged using the 18-element anterior array coil. 10 healthy volunteers (5 female[23-36 years, 29 average], 5 male[24-56 years, 34 average]) were scanned using the STEAM-SASHA sequence with a Chow saturation pulse [339] and 10 healthy volunteers (4 female[26-36 years, 30 average], 6 male[24-56 years, 38 average]) using the STEAM-SASHA with the standard saturation pulse (see later). A further test of the STEAM-SASHA sequence was performed in a single rTOF patient (male, age=20), with all parameters kept the same when compared with the volunteer scans. A 5b(3b)3b product MOLLI [340] sequence (Siemens Vida 3T) was acquired with every scan as reference. A single mid-ventricular short-axis slice was imaged near peak systole with all sequences. Each healthy volunteer was scanned twice with repositioning in-between the two studies to allow calculation of inter-study reproducibility measures. The acquisition was planned as described in Chapter 10.3 to image the RV in a short axis plane.

13.2.1 MOLLI

Breath-hold 5b(3b)3b MOLLI data was acquired with a minimum TI = 100ms (increment 80ms), bSSFP readout, acquired resolution (phase x frequency encode) $2.4 \times 2.0\text{mm}^2$, FOV (phase x frequency encode) $307 \times 360\text{ mm}^2$, slice thickness=8 mm, receiver bandwidth=208.3 kHz, 7/8ths partial Fourier, GRAPPA 2x, TE=1.0 ms, TR=2.4 ms, flip angle=20°. The trigger delay was adjusted to acquire each image at peak-systole. For each scan of the pair used for reproducibility, the acquisition was acquired twice (i.e., 4 T₁ maps were acquired in each volunteer), as is performed routinely at our institution in research T₁-mapping scans to reduce the effects of noise on the T₁ measures.

Pixelwise T₁ maps were generated using the online ("Myomaps") product image reconstruction and calculation. Using the ImageJ image processing platform, the mean T₁ within ROIs (drawn based on the criteria covered in the post processing Section 13.2.2.1.1 here) was calculated for each T₁ map and the T₁ from each ROI was averaged over the two acquisitions in each scan.

13.2.2 STEAM-SASHA

13.2.2.1 Sequence

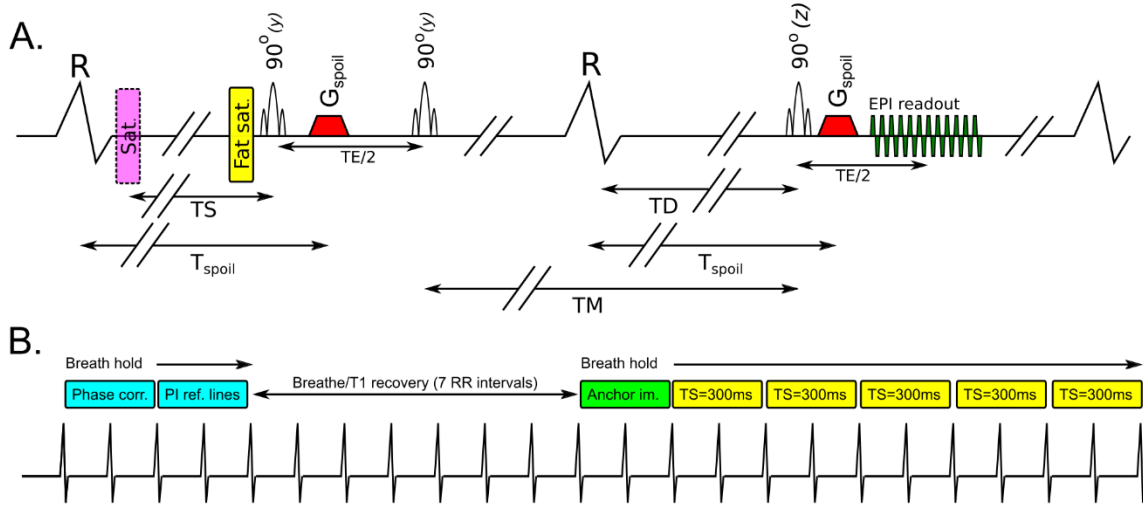


Figure 121: Each single shot STEAM EPI takes two heartbeats (A). The first 2 RF pulses are selective in the phase encode direction (y), and the 3rd in through-plane (z), reducing the phase encode FOV and therefore the readout duration. Spoilers (G_{spoil}) remove components other than the stimulated echo and are run at the same delay (T_{spoil}) in both heartbeats to ensure the same location of the heart when they are run. Spoiler gradients and washout during the mixing time (TM) eliminates blood signal. A saturation pulse provides T_1 weighting, $TS=300$ ms. (B) Each acquisition consists of 8 stimulated echoes over 2 breath holds pausing for T_1 recovery between preparation scans and the anchor image. Each of these sequence results in 1 anchor image and 5 $TS=300$ ms images. Reproduced from [341].

The STEAM-SASHA sequence presented here is an EPI single shot acquisition that splits signal preparation over two consecutive cardiac cycles (Figure 121.A).

Here the stimulated echo is created by three 90° pulses of which the first two are run after the first R wave trigger and the last after the second R wave trigger. After the first and third pulse a spoiler gradient is run. The spoiler gradients eliminate echoes and free-induction decay signals, (particularly the FID signal from the third RF pulse) leaving only the stimulated echo. Blood signal is minimised via the spoiler gradients and the outflow of blood during the mixing time (TM) between the second and third RF pulses. Important to note is that the spoiler gradients will result in a small amount of diffusion encoding ($b = 100 \text{ s/mm}^2$) in the myocardium. In order to minimise any directional dependence of this diffusion weighting, the orientation of the spoiler gradients was cycled when repeating the sequence for multiple averages. By making the first two pulses selective in the phase-encoding-plane direction and the third slice selective in the through plane direction, a zonal excited FOV can be generated which enables the use of a more robust shortened EPI readout [342]. The peak of the stimulated echo in this setup is determined by the time ($TE/2$) between the first and

the second RF pulse and so the centre of the EPI readout is run $TE/2$ after the third RF pulse. Fat signal is suppressed via the fat suppression pulse and the T_1 decay of fat during TM. The saturation pulse was fixed at a time $TS=300$ ms before the first RF pulse. While a higher TS might be beneficial for the accuracy of T_1 mapping [146], a value of $TS=300$ ms allows the imaging data to be acquired at approximately peak systole when the ventricles are thickest via running the saturation pulse immediately after the ECG R-wave.

Each acquisition consisted (Figure 121.B) of two stimulated echoes (4 RR-intervals) for EPI phase correction and parallel imaging reference during breath holding, followed by 7 RR-intervals T_1 recovery time (1 breathing cycle), and then during breath hold, an anchor image (2 RR-intervals) and 5 images (10 RR-intervals) with $TS=300$ ms. STEAM-SASHA images used in this thesis were acquired with $TE=36$ ms, $TR=2$ RR-intervals, acquired resolution (frequency encode x phase encode) 2.8×2.8 mm², slice thickness=8 mm, receiver bandwidth=312.5 kHz, FOV (frequency encode x phase encode) 360×270 mm², echo train length=47 ms, 6/8 partial Fourier, SENSE acceleration factor 2 and $TS=300$ ms (fixed).

A common source of error in T_1 mapping methods is imperfectly saturated magnetization, which is particularly problematic at higher field strength due to increased B_0 and B_1 field inhomogeneities [158]. Chow et. al [148] thus proposed an improvement over the standard $90^\circ 90^\circ 90^\circ$ saturation pulse train [343] to reduce errors in SASHA T_1 mapping. Consequently, here the proposed 6 pulse train optimized for 3 T [339] was used in an attempt to reduce errors in the calculated T_1 values due to residual longitudinal magnetisation. Chow et al. [148] used numerical optimisation to determine the optimal flip angles for the 6-pulse train in the face of realistic B_0 and B_1 inhomogeneities and validated the results both on phantom and *in vivo* subjects. Compared to the standard saturation pulse the pulse duration is significantly longer in the 6-pulse design; 32.8 ms compared to 18.7 ms. The relative RF energy and peak RF power is also higher by a factor of 3.6 and 1.4 in the 6-pulse design compared to the standard pulse. However, when measuring the residual longitudinal magnetisation at 3 T *in vivo* myocardial tissue Chow et al. [339] found that the 6-pulse design performs better with reduced residual magnetisation following saturation using higher peak RF power and energy.

The following parameters were used for the standard saturation pulse: 90° , 90° , 90° flip angles, a total duration of 11.5 ms and a peak gradient amplitude on a single axis of 10 mT/m. The Chow 6-pulse design was run with nominally 115° , 90° , 125° , 85° , 176° , 223° flip angles, a total duration of 32.9 ms and a peak gradient amplitude on a single axis of 24 mT/m.

In the STEAM-SASHA sequence presented a fixed saturation duration of $TS=300$ ms is used. This approach was chosen based on a study by Kellman et al. [344] who found that using a fixed saturation time the precision of SASHA is improved in the native T_1 range. While in the same study a $TS=591$ ms was found optimal for native myocardial mapping, here $TS=300$ ms was chosen to allow the image acquisition in a cardiac phase near to end-systole with the saturation pulse immediately after the R-wave. The TS chosen here is still within a reasonable range as Kellman et al. [344] found 290 ms an optimal value to measure wider ranges of myocardial T_1 . The end-systolic configuration was chosen as it provides the phase with the lowest susceptibility to partial voluming effects [345]–[347] and has shown more robustness to RR variations [348], [349]. Longer saturation durations would mean acquiring the imaging data later in the cardiac cycle or running the saturation pulse in the previous cardiac cycle with RR-interval dependent saturation times.

Given the inherent SNR penalty of STEAM [184], [186] here we choose the same initial number of scan repeats used in DT-CMR applications. However instead of large b values common in these applications here only a small spoiler gradient is run (effective $b=100$ s/mm², while typical DT-CMR applications use b values=300–600 s/mm² [179], [186], [206]), to minimise the loss of SNR. The saturation pulse results in a reduction in SNR in the saturation recovery images. Thus, to determine if <8 averages can be used without a loss of accuracy and precision the *in vivo* datasets were each processed using a range of averages [2,3,4,5,6,7,8], with 8 used as the ground truth.

To demonstrate the effectiveness of the blood suppression provided by the STEAM-SASHA sequence and demonstrate that the T_1 weighted signal was above the background noise floor, the signal in 2 regions of interest (RV blood pool, septum) was measured in three different image types (anchor, $TS=300$ ms, separate noise image acquired using a 2-RR STEAM EPI approach with the same parameters as for the anchor and $TS=300$ ms images but with the RF pulses switched off). For both the anchor and $TS=300$ ms septal region, the mean was taken across all pixels of the 8 averages. All other areas were analysed by calculating the histogram for the pixel regions (across averages) and then fitting a Rayleigh distribution function. This approach is necessary as the signal intensity in “noise only” regions in magnitude MR images does not follow a Gaussian distribution or other symmetric distribution [350].

13.2.2.1.1 Post Processing

Analysis software was developed using Python + Plotly Dash to provide T₁ measures from the STEAM-SASHA data. The general workflow is shown in Figure 122 and consists of:

1. Discarding individual images that show clear motion or distortion artefacts based on manual selection.
2. Manual crop of the images to a region around the two ventricles.
3. Mask the background once for every breath hold manually. The aim is to remove any signal outside of the myocardium to improve registration performance. It is assumed that motion within each breathhold is negligible and therefore masks are copied between images acquired within a breath-hold.
4. The anchor images from each breath hold were co-registered using a rigid registration algorithm (SimpleElastix). The resulting motion fields are then applied to all the TS=300 ms images acquired in the corresponding breath hold.
5. Manual segmentation of the myocardium into 7 regions. Segmentation is initially performed on a single anchor image and then the regions are copied and adjusted to account for differences in myocardial shape between each breath hold.
6. Calculation of a pixel wise T₁ map and region wise T₁ values based on the segmentation. For the T₁ map all anchor images are averaged and all TS=300 ms images are averaged before being passed into Equation 67 to calculate the T₁ at each pixel. For the region wise T₁ calculation, the intensity was averaged over each region of interest before averaging over all anchor images or all TS=300 ms images. The two datapoints for each region (S_{Anchor} and $S_{TS\ 300ms}$) are used to calculate T₁ using Equation 67.

$$T1[ms] = \frac{-300ms}{1 - S_{TS\ 300ms}/S_{Anchor}} \quad 67$$

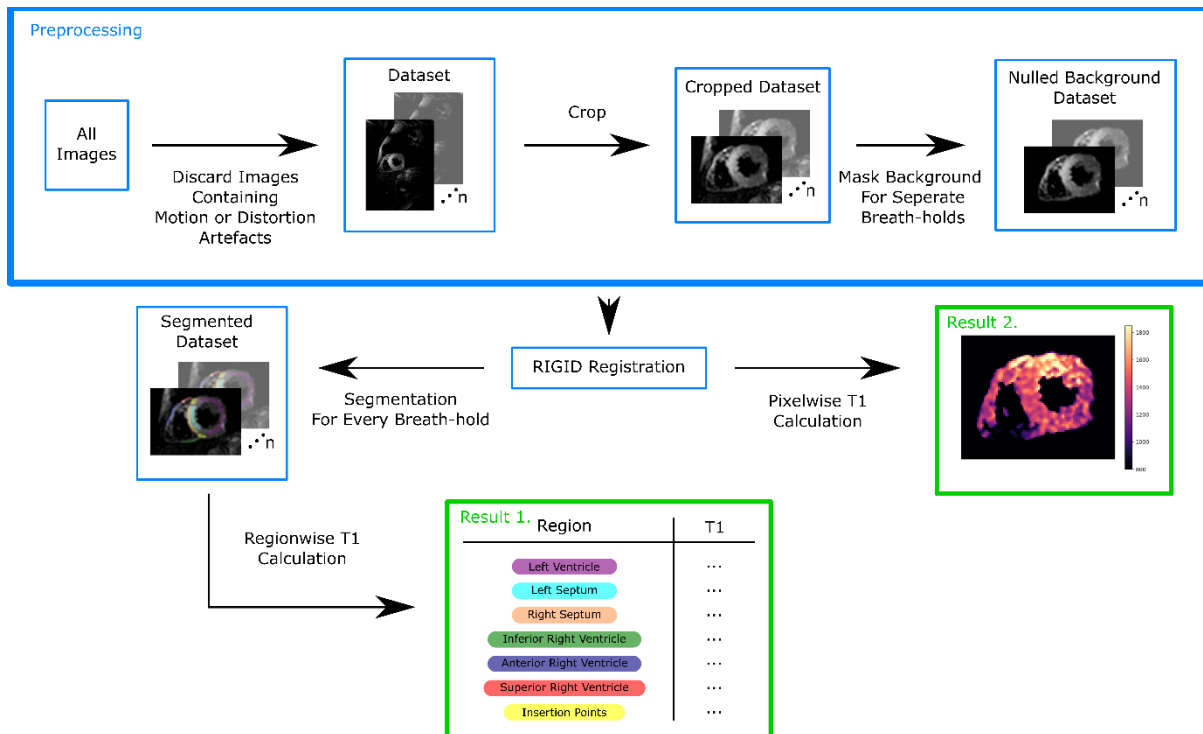


Figure 122: STEAM-SASHA analysis workflow. The pre-processing step consists of discarding images that are affected by motion or distortion artefacts, cropping all images to a minimum size at which only the heart remains and then nulling the background signal. Then after applying a RIGID registration the data is segmented into 7 different regions (LV, Left Ventricular Septum, Right Ventricular Septum, inferior RV, anterior RV, superior RV, insertion points) allowing for a region-based result (Result 1.) to be calculated. Alternatively, a pixel wise T1 map can be created after the registration step (Result 2.).

After consultation with clinical colleagues, the 7 segmentation regions (Figure 123) were defined as described in Table 13.

To avoid contamination through non compact myocardium and partial voluming effects all regions were drawn to avoid myocardial edge pixels.

<i>Region</i>	<i>Description</i>	<i>Clinical Interest</i>
<i>LV</i>	Covering the LV free wall, while staying clear of the insertion points.	While not the focus of this thesis it can be used as reference value to compare to other methods in which RV values are not often measured.
<i>LV septum</i>	Covering the mid and endocardial region of the septum, while staying clear of the insertion points. In some images a bright band located in a mid-epicardial region can be used as orientation to separate from the RV septum region.	These two LV measures can be used as reference value. However, since the septum is part of both the RV and the LV chamber there is ongoing interest in the role it plays in RV function. This is also the reason why here the septum is separated in two regions.
<i>RV septum</i>	Covering the epicardial region of the septum, avoiding the insertion points.	
<i>inferior RV</i>	Beginning at the on the RV side of the inferior insertion point this region follows the RV free wall to the point where the wall starts curving towards the anterior tip of the RV.	The inferior RV is often the thickest and most stable part when imaging the RV. Thus, in previous studies this has been the most reliable value of RV T ₁ analysis [351].
<i>anterior RV</i>	Staying clear of the anterior tip of the RF this region follows the straight section of the RV free wall until shortly after the moderator band. In some cases, the region can be defined as the RV section parallel to the chest wall.	Due to the complex anatomy and proximity to the chest wall this region is susceptible to partial voluming effects and so has been difficult to measure in previous work. It further is expected to show a higher fibrosis content in rTOF [351].
<i>superior RV</i>	This covers the region between the RV edge of the anterior insertion point and the anterior RV region.	Like the anterior RV this region has been very challenging to obtain T ₁ values from in the past and is expected to have higher content of fibrosis in rTOF patients [351].
<i>insertion points (superior and inferior)</i>	These regions cover the area where the RV myocardium meets the LV and only the epicardial half of the LV myocardium should be included.	These areas are linked to patient outcomes in LGE imaging [352], [353]

Table 13: Seven regions used in the analysis of T₁ values.

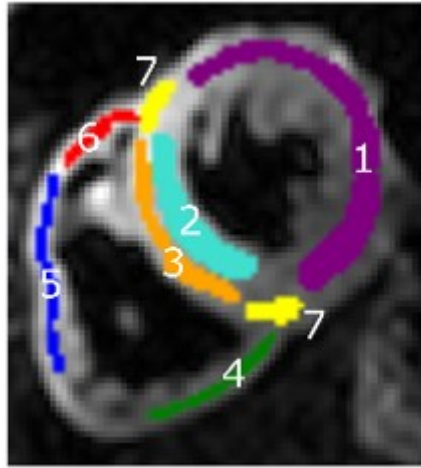


Figure 123: Figure showing an example of the 7 regions of interest. 1. LV ,2. LV septum,3. RV septum,4. inferior RV,5. anterior RV,6. superior RV,7. insertion points

To test both, inter and intra observer variability, the processing was repeated both by the operator 1 (the author, to provide intra observer variability) and by a second operator (to provide interobserver variability). The first observer analysed both the initial and repeat acquisitions in each subject to provide inter-study reproducibility measures.

13.3 Results

13.3.1 Phantom Validation

Figure 124 shows both the averaged anchor image and the averaged TS=300 ms image for two sequence repeats of the STEAM-SASHA protocol (2 averages of the anchor image and 10 images of the TS=300 ms images), as well as the pixel wise T₁ Maps from both the MOLLI and the STEAM-SASHA sequences in the T₁MES phantom. STEAM-SASHA data was acquired using the standard 3 pulse design. The STEAM-SASHA T₁ Map is visibly noisier, which might be expected due to the inherent SNR inefficiencies of STEAM. In Figure 125 the T₁ measurements from the 9 different tubes within the T₁MES phantom are shown in a Bland-Altman-like plot for both MOLLI and STEAM-SASHA. For the ground truth, the reference slow IR values [338] were used. Generally, MOLLI underestimated while STEAM-SASHA overestimated T₁ with a mean absolute error 3.0 % and 7.0 % respectively compared to the ground truth. At typical T₁ values for myocardium obtained *in vivo* (T₁>1200ms), STEAM-SASHA provides results closer to the ground truth than the MOLLI sequence (Figure 125), with errors of <2.5 % in this regime.

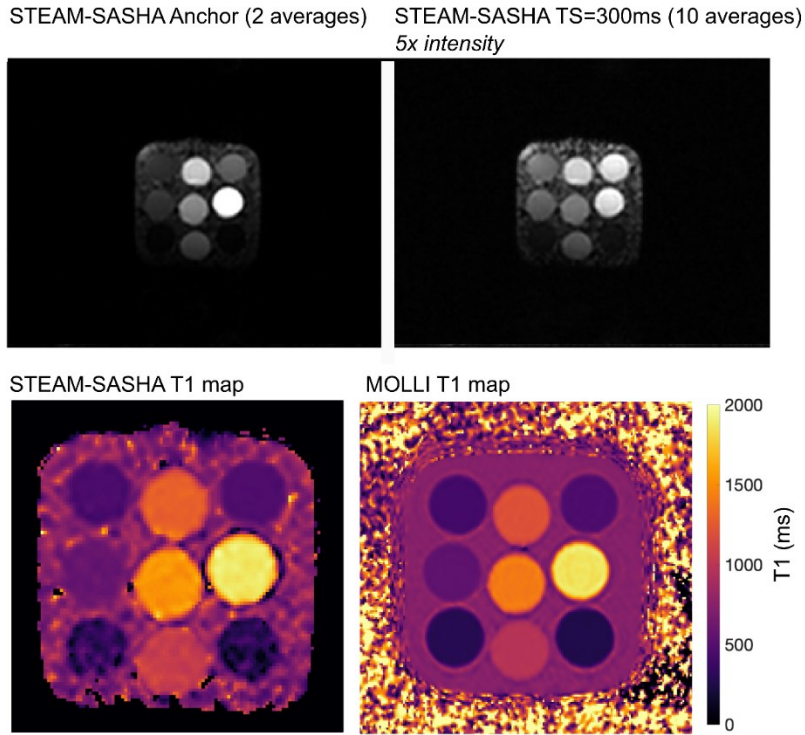


Figure 124: Example of raw data and T_1 maps for STEAM-SASHA (obtained from 2 sequence repeats/ $\frac{1}{4}$ breath holds) and MOLLI (obtained from 2 sequence repeats/ $\frac{1}{2}$ breath holds).

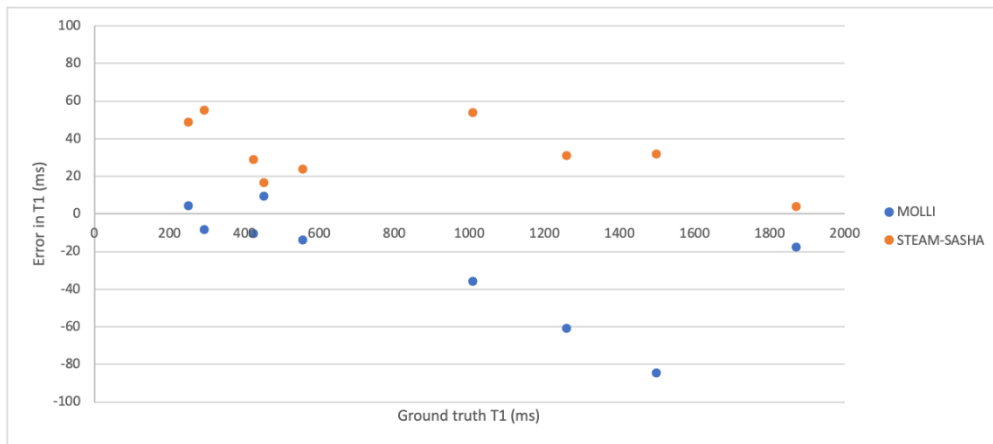


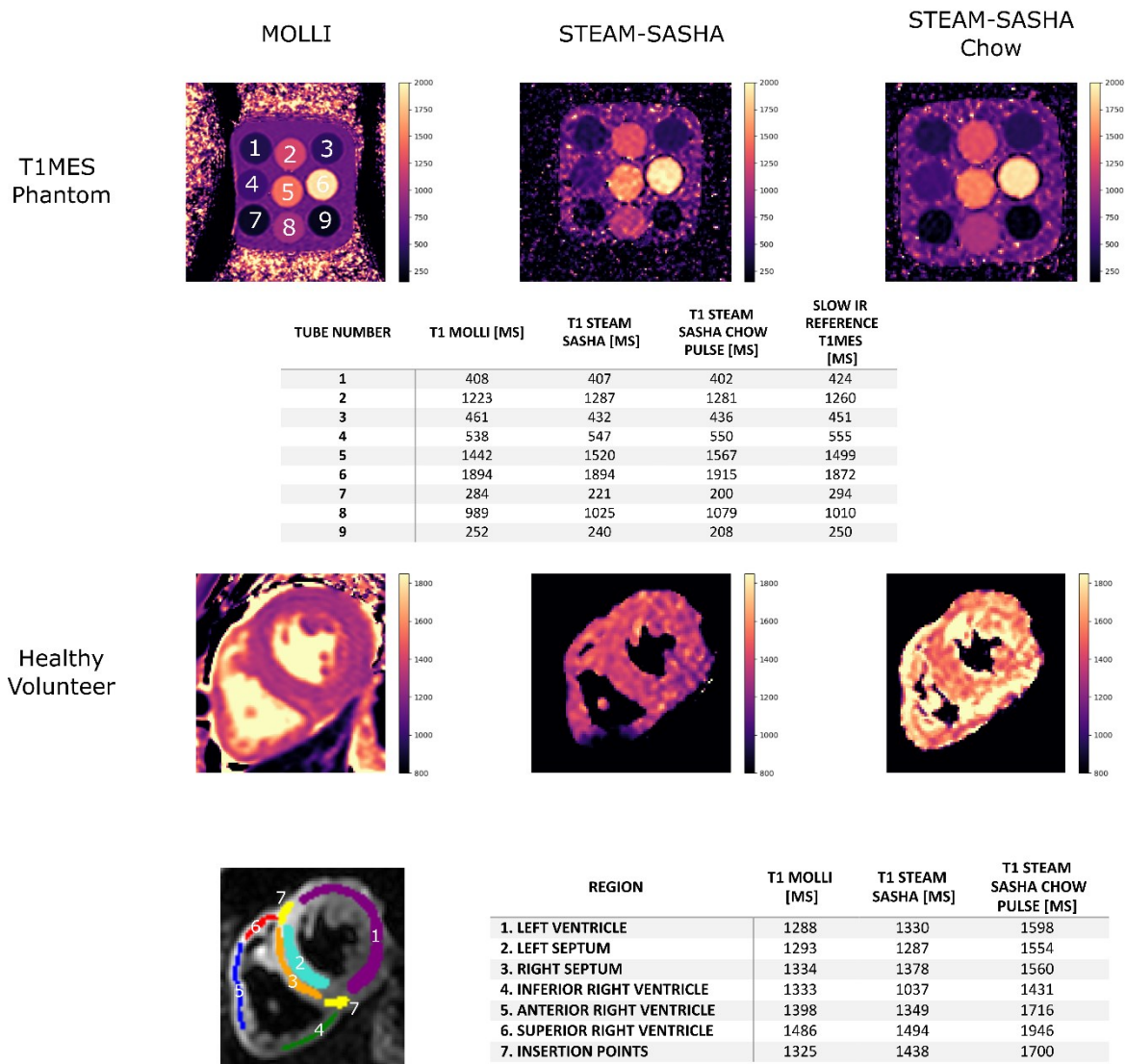
Figure 125: Bland-Altman-like plot of MOLLI and STEAM-SASHA using the Times phantom. Slow IR values from [338] were taken as ground truth.

13.3.2 Saturation Pulse Test

Here the results of both the standard saturation pulse and the optimised Chow pulse used in the STEAM-SASHA sequence are shown both in the T1MES phantom [338] and *in vivo*. MOLLI reference acquisitions are also shown.

Figure 126 shows averaged T₁ maps from 2 sequence repeats of the STEAM-SASHA and MOLLI sequences in the T1MES phantom. The T1MES phantom was placed within an annular loader which is designed to mimic the resistive load of a human in the scanner and hence allow the scanner to adjust the transmit power appropriately. All T₁ results are close to reference values in the literature [338], which were acquired with a slow IR-based sequence. There is no clear systematic difference between the results using the optimised Chow pulse and the standard saturation pulse.

In Figure 126 an example of a healthy volunteer T₁ analysis is shown from data acquired using both the Chow and standard pulse design. From both the pixelwise T₁ map and the region-based values it is visible that the sequence using the Chow pulse has consistently elevated T₁ values (by more than 200ms for this example). This is further supported by Figure 127 which shows a Bland-Altman plot for all *in vivo* acquisitions of the Chow pulse STEAM-SASHA sequence, which shows values typically in the range of 1600–1800 ms, which is substantially higher than the typical values expected for myocardial SASHA T₁ values acquired at 3T. As a result of this failure of the Chow saturation pulse subsequent data presented in this chapter were acquired with the standard saturation pulse.



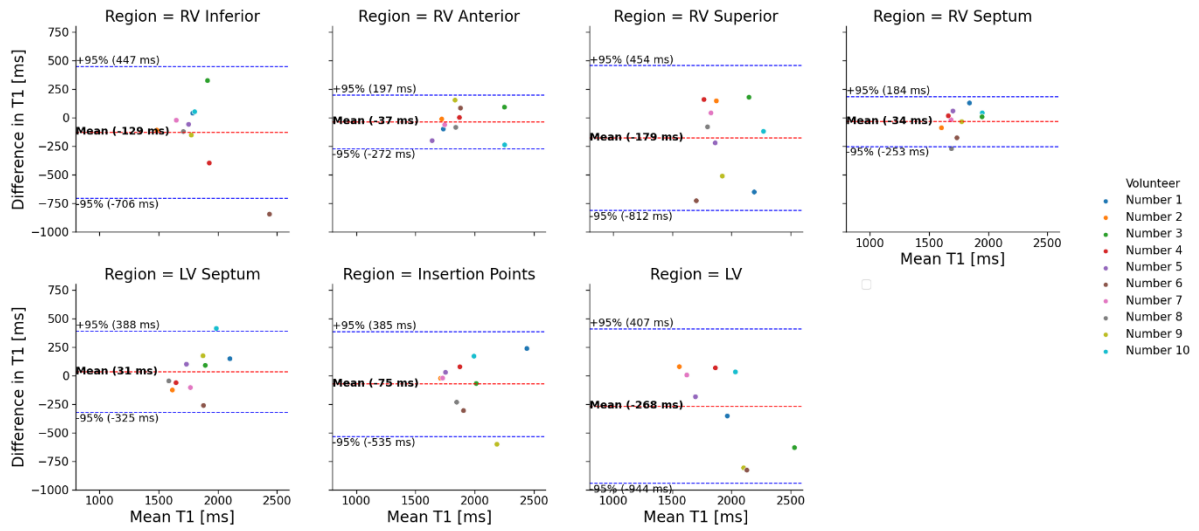


Figure 127: Inter-study Bland-Altman plot for the STEAM-SASHA sequence using the Chow pulse for different myocardial regions. For each of the 10 volunteers (each plotted in a different colour), two repeated scans were acquired with subject repositioning performed between acquisitions. The plot shows the difference in T_1 between acquisitions vs. the mean T_1 over both repeats. The dotted blue line marks the 95% confidence interval of the difference, while the red dotted line is the mean difference between repeats. Mean T_1 values are substantially greater than those reported in the literature for healthy subjects using SASHA-based methods at $3T$ [354].

13.3.3 Average Test

To test the effect of the number of averages used for a single STEAM-SASHA slice on the accuracy and precision of T_1 values, all volunteer scans were reanalysed using an increasing number of averages until reaching the maximum of 8 anchor images and 40 TS=300 ms images (8 sequence repeats = 16 breath holds).

Figure 128 shows the absolute difference in T_1 of averages [2,3,4,5,6,7] compared to the assumed ground truth of 8 in the different myocardial regions and scans. The general trend is a reduction of both the overall variability and value of the difference with increasing number of averages.

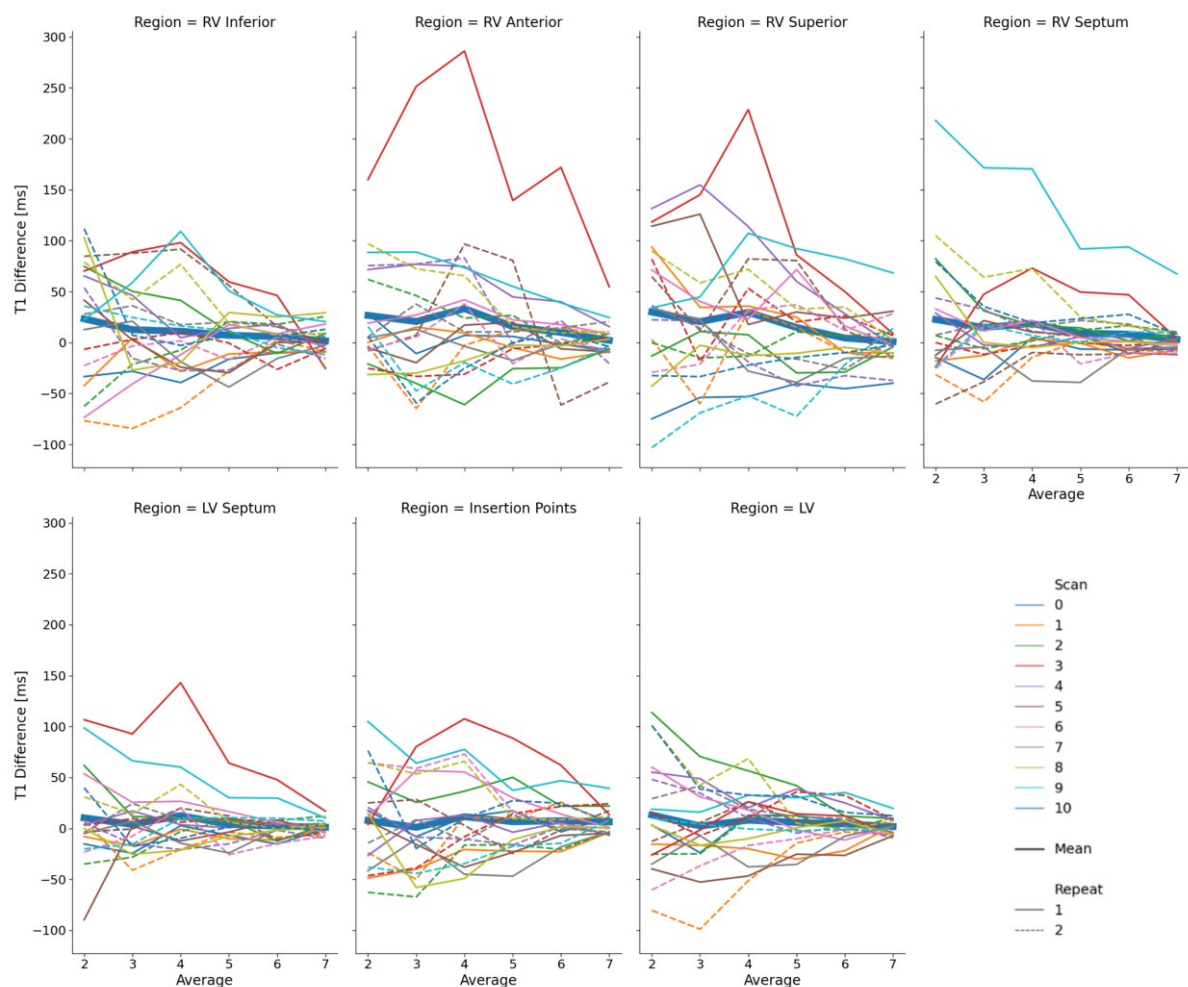


Figure 128: Figure showing the mean absolute difference in T_1 relative to 8 averages with an increasing number of averages for the 7 myocardial regions in all scans. Since each subject was scanned twice the second repeat is shown as a dotted line. The mean of all scans within one average is shown as thicker blue line.

13.3.4 Noise Floor and Blood Suppression Tests

Figure 129 and Figure 130 show mean values of signal intensity in both the blood pool and the septal myocardium for three different imaging datasets (noise, anchor, TS=300ms).

In the blood pool of the TS=300 ms and “noise only” data the signal behaviour is similar. While the range of signal intensities for the anchor image for the same region has a similar lower bound (13.5), it has an elevated upper range bound of 28 compared to 19 in both the noise only and TS=300 ms data.

In the septum the mean noise value is in the same region of the noise and other blood pool measures (mean of 20). The mean signal intensity in the septum of the TS=300 ms data is 96, while the equivalent measures in the anchor image values range from 380 to 640. Thus, the signal level of the Ts=300 ms images is >4 times larger than the noise level, while the anchor image is > 19 times larger.

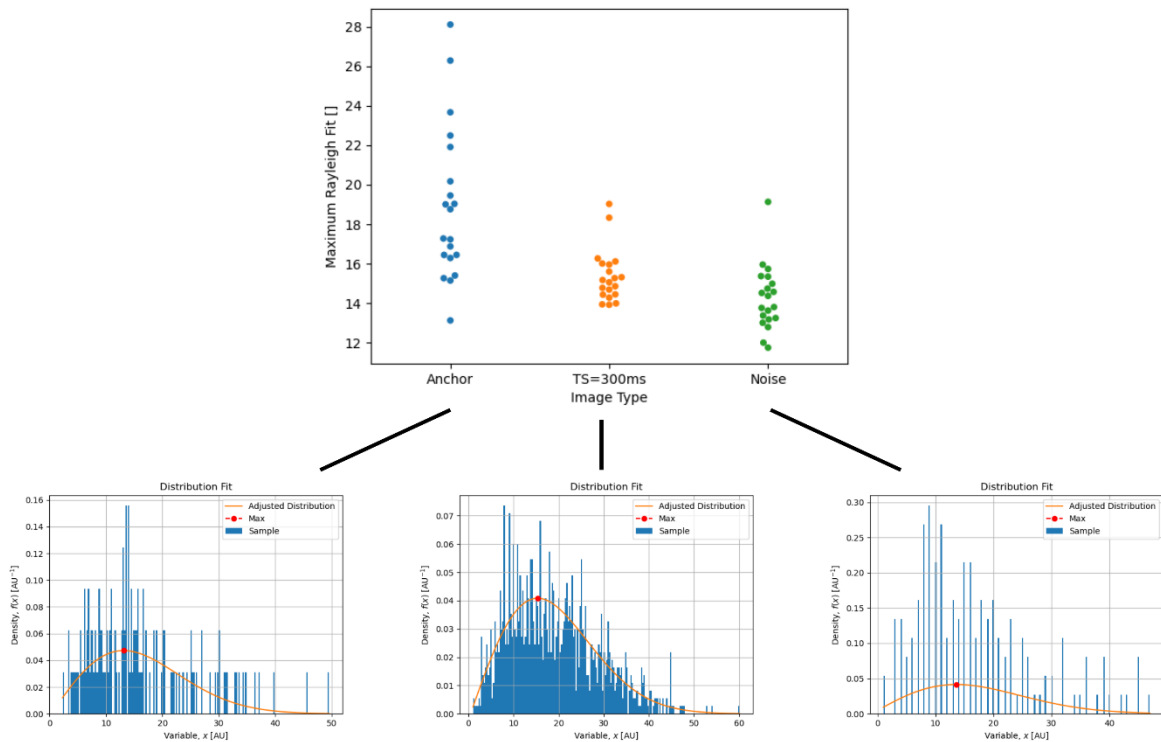


Figure 129: The average signal levels in all scans for 3 different image types (anchor, TS=300 ms, noise) in the RV blood pool. The individual average points are calculated by fitting a Rayleigh distribution to the histogram of the underlying regional pixel values and then using the maximum of this distribution.

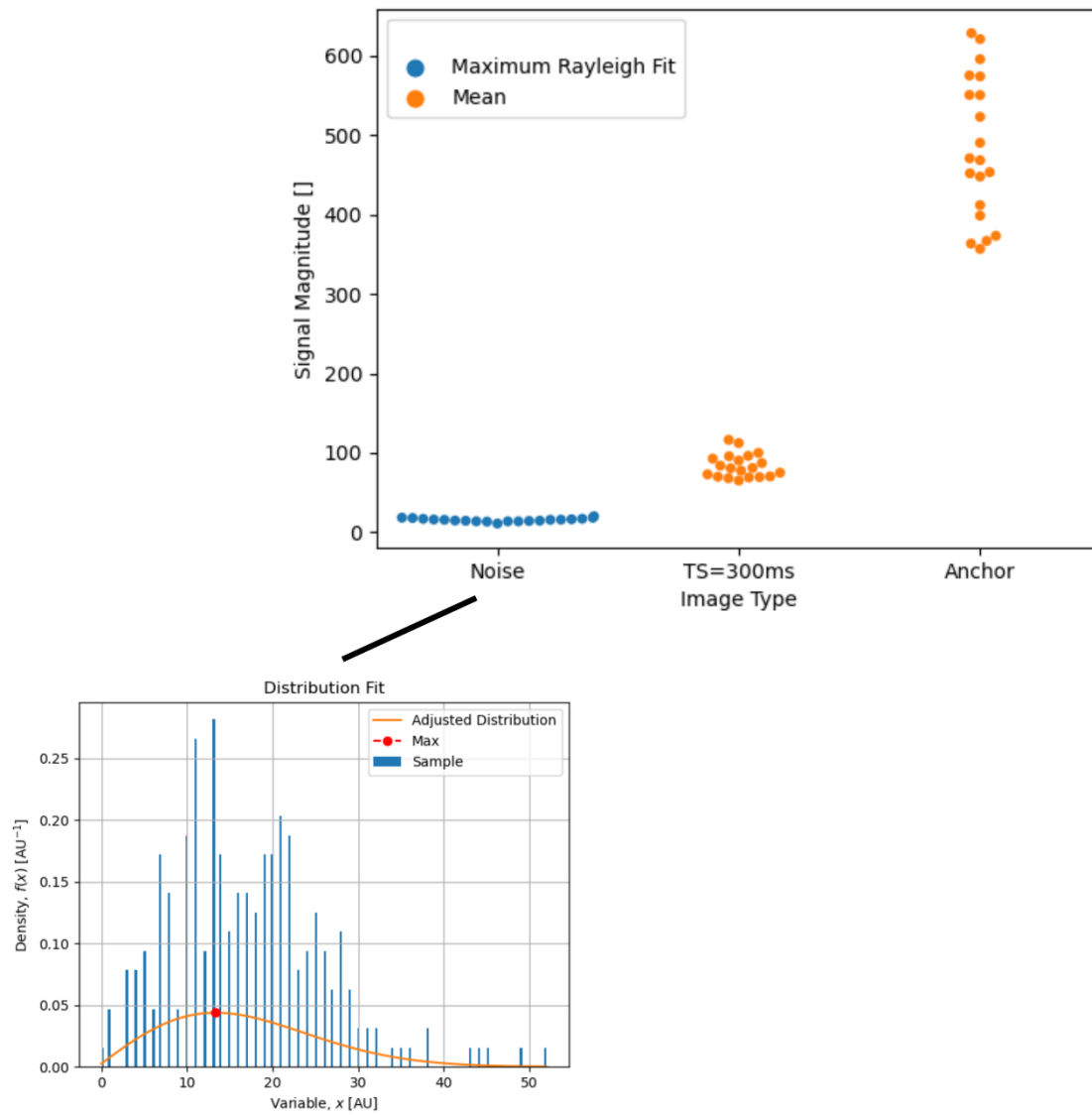


Figure 130: The average signal levels in all scans for 3 different image types (noise, TS=300 ms, anchor) in the septum. The individual points for the noise images are calculated by fitting a Rayleigh distribution to the histogram of the underlying regional pixel values and then using the maximum of this distribution. For the Ts=300 ms and anchor regions the mean value of the underlying pixels is used.

13.3.5 Native T1 Values in the Healthy RV

Both MOLLI and STEAM-SASHA were successfully acquired in each of the 20 healthy volunteer scans (4 female, 6 male, 2 scans each). Figure 131 shows exemplary pixel wise T1 maps of both sequences acquired. To give a fair visual comparison 3 different volunteers are shown based on their data quality (poor, typical, high).

The T1 values obtained from the 7 regions are shown in Figure 131. For reference, typical T1 values obtained in the LV septum using a standard SASHA sequence at 3T in 20 healthy volunteers (from Weingärtner et al. [354]) are also shown for reference. As shown in Figure 131, STEAM-SASHA has a greater inter-subject standard deviation in all regions, except for the anterior RV wall, when compared to MOLLI. STEAM-SASHA produces lower median T1-values than MOLLI in the anterior, superior, and inferior RV, but higher values in the other regions. The reference SASHA values taken from Weingärtner et al. [354] are both (LV=1500±66 ms, septum=1523±56 ms) higher than the mean values for the STEAM-SASHA acquisition (LV=1357±114 ms, LV septum=1391±96 ms, RV septum=1451±132 ms) in the corresponding regions, although the reference values lie within the range of the values acquired using STEAM-SASHA.

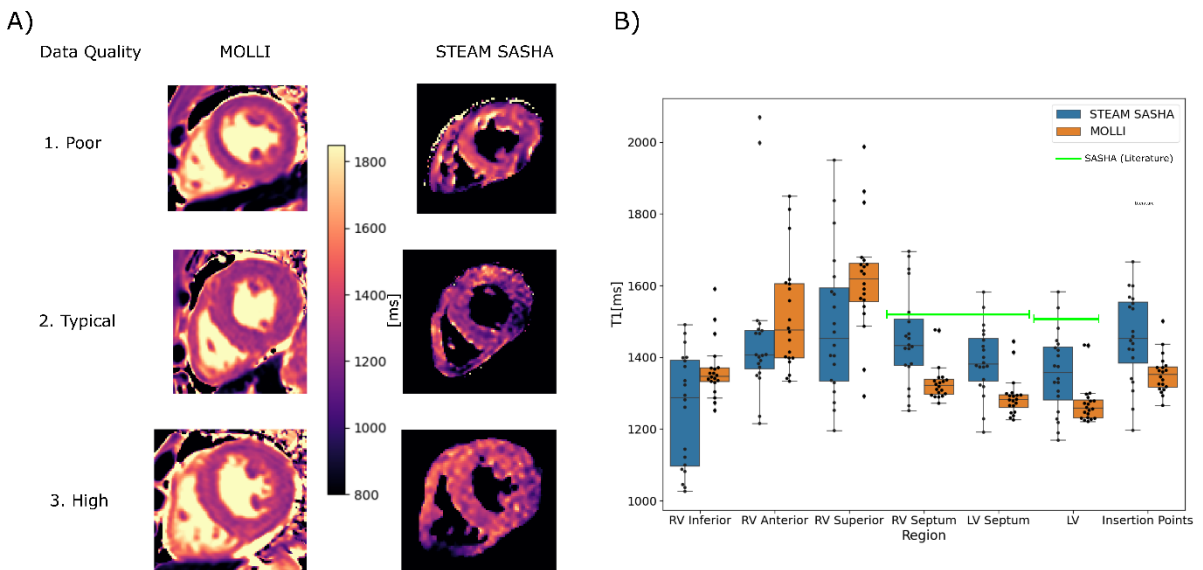


Figure 131: Example T1 maps from both MOLLI and STEAM-SASHA (left). Poor, typical and high-quality examples (based on the STEAM-SASHA data) are provided. The plot on the right shows the native T1 values obtained using MOLLI and STEAM-SASHA for all of the in vivo acquisitions (10 subjects each scanned twice) measured in the 7 different regions, with box plots showing the range and quartiles. Reference values acquired using a standard SASHA sequence at 3T are shown in green [354].

13.3.6 Reproducibility

The following Bland-Altman plots show the inter study (Figure 132 and Figure 133), the intra observer (Figure 134 and Figure 135) and the inter observer (Figure 136 and Figure 137) results in the different myocardial regions for both MOLLI and STEAM-SASHA. Further Figure 138 shows the COV for all three reproducibility types. Table 14 shows the geometric mean of absolute difference for all three scenarios.

The overall bias in all Bland-Altman plots is small with the maximal value (58ms) occurring in the superior RV of the inter study STEAM-SASHA, with other bias values staying below 10ms. It is notable that in all cases the bias in the STEAM-SASHA anterior region is smaller when compared to MOLLI.

In most cases MOLLI appears more reproducible across regions and scenarios, with both the bias and the 95% interval being lower when compared to the respective STEAM-SASHA sequence. This is evident from Figure 138 with all COVs being lower for MOLLI than STEAM-SASHA and the lower geometric mean of absolute difference is also lower.

When comparing the reproducibility of regions in MOLLI and STEAM-SASHA, the complete LV containing the regions RV septum, LV septum, LV, and insertion points yields more reproducible results than the RV regions. This is evident from the plot showing COVs and the geometric mean of absolute difference.

One notable difference when inspecting the RV regions is that for the RV anterior region the STEAM-SASHA measurements are less variable than MOLLI in terms of the final T₁. This can be seen when comparing the spread of points on the x axis (all figures in the RV anterior region). While in most other regions the spread of points for MOLLI is lower.

Comparing the variance of the three different scenarios (inter study, inter observer, intra observer) the highest variability when considering the COVs are encountered for the inter observer case, however the increases over the other two methods are small (the maximal difference being 3% in case of the MOLLI LV). In general, the coefficients of variation are small with a maximum of 14%.

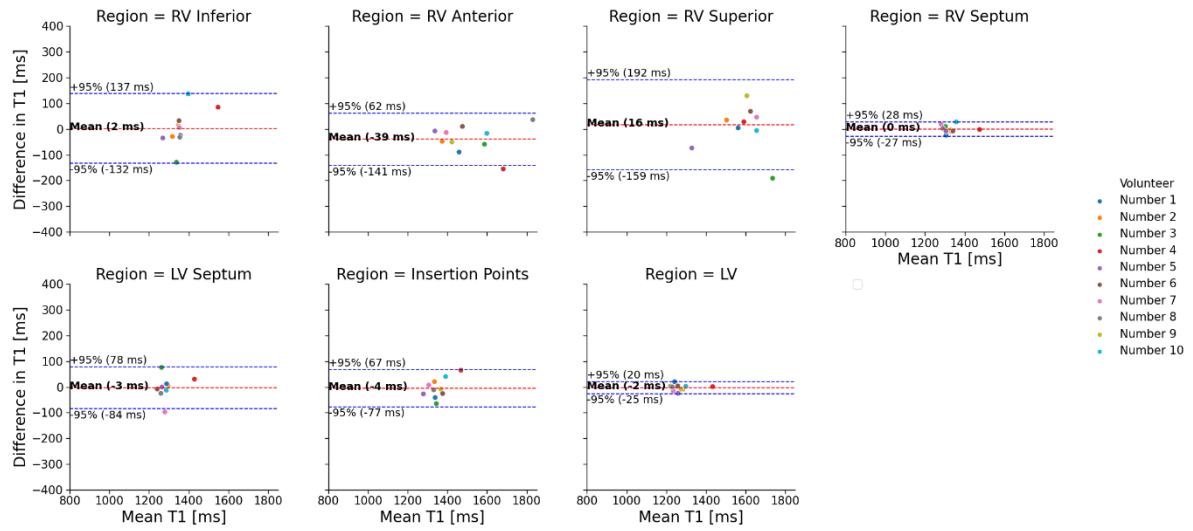


Figure 132: Inter-study Bland-Altman plot for the MOLLI sequence for different myocardial regions. For each of the 10 volunteers (each plotted in a different colour), two repeated scans were acquired with subject repositioning performed between acquisitions. The plot shows the difference in T₁ between acquisitions vs. the mean T₁ over both repeats. The dotted blue line marks the 95% confidence interval of the difference, while the red dotted line is the mean difference between repeats (bias).

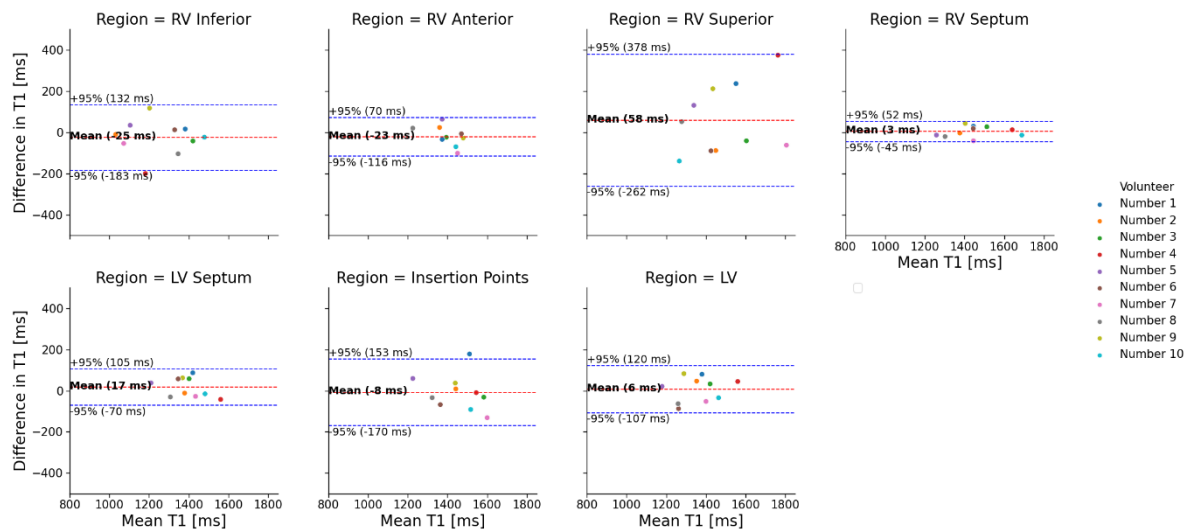


Figure 133: Inter-study Bland-Altman plot for the STEAM-SASHA sequence for different myocardial regions. For detailed description see above.

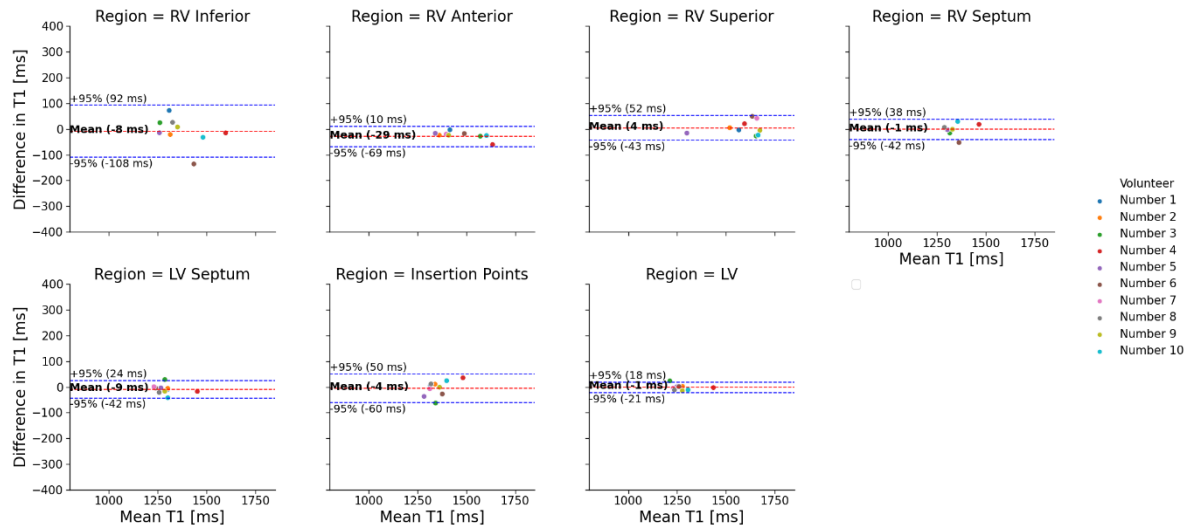


Figure 134: Intra Observer Bland-Altman plot for the MOLLI sequence for different myocardial regions. For each of the 10 volunteers (each plotted in a different colour), the same image reader performed the analysis spaced 2 weeks apart. The plot shows the difference in T_1 between acquisitions vs. the mean T_1 over both repeats. The dotted blue line marks the 95% confidence interval of the difference, while the red dotted line is the mean difference between repeats.

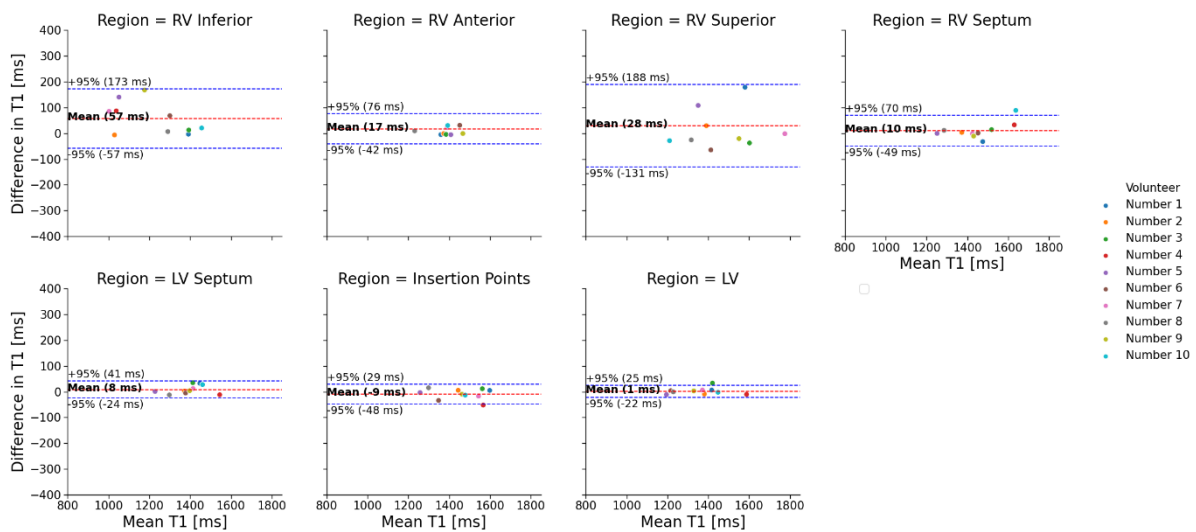


Figure 135: Intra Observer Bland-Altman plot for the STEAM-SASHA sequence for different myocardial regions. For detailed description see above.

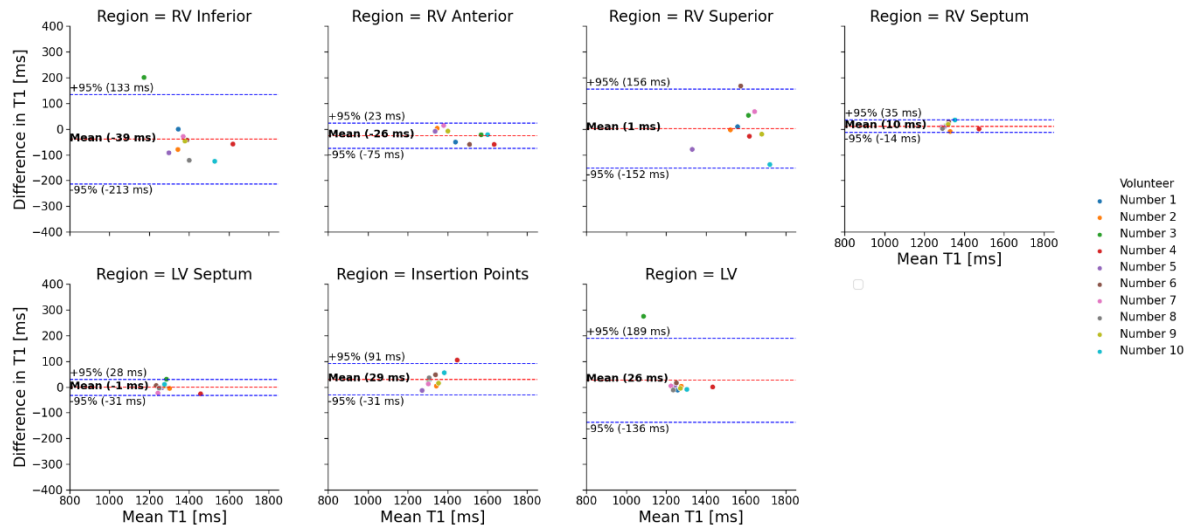


Figure 136: Inter Observer Bland-Altman plot for the MOLLI sequence for different myocardial regions. For each of the 10 volunteers (each plotted in a different colour), two different image readers performed the analysis. The plot shows the difference in T₁ between acquisitions vs. the mean T₁ over both repeats. The dotted blue line marks the 95% confidence interval of the difference, while the red dotted line is the mean difference between repeats.

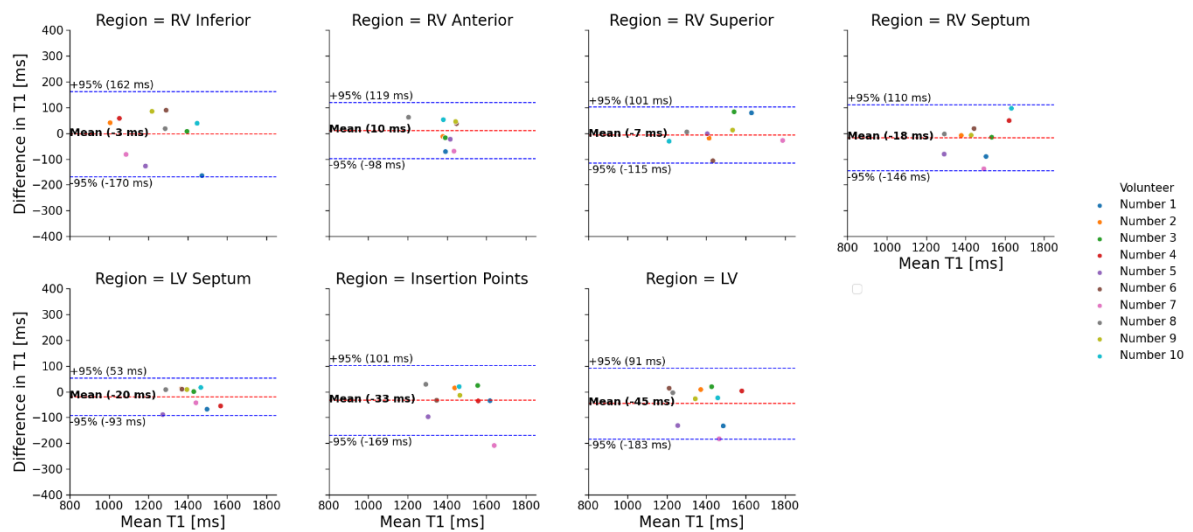


Figure 137: Inter Observer Bland-Altman plot for the STEAM-SASHA sequence for different myocardial regions. For detailed description see above.

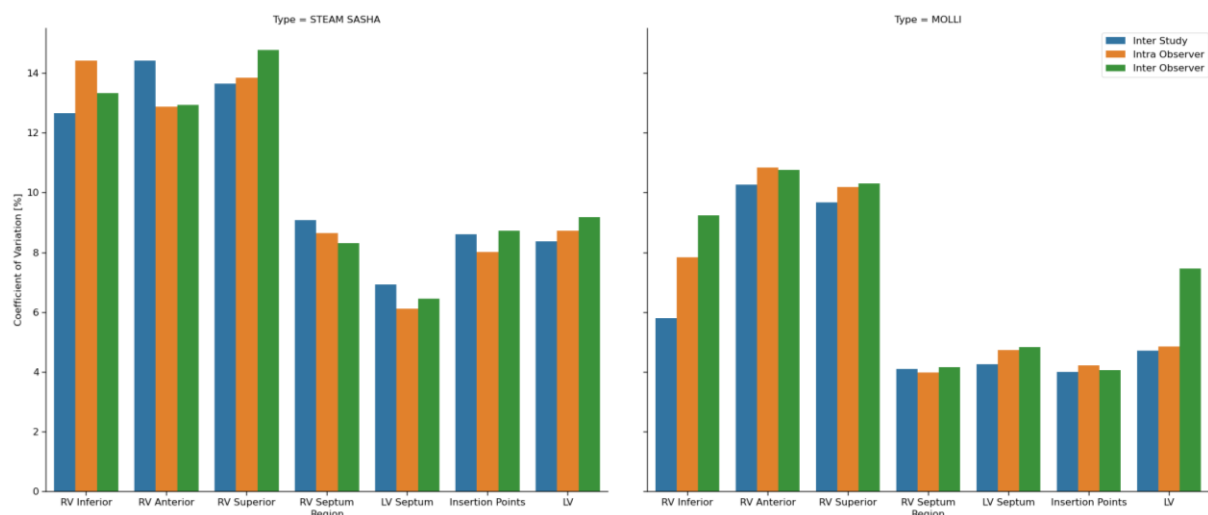


Figure 138: The coefficient of variation in percent for all three reproducibility types (Inter study, Intra Observer, Inter Observer) for myocardial regions of both MOLLI and STEAM-SASHA.

	LV		LV septum		RV septum		RV inferior		RV anterior		RV superior		insertion points	
MOLLI	Geometric Mean of Absolute Difference [ms]	95% CI	Geometric Mean of Absolute Difference [ms]	95% CI	Geometric Mean of Absolute Difference [ms]	95% CI	Geometric Mean of Absolute Difference [ms]	95% CI	Geometric Mean of Absolute Difference [ms]	95% CI	Geometric Mean of Absolute Difference [ms]	95% CI	Geometric Mean of Absolute Difference [ms]	95% CI
Inter Study	5	[1, 56]	14	[1, 210]	8	[2, 43]	36	[6, 215]	33	[5, 204]	42	[4, 456]	24	[6, 105]
Intra Observer	4	[1, 43]	9	[1, 91]	7	[1, 77]	23	[4, 130]	23	[5, 110]	10	[1, 17]	14	[2, 123]
Inter Observer	8	[0, 167]	8	[1, 44]	6	[0, 192]	48	[3, 847]	20	[3, 136]	32	[3, 341]	22	[4, 133]
STEAM-SASHA														
Inter Study	50	[21, 118]	37	[11, 118]	19	[5, 69]	39	[6, 257]	35	[8, 151]	114	[31, 424]	44	[7, 289]
Intra Observer	6	[1, 34]	8	[1, 90]	7	[0, 167]	29	[2, 412]	9	[1, 129]	38	[3, 423]	12	[2, 59]
Inter Observer	24	[2, 354]	14	[1, 391]	28	[2, 318]	52	[9, 306]	41	[12, 147]	25	[2, 284]	35	[7, 165]

Table 14: The geometric mean of absolute difference and 95% CI for inter study, intra and inter observer variability in both MOLLI and STEAM-SASHA

13.3.7 Test Case on a rTOF

Both the pixelwise T_1 map and the regional values of T_1 obtained using STEAM-SASHA and MOLLI are shown in Figure 139. T_1 values acquired with STEAM-SASHA and MOLLI are also provided from the 10 healthy volunteers scanned for this chapter for reference. In all regions the T_1 measured in the rTOF patient using STEAM-SASHA is higher than the corresponding MOLLI T_1 value. This is most extreme in the anterior RV with STEAM-SASHA providing a value 356ms higher. The closest agreement between the two methods is in the inferior RV and the insertion points with differences of 67ms and 71ms respectively. Most notable is that STEAM-SASHA measures consistently higher values in the patient when compared to the volunteers, while for MOLLI this is not the case.

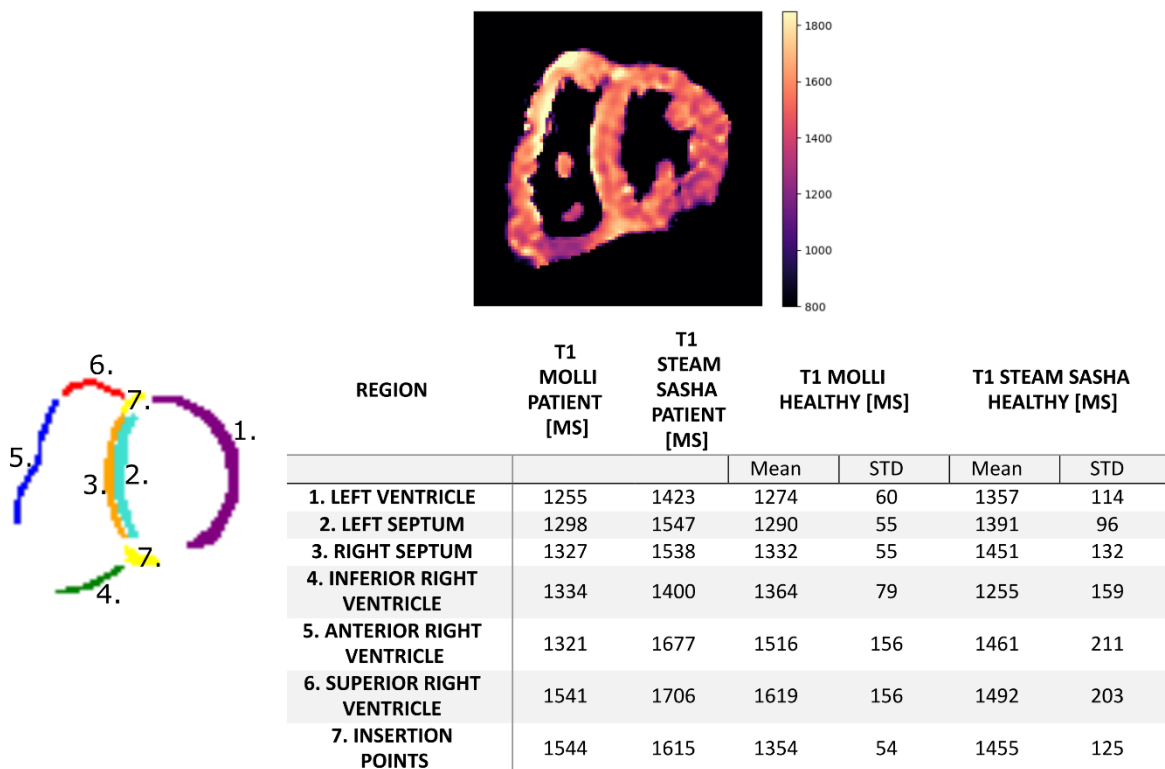


Figure 139: Example STEAM-SASHA data for a rTOF patient. The pixelwise T_1 map is shown (top, STEAM-SASHA) and the regional T_1 values are shown for both the STEAM-SASHA and MOLLI sequence. Corresponding mean and SD values from the healthy subjects imaged in this chapter with the same sequences are also provided for reference.

13.4 Discussion

The STEAM-SASHA sequence developed in this work has been shown to provide both accurate and reproducible T_1 values with excellent fat and blood suppression. The accuracy of the STEAM-SASHA was validated in the T1MES phantom. In the typical native myocardial T_1 range STEAM-SASHA provides higher accuracy than a standard MOLLI sequence when assessed in a phantom. STEAM-SASHA also provides T_1 values consistent with results in the literature acquired with saturation type sequences [354]. This however was only the case when the standard saturation pulse was used. The B_1+ and B_0 inhomogeneity-resistant saturation pulse first introduced by Chow et al. [339] was tested in hope of achieving more accurate T_1 values. This was thought to be particularly important given that a 3T magnet was used in this work where off-resonance and B_1+ absorption effects are worse. However, the Chow pulse failed to provide T_1 values consistent with T_1 values obtained in the literature using SASHA. After further investigation, the reason for this was determined to be a scanner software bug in the XVA11A software version, which clips the saturation pulse at high amplitudes in the Chow pulse design. Due to limited resources, it was not possible to fix this error in the current software version and so all other experiments presented in this chapter were performed using the standard pulse, which does not include the bug causing the clipping. A further limitation that must be addressed here is the lack of a comparison to a standard SASHA sequence. This was due to the required software package missing for the scanner used in this thesis and the time investment necessary to implement a standard SASHA sequence.

The mean $\pm$ SD LV values measured in the reference MOLLI sequence (LV=1275 $\pm$ 60 ms, LV septum=1290 $\pm$ 55 ms, RV septum=1332 $\pm$ 55 ms) are only marginally higher than previous studies [329], [355]. In a meta-analysis conducted by Gottbrecht et al. [329] the results for Siemens scanners are an average [95% CI] of 1192 [1171,1214] ms (18 different studies). However, T_1 values can vary greatly depending on sequence parameters. Taking this into account, another meta-analysis by Popescu et al. [355], who clustered results based on typical TE, TR, Flip angle and vendor gives a more fair comparison. While none of the clusters used were an exact fit to the MOLLI protocol used in this thesis the closest fit is cluster 3 with a typical TE of 1.07 ms, TR of 2.5 ms, Flip Angle of 35° resulting in a cluster 3T average of 1227 $\pm$ 19 ms and thus closer to the MOLLI values shown here.

Native healthy myocardial SASHA values at 3T have been reported in the literature with different mean $\pm$ SD values Gou et al. (LV=1560 $\pm$ 97 ms , septum=1567 $\pm$ 57 ms) [356] , Weingärtner et al. (LV=1500 $\pm$ 66 ms, septum=1523 $\pm$ 56 ms) [354]. Thus, the STEAM-SASHA sequence shown here has mean $\pm$ SD lower values in the LV (1357 $\pm$ 114 ms) and septum (LV septum=1391 $\pm$ 96 ms, RV septum=1451 $\pm$ 132 ms). Taking into account that SASHA overestimates T₁ [146] it can be argued that STEAM-SASHA gives more accurate results. However, as previously mentioned a direct comparison between STEAM-SASHA and a standard SASHA protocol would be an important experimental test for the future.

This work has shown that the number of sequence repeats is important to maximise accuracy and precision of the STEAM-SASHA data. The STEAM sequence, while providing excellent blood and fat suppression, has an inherently low SNR. This penalty is well investigated in DT-CMR studies [49], [179], [196], [244], [245], where around 8 sequence repeats per slice and diffusion encoding direction is typical for the spatial resolution used here. For the work in this chapter the maximum number of sequence repeats was based on these 8 averages often used in clinical DT-CMR research studies. Reducing the number of sequence repeats resulted in a reduction in the precision of the T₁ values, which cannot be recommended for the STEAM-SASHA sequence.

In the background noise analysis it has been shown that the TS=300 ms imaging data is >4x times above the noise floor in the myocardium and as such sufficient for analysis without substantial noise floor effects[350]. Further the signal distributions in the blood pool of the central cavity have been analysed. The TS=300 ms result shows that blood was successfully suppressed, while the Anchor image data shows a larger spread of mean noise between volunteers. However, this increase can be seen as marginal when compared to the anchor myocardial signal level that is >19 times higher.

Both MOLLI and STEAM-SASHA methods provide fair to good reproducibility for inter-observer, intra-observer and inter-study in all regions evaluated. When evaluating all results from the reproducibility experiments STEAM-SASHA is less precise and less reproducible when compared to MOLLI in most regions. These findings are in line with other studies [146], [354], in which SASHA type methods were shown to be less reproducible and precise. The one notable exception is the anterior RV where STEAM-SASHA shows a smaller spread in the Bland-Altman plots when compared to MOLLI, possibly benefiting from the improved blood and fat suppression of STEAM-SASHA. A potential explanation for the reduced reproducibility using STEAM-SASHA in addition to the known inherent limitations of SASHA [146](reduced dynamic range), is the need for more sequence repeats. This requires additional ROIs to be drawn and potentially results in less precise registration due to inter breathhold motion, all adding to increase the variability.

Weingärtner et al. [354] quoted both inter and intra observer reproducibility for MOLLI and SASHA in terms of the geometric mean of absolute difference. When comparing the LV results of Table 14 to these values the MOLLI sequence presented here appears similarly reproducible in terms of the geometric mean of absolute difference, even if the 95% CI is larger. The same can be said for the STEAM-SASHA results in comparison to the SASHA results as quoted by [354]. It is concluded that the new STEAM-SASHA sequence shown here has a slightly reduced reproducibility when compared to other established T₁ mapping methods.

Without a full age and sex matched comparison between a sufficient number of control and rTOF patients it is difficult to make any conclusive statements on the ability of the STEAM-SASHA technique to detect changes in T₁ due to disease. Further, to the knowledge of the author, no SASHA-based approach been applied in the RV in healthy and patient cohorts at 3T. As such this study can be used as initial point on which future RV SASHA based methods build upon on.

While STEAM-SASHA maybe less precise, the SASHA results are generally considered to be more accurate than MOLLI-based measures and the results presented here are consistent with a reduction in contamination of the T₁ values by fat and blood in the RV myocardium. Figure 131 shows that native RV T₁ values are comparable with the corresponding LV values when using the STEAM-SASHA sequence, while the same regions were found to have elevated MOLLI T₁ values in the RV. This is believed to be due to a reduction in T₁ signal contamination from blood in the STEAM-SASHA sequence.

While inter breath-hold motion is a concern for precision/reproducibility in STEAM-SASHA, the processing pipeline developed here does correct for rigid motion. The effect of intra-breathhold motion was assumed to be on a sufficiently small scale that the ROIs from the processing step still cover a sufficiently similar portion of the signal (it should be noted that this is a different problem to the one discussed in the *in vivo* DT-CMR case due to the region-based processing). This was validated by carefully investigating the T₁ weighted images, such as the representative example shown in Figure 140.

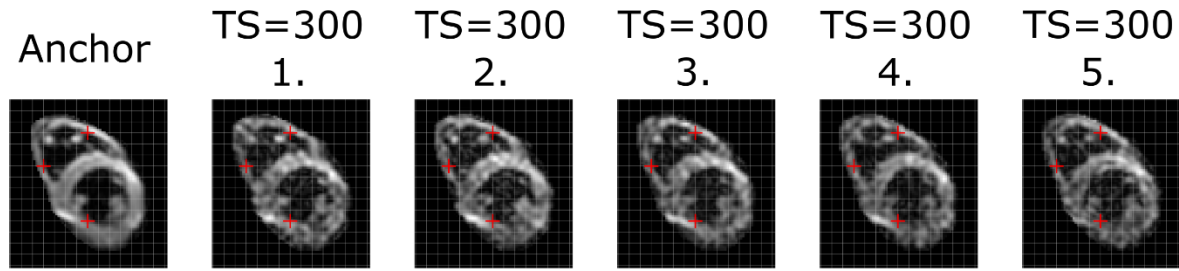


Figure 140: T₁ weighted images from a single T₁ STEAM-SASHA breath-hold showing small amounts of residual intra-breath hold respiratory motion. The red markers are placed at the same spatial location in the images and the similar cardiac morphology at each of the red markers demonstrates the minimal motion between the images.

The exemplary rTOF patient scan STEAM-SASHA (Figure 139) demonstrated elevated T₁ values when compared to the T₁ values obtained in healthy volunteers. In contrast, for the MOLLI sequence there was no clear increase in T₁ for the patient dataset apart from at the insertion points. In fact, the measurements in the anterior and superior RV suggest reduced T₁ values using MOLLI when compared to healthy volunteers. The increased interstitial collagen expected in rTOF patients would be generally expected to result in elevated T₁ and this is a promising first demonstration of the method, but a larger patient cohort will be required to provide more confidence in the utility of the method in patients.

During the TM of the STEAM sequence the stored magnetisation decays with T₁. As a result, heart rate variations during an acquisition would result in changes in the T₁-weighted signal loss between images. Inter-breath hold heart rate variations should not lead to errors as each breath hold contains both anchor and TS=300 ms images, but intra-breath hold variation in heart rate will cause errors. Furthermore, the STEAM sequence is sensitive to diffusion during the mixing time (effective diffusion weighting of this sequence was $b=100 \text{ s/mm}^2$) and variations in heart rate would also result in errors in measured T₁ due to changes in diffusion weighting with heart rate, but heart rate variability induced errors could be minimised in future using an RR-interval based correction for diffusivity as well as T₁ decay during TM.

13.5 Future Work

Further work remains in validating the new STEAM-SASHA technique in terms of assessing the performance in patient groups. The influence of RR variation must be evaluated and a correction may need to be implemented. In addition, the SNR that can be achieved with the STEAM-SASHA sequence must be improved. Post-processing denoising methods may assist in improving SNR. It should also be possible to combine STEAM-SASHA with the interleaved spiral trajectories as described in the rest of this thesis for application in DT-CMR work, which may provide improved spatial resolution. Further a free breathing approach that continuously builds up averages might be of use to improve SNR. Improvements in T_1 precision may be possible if the saturation pulse can be applied in the cardiac cycle prior to the first RF pulse of the stimulated echo to achieve the ideal TS range of 500-600 ms, rather than the current TS = 300 ms. Finally, MRI scanner software updates may avoid the clipping problems with the Chow saturation pulse and may provide more exact saturation supporting potentially more accurate and precise STEAM-SASHA T_1 values.

13.6 Conclusion

This work has introduced a novel saturation recovery prepared STEAM sequence (STEAM-SASHA) that provides accurate and reproducible T_1 values with excellent blood and fat suppression. Results in phantoms and *in vivo* demonstrate the performance of the technique and initial results suggest that STEAM-SASHA may be less affected by confounding effects in the RV.

This work was presented on the Annual Meeting of the International Society for Magnetic Resonance in Medicine 2021 with the Abstract No. 3606.

14 Discussion

There is a lack of methods available that provide robust and reliable quantitative tissue characterisation in the right ventricle. Of particular interest are here CHD patient groups such as rTOF that require routine assessment of cardiac function, based on which critical clinical decisions must be taken. Typical methods employed in the LV cannot be directly transferred due to the more challenging RV anatomy due to its thin and highly mobile nature. Thus, in this work STEAM-based sequences were leveraged to provide RV specific methods for reproducible and reliable quantitative characterisation of the RV myocardium.

For microstructural assessment, a novel interleaved high-resolution STEAM DT-CMR sequence, first shown by Gorodezky et al. [244], was implemented, adapted to the RV, optimised, and thoroughly evaluated in both an *ex vivo* and *in vivo* setting.

In this thesis a novel T₁ fat and blood suppressed mapping method was developed and evaluated *in vivo*. This novel STEAM-SASHA sequence has not only shown to provide reproducible RV T₁ assessment, but also promising findings in an initial rTOF patient to detect potentially diffused fibrotic tissue, something not possible with the MOLLI sequence.

14.1 Summary of Findings

14.1.1 DT-CMR Simulation

In Chapter 9 a framework to simulate DT-CMR data using an interleaved spiral readout was presented. In addition to simulating the individual DWI, the simulation framework allowed for the addition of realistic noise levels to the data and the introduction of the effects of both spatially-varying off-resonance and T₂^{*} decay.

Using this framework, it was possible to evaluate the performance of the frequency segmented off-resonance correction developed by Noll et al. [285] and a novel spatially-varying T₂^{*} correction developed in this work. Both methods were shown to reduce blurring effects associated with the respective signal degeneration process. Furthermore, for both algorithms the optimal number of bins (constant frequency/T₂^{*} values used to discretise the off-resonance /T₂^{*} map) was determined.

The simulations demonstrated that rapid spatial changes in frequency caused an artefact that extends beyond the location of the rapid gradient and cannot be fully recovered using the frequency segmented method. The frequency segmented off-resonance correction was shown to provide excellent results with increased sharpness measures and reduced bias in the resultant DT-CMR data compared to uncorrected data or data corrected assuming a spatially constant frequency.

The spatially-varying T_2^* correction did not demonstrate the same artefacts in regions near rapid gradients in T_2^* . While the correction showed a general sharpening effect in the parameters tested, the overall sharpening effect was less when compared to the off-resonance correction. The results of this chapter showed that T_2^* decay results in a reduction of the signal at high spatial frequencies, which results in an amplification of noise at these frequencies when the correction is performed. This reduction in SNR is detrimental to the overall error and variability of the DT-CMR parameters after correction. Furthermore, it was shown that in regions of low SNR the sharpening effect of the technique is less effective.

While for the moment the novel T_2^* correction is not useful for spiral DT-CMR (and was not used in the subsequent work) it could provide benefits for other sequences imaging organs with short T_2^* values or long readouts which do not suffer under the same SNR constraints as STEAM DT-CMR.

The chapter further showed the need for more advanced off-resonance correction methods to tackle the problem of steep gradients in off-resonance, possibly implemented into the same simulation framework.

This work addresses the stated aim of the thesis to: ***“Develop an optimised spiral STEAM acquisition and reconstruction, including corrections to address off-resonance and spatially-varying T_2^* blurring”.***

14.1.2 Technical Development DT-CMR

The technical development Chapter 10 introduced the sequence development, image planning and image reconstruction/correction steps that were necessary to allow for interleaved spiral DT-CMR using the STEAM sequence. This chapter also presented results from validation experiments for the individual correction steps.

The interleaved spiral sequence including spiral trajectories was implemented within the scanner software to allow for on-the-fly alteration of sequence parameters. This allowed for protocol changes at the scanner, which lead to faster testing/development cycles and the flexibility to adapt to challenging situations in *in vivo* scans and as such avoiding rescans of volunteers/patients. Another benefit was that both *in vivo* and *ex vivo* sequences used the same codebase and as such differences between them were minimised.

For the reconstruction pipeline a novel Gadgetron/mongoDB/Python server reconstruction chain was implemented. This reconstruction pipeline allowed the “online” functionality of the Gadgetron framework to be combined with the robustness and flexibility of a modern SQL-free database. This approach took advantage of high-level functions available within Python for tasks such as image processing and gridding, visualisation, and other mathematical libraries, most of which are not as readily available in C++.

The work in Chapter 10 achieves the stated aim of: ***“Develop online reconstruction tools that provide images at the scanner, at the time of the scan, to provide methods suitable for use in clinical research studies”***.

The corrections included in this chapter cover: gradient timing errors (discard value); off-isocentre shifts of the FOV; coil sensitivity calculation and, based on this, coil combination; motion induced phase correction; field map calculation and off-resonance correction using the field map. All corrections were implemented within the on-the-fly reconstruction pipeline and validated with phantom experiments. The optimal discard value for synchronising the beginning of the readout with the beginning of the data sampling and the alignment value used for the FOV centre shift were determined in experiments. For the off-resonance correction, a range of -120 Hz to 120 Hz was shown to be successfully corrected.

To test the physically achieved resolution in any sequence (not the contribution of the reconstruction) a novel resolution phantom using the intrinsic properties of “spin-warp” was designed, constructed, and tested. Using this method, it was possible to determine that the resolution achieved with the prescribed $2 \times 2 \text{ mm}^2$ spirals is in fact higher at $1.9 \times 1.9 \text{ mm}^2$.

The work contained in this chapter as such fulfils the stated aim of: ***“Develop an optimised spiral STEAM acquisition and reconstruction, including corrections to address off-resonance and spatially-varying T_2^* blurring”***.

14.1.3 Ex Vivo DT-CMR

The interleaved spiral readout was modified to allow for higher resolution *ex vivo* STEAM DT-CMR imaging on a clinical 3T system than currently possible with other STEAM-based methods. To the best knowledge of the author was this the first adoption of spiral imaging in combination with the STEAM sequence for DT-CMR in *ex vivo* hearts. The sequence parameters (number of interleaves and averages, b value, resolution, coil combination method and diffusion time) for the interleaved spiral sequence were optimised on recently fixed porcine hearts. The optimised spiral sequence was compared to a time and resolution matched single shot EPI method. Here the spiral sequence showed superior performance and good quality DT-CMR maps at a resolution of $1 \times 1 \times 2 \text{ mm}^3$. It was further shown that the higher resolution data can potentially resolve structures not adequately visualised with lower resolution approaches.

After adapting the diffusion time and number of averages to counter the lower SNR in more dehydrated human hearts due to longer fixation times, it was possible to acquire preliminary high-resolution data in two healthy and one rTOF specimen. Initial findings of this data show that the E_2A changes from a low value in the RV free wall to a higher value in the LV and septum in both healthy and rTOF hearts. Furthermore, the results suggest that in the healthy heart, there is no transmural rotation of the IA across the RV myocardium, while in the rTOF heart a small region of the RV shows a transmural change of angle.

The presented interleaved spiral method for *ex vivo* DT-CMR provides a method to generate high-resolution DT-CMR data on a clinical MRI system with a sequence closely matched to the sequence used *in vivo*. The smaller required FOV means that the technique is more suitable for interleaved multi-slice imaging than the *in vivo* STEAM sequence, increasing imaging efficiency above that demonstrated here. The use of clinical MRI systems for *ex vivo* imaging, avoids both the need for additional pre-clinical scanners and the FOV limitations of such small-bore systems and can typically be performed out of normal scanning hours, making most use of the available hardware. This new application of spiral STEAM DT-CMR provides researchers with a comparable method for studying *ex vivo* microstructure at high-resolution which is directly comparable to the data acquired *in vivo* in similar patient cohorts at lower spatial resolution.

This work addresses the aim to: ***“Develop an ex vivo protocol that utilises the interleaved spiral design to achieve a higher resolution to reduce partial voluming effects in exploratory work into the RV microstructure of healthy and rTOF hearts”.***

14.1.4 In Vivo DT-CMR

Chapter 12 described an *in vivo* DT-CMR study conducted on n=10 healthy volunteers using both a single shot STEAM EPI sequence at the frequently used spatial resolution of $2.8 \times 2.8 \text{ mm}^2$ and the high-resolution interleaved spiral STEAM method at $2 \times 2 \text{ mm}^2$ to provide data in the RV and septal myocardium for both a systolic and diastolic phase. Acquisitions were repeated to allow for the assessment of inter-study reproducibility.

It was shown that in systole both sequences provide reproducible results in the RV free wall and the septum with coefficients of variation less than 20%. In the diastolic phase both sequences were largely comparably reproducible as compared to systole, but the sequences were found to be less reliable with data considered unusable in 7 out of 20 cases for the spiral sequence and in a single case for the EPI sequence. This poorer diastolic performance for spiral acquisitions is likely due to the motion registration algorithm failing to adequately register the RV free wall despite improvements to the registration algorithms for use in the RV.

In general, the EPI sequence was shown to be slightly more reproducible; it requires fewer breath holds per image and the SNR per image was slightly improved when compared to the spiral approach. However, the higher spatial resolution provided by the spiral sequence was able to clearly resolve features that the EPI data struggled to depict. It should be that this was on a per subject basis and on a study wide basis significant difference between sequences were found in SNR, MD and FA.

Both sequences in both cardiac phases produced septal values of DT-CMR parameters consistent with published literature values. To the best knowledge of the author this was the first time that *in vivo* values of DT-CMR parameters have been provided for the RV. This work addresses the stated aim to: ***“Demonstrate the ability of the STEAM sequence to acquire native T_1 and DT-CMR parameters to provide reproducible results in healthy volunteers and to provide an assessment of the RV in rTOF patients”.***

14.1.5 T1 Mapping

In Chapter 13 the development of a novel STEAM-SASHA technique for providing robustly blood and fat suppressed measurements of myocardial T₁ values was presented. This new method was evaluated in comparison to a widely used MOLLI protocol and the intra-observer, inter-observer and inter-study reproducibility of both techniques was compared in regions within the left and right ventricle in n=10 healthy volunteers.

The two sequences first were evaluated in the T₁MES phantom [338], with both sequences providing results close to the ground truth. However, in the range of T₁ values expected in the native myocardium the STEAM-SASHA sequence was shown to provide results closer to the ground truth when compared with MOLLI.

Both sequences were shown to provide reproducible measures of T₁ in an inter-study, inter-observer and intra-observer setting, with overall slightly more reproducible values provided by the MOLLI sequence.

The STEAM-SASHA technique was shown to provide excellent blood suppression and left ventricular T₁ values in line with literature values obtained with a SASHA sequence. Results obtained in an initial rTOF patient are consistent with reduced signal contamination from blood or fat in the RV free wall using the STEAM-SASHA sequence compared to MOLLI.

The chapter fulfils the second half of the thesis aim to: ***“Demonstrate the ability of the STEAM sequence to acquire native T₁ and DT-CMR parameters to provide reproducible results in healthy volunteers and to provide an assessment of the RV in rTOF patients”.***

14.2 Study Limitations

A notable limitation of the simulation work was that there was no investigation of the influence of the quality of the underlying off-resonance/ T_2^* map on the performance of the correction. It would also have been interesting to conduct simulations of different spatial resolutions of the imaging and mapping data in combination with different simulated thicknesses of the myocardium. This may have provided results that were more relevant for the RV where the myocardium is much thinner.

One key limitation of the *in vivo* methods presented in this thesis is the lack of more sophisticated registration methods to align the RV free wall in the DWI/saturation recovery images. It was shown that due to the more complex, thinner, and more mobile shape of the RV even small misregistration can impact the overall data quality significantly. This is particularly apparent in the diastolic spiral RV DT-CMR data, where inadequate registration led to considerable artefacts in the images and required 7/20 scans to be discarded. While for the STEAM-SASHA data, regional averages of the signal within a region could be calculated before fitting to provide regional T_1 values, this was not possible for DT-CMR. DT-CMR is based on pixel wise parametric maps and angular measures often change rapidly in space, making it incompatible with regional averaging prior to the tensor calculation.

For both the spiral STEAM DT-CMR and STEAM-SASHA technique, the SNR efficiency is relatively low. Both sequences use the STEAM preparation which discards 50% of the magnetisation generally available for imaging and suffers from T_1 -related signal loss during the mixing time. Furthermore, the high b values used in the DT-CMR sequence and the saturation pulse used in SASHA T_1 mapping contribute further to the low SNR per image. As a result, a substantial number of averages acquired over multiple breath holds are used to build up sufficient SNR. The combination of data from multiple breath holds contributes to the image registration problems discussed above. The multiple breath holds also add considerable time to the acquisition workflow and increased efficiency will be required before the methods are clinically feasible.

14.2.1 Efficiency of Fat Saturation Methods

The theoretical background of how the STEAM sequence suppresses fat and blood were covered previously in chapter 10, 13. In chapter 13 we measure the effectiveness of the STEAM blood suppression in the RV blood pool and demonstrate that the signal in the blood pool is in the region of the background noise. However, the effectiveness of the fat suppression was not quantified and it is possible that blood signal could pool within the trabeculations of the

myocardium, contributing the DT-CMR signal measured. Investigations of the effectiveness of signal suppression could be performed by acquiring a dark blood prepared image (for testing blood suppression) and a Dixon based image (for fat suppression) in the same plane as the STEAM acquisition. By measuring the relative signal in the fat, myocardium and blood pool in both the reference and STEAM images, it would be possible to provide quantitative estimates of the degree to which the blood and fat are suppressed in the STEAM data. While neither a dark blood prepared nor a Dixon method were acquired during this thesis it is possible to compare a cardiac phase matched balanced steady state precession (bSSFP) cine image that was acquired in the same plane as the STEAM DWI (spiral, EPI), STEAM-SAHSA image and an inversion recovery balanced steady state free precession from a MOLLI acquisition (Figure 141). When comparing the images presented here it appears that the STEAM based methods show little to no signal from the large pools of blood or fat that are visible in both the bSSFP cine and the IR bSSFP images. While there may be some blood trapped in the trabeculations contributing to the RV myocardial signal, particularly in the anterior RV wall, as noted on the image, in general the STEAM sequence has good suppression capabilities for both blood and fat.

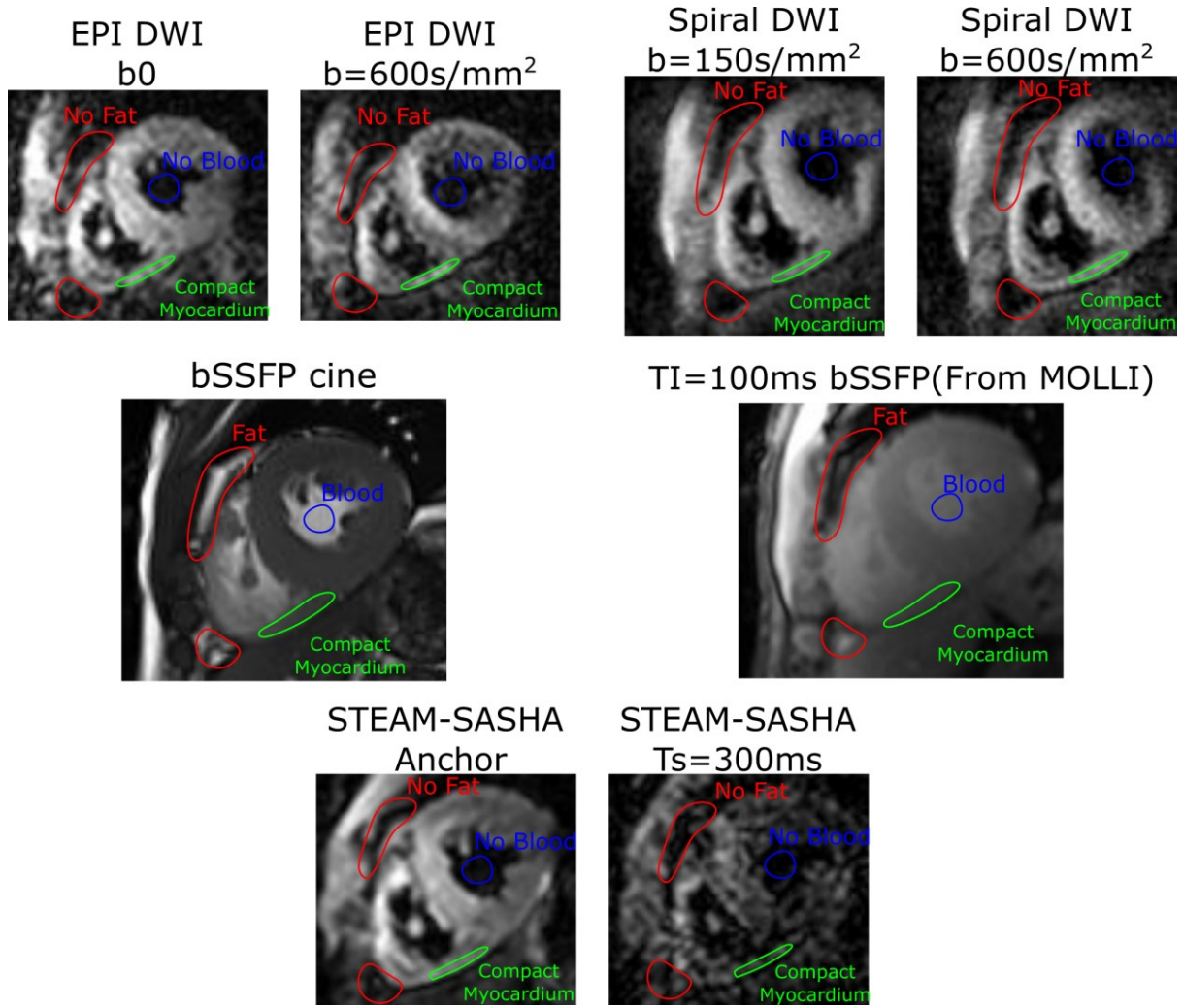


Figure 141: Example images acquired in the same plane using the STEAM DWI (spiral [$b=150, 600\text{s/mm}^2$], EPI [$b=0, 600\text{s/mm}^2$]), STEAM-SASHA [Anchor, $T_s=300\text{ms}$] and a bSSFP image from the MOLLI sequence with $TI=100\text{ms}$.

14.2.2 Interleaved Spiral DT-CMR

One limitation of both the *in vivo* and *ex vivo* DT-CMR work in this thesis, is the lack of an exactly matched protocol for the EPI and the spiral sequences. The STEAM EPI DT-CMR sequence used *in vivo* is a single shot approach (with parallel imaging) while the spiral sequence uses two interleaves (without parallel imaging), therefore doubling the acquisition time in order to improve spatial resolution by a factor of 1.4 (in pixel volume). In future segmented/interleaved EPI sequences may be investigated for a more closely matched comparison at the same spatial resolution. Spiral sequences lend themselves to interleaved imaging as the centre of k-space is sampled in every interleave, which is useful when using a motion-induced phase correction but not easily achieved with the EPI sequence. However, due to the differences in the acquisition techniques is the PSF in spiral wider than in a

resolution matched EPI sequence (as shown in section 10.6), something that should be taken into account in future. The intrinsic differences between the sequences should be considered when comparing results from the EPI and spiral data.

A large amount of time during the PhD was spent implementing an online reconstruction using the Gadgetron framework. While in the final implementation a small portion of the initial Gadgetron implementation was used, this was only to export raw data from the scanner at acquisition time. The reconstruction pipeline implemented within the Gadgetron was deemed not suitable, due to a memory leak in the NUFFT library provided with the Gadgetron. Identifying that memory leak was only possible due to the open-source nature of the Gadgetron and may not have been possible with a supplied manufacturer reconstruction framework. However, the requirement to implement any new gridding algorithm for the Gadgetron as a C++ template structure, the lack of documentation and the time-consuming task of implementing such an algorithm in a computational efficient manner from scratch in C++ made full use of the Gadgetron impracticable for this project. While in future Gadgetron releases (here version 3.9 was used) these problems are likely to have been addressed, other solutions may be more suitable for online reconstruction during technical development phases of research. One such alternative solution was presented in Chapter 10.4.1.7.

14.2.3 STEAM-SASHA

While MOLLI sequences are the most widely adopted T₁ mapping methods, a direct comparison between the STEAM-SASHA and a conventional SASHA may have been useful. SASHA sequences are known to be more accurate but less precise [146], which the results from this work are also consistent with for the STEAM-SASHA method (when compared to MOLLI). While STEAM-SASHA derived values were compared to literature values, a true comparison on a per subject basis would enable a separation of the effects of the T₁-preparation method from the differences due to the use of STEAM and EPI trajectories.

Another shortcoming of the T₁ study presented here was that due to a scanner software bug the saturation pulse optimised for SASHA could not be used. This is important as the sequence was run on a 3T system where off-resonances are larger than when compared to the more commonly used 1.5T machines. The optimised 6-pulse saturation design is known to provide more effective saturation, particularly where there is off-resonance and as such may have improved the accuracy and reproducibility of the STEAM-SASHA method. Due to this error a number of healthy volunteer scans were discarded and had to be repeated. This is time which could have been spend imaging more volunteers or patients.

14.3 Future work

The most important work to improve RV microstructural/parametric mapping methods will be the implementation of an improved motion registration method. This could be a carefully tailored non-rigid approach or potentially an AI network trained to achieve more accurate registration [357], [358] than is possible with current state of the art non-AI methods. An important piece of groundwork for this would be the acquisition of a cine-like dataset, which uses a STEAM-based sequence in each cardiac phase. Due to the long preparation times of the STEAM sequence this would have to be run over multiple breath holds. A few exploratory datasets of this kind could be used to provide a better understanding of the amplitude and types of inter-shot motion encountered and which registration methods might be capable of correct these. Further this dataset would provide new insights into the motion of the RV during the cardiac cycle, something thought to be particular useful in the RV which does not display such a clear global RV end-systolic pause and diastasis as the LV. One source of additional information for new motion registration methods could be the new Pilot Tone (Siemens Healthineers, Erlangen, Germany) [359], [360] which is implemented in some modern scanners (including the Vida system).

While tailored methods for RV registration in STEAM images may be required, the use of well-established non-rigid motion correction algorithms such as developed by Merlocco et al. [361] could be evaluated in a first stage. However, the application of non-rigid methods should be approached with care, as any resultant change in image intensity will impact the fitting algorithms used and therefore the parametric maps.

As described throughout, STEAM based methods are SNR inefficient. One potential remedy for this could be the use of deep learning denoising networks. In recent work by Phipps et al. [324] such techniques have shown a substantial benefit in DT-CMR, by either reducing scan time or increasing SNR which will should lead to more accurate and precise measurements.

Both the interleaved spiral STEAM DT-CMR and STEAM-SASHA sequence were implemented on a clinical 3T system. However, most of the clinical CMR scans are performed using 1.5T scanners, which limits the adoption of the methods proposed here to a smaller number of sites with 3T scanners. Translating STEAM-based methods for use at 1.5T is hampered by the low SNR efficiency of STEAM, as SNR would be reduced by the smaller net magnetisation available for imaging at lower field strength [362]. The shorter T_1 at lower field strengths would reduce SNR further since the magnetisation available for imaging decays with T_1 during the mixing time, although this may be partially compensated for by the increased longitudinal recovery of magnetisation between sequence repeats. Therefore, it seems inevitable that at 1.5T either longer scan times or other means (e.g., denoising methods) would be required. It's important to note however that off-resonance effects are less severe at 1.5T and also T_2^* blurring is less due to T_2^* values being longer[251]. Thus, the SNR inefficiency at 1.5T may be reduced due to the possibility of using longer readouts.

Despite best efforts to recruit rTOF patients to investigate the ability of both the DT-CMR and STEAM-SASHA T_1 to detect diffused fibrosis this was not possible due to the Corona virus pandemic. Only a single rTOF patient was successfully scanned in the T_1 mapping work, and while this can be seen as an initial test of the technique with interesting initial results, more patients are required to evaluate the suitability of both proposed methods.

14.3.1 Interleaved Spiral DT-CMR

The addition of a parallel imaging method to the interleaved spiral DT-CMR sequence would be a logical step to reduce scan time. Due to the similarities between diffusion encoding directions for the same slice, it may be possible to use a through time GRAPPA approach [363], where the diffusion encoding directions and scan repeats make up the “time” dimension. This would require testing for compatibility with the variations in diffusion induced signal loss encountered in each image. GRAPPA based methods have the benefit of not enforcing fitting restraints based on the model or other assumptions about the data, thus often being more robust than for example SENSE type acquisitions [364]. A non-Cartesian SENSE approach however may be suitable due to the fact that the data in this thesis provides a CSM and is fully sampled, allowing the data acquired here to be used in a retrospective study. One concern for both implementations is whether there is sufficient spatial variation in the CSMs to allow unwrapping of the aliased signals and this will have to be investigated in a future study.

Further spiral specific corrections could provide improve overall data quality and reliability. Corrections for trajectory inaccuracies are known to reduce blurring in spiral images [334]. One such method is the GIRF trajectory correction. This correction has been shown to make important improvements to image quality in other applications[334] and may be an important addition to further improve robustness of the presented method. Other studies have shown that NMR field probes can be used to directly measure the trajectories and allow for an optimal reconstruction in the case of time varying gradients such as spiral imaging [365]–[368].

Another investigation for both *in* and *ex vivo* imaging is the development of a spiral SE DT-CMR sequence, either using simple monopolar gradients for *ex vivo* imaging or motion compensated gradients for *in vivo* imaging. While, the SE approach probes a different scale of microstructure, it has the advantage of having theoretically higher SNR efficiency, this is further boosted through the fact that SE is better suited to slice interleaved imaging. SE based methods can also be implemented with single RR interval triggering ($TR=1RR\text{-interval}$) which is more suitable for free breathing approaches. In combination with the spiral readout which samples the centre of k-space with each interleave it is plausible that a SE interleaved spiral approach could allow for robust free breathing applications. But difficulties remain with the SE approach due to the longer diffusion encoding gradients and the difficulty of producing a reduced FOV in two dimensions with only two RF pulses. Larger FOVs require either longer readout durations or the need for more spiral interleaves to provide the same resolution. Also, the need for longer diffusion encoding gradients results in longer TEs for SE sequences than for STEAM.

For the *ex vivo* scans the proposed slice interleaving and optimised TR described in Chapter 11.5, would provide a more efficient method to provide greater coverage of the explanted hearts in the through plane direction. It would also be important to investigate if an isotropic resolution of $1\times1\times1\text{ mm}^3$ is possible, given that the SNR would be reduced by a factor of $\sqrt{2}$. This would not only reduce partial volume in the slice encode direction but would provide ideal data for more sophisticated data visualisation algorithms such as tractography.

The inefficiency of STEAM-based methods that require a TR of 2 RR intervals means that they are less well-suited to methods which require multiple RF pulses during the readout train. Other EPI or spiral-like readout trajectories could be used to accelerate or improve the robustness of the methods presented here. Spiral design variants may be well-suited to accelerated imaging and EPI variants such as short-axis PROPELLER [369] may facilitate interleaved imaging. A potential alternative to the spiral trajectories presented here could be a spiral in-out trajectory as shown by Fielden et al. [370] which have shown beneficial off-resonance robustness, but would result in an increase in TE.

Other than cardiac applications spiral trajectories have shown to provide benefit to brain DTI [371]–[373] and the work shown here on spatially-varying T_2^* correction may find utility in this field.

14.3.2 STEAM-SASHA

The logical first step in improving the performance of the STEAM-SASHA sequence is to resolve the clipping of the 6-pulse saturation pulse that were present in the current implementation. This may be straightforward in more recent versions of the scanner software, but alternatively may require the re-implementation of the pulse-train in the IDEA framework.

Another development that may improve accuracy and precision in STEAM-SASHA would be to investigate if shifting the saturation time closer to the optimal $TS=500-600$ ms value found by Kellman et al. [344] is possible. While this could be achieved by imaging during diastasis, the RV myocardium is much thinner in this cardiac phase and initial tests suggested that image quality was not sufficient for RV T_1 mapping with this timing. The alternative approach is to move the saturation pulse into the cardiac cycle prior to the cardiac cycle containing the image acquisition. However, cardiac cycle variability would mean that the saturation time would vary slightly between sequence repeats, requiring correction during the T_1 calculation. Simulations could be performed to evaluate the accuracy and precision of STEAM-SASHA with a heart rate dependent TS . Such simulations would also be suitable for investigating a correction factor for the effects of varying amounts of T_1 decay during the 1 cardiac cycle mixing time in the STEAM sequence.

If the further improvements provide a robust high-resolution spiral STEAM DT-CMR sequence then an interleaved spiral STEAM-SASHA technique could be investigated. This would combine the robust blood and fat suppression of STEAM with the improved spatial resolution provided by the interleaved spirals.

From a more clinical perspective the proposed technique will need to be evaluated in a larger clinical study with both more healthy controls and patients with a history of diffuse fibrosis in the RV (rTOF). The main aim of this would be to investigate whether baseline values for T_1 can be found that allow differentiation between diseased and healthy subjects. This clinical study should ideally include a comparison with both MOLLI and SASHA-based sequences.

Finally, the presented method could be useful in other imaging settings where either fat or blood partial voluming pose a problem for accurate T_1 measurements such as in patients with thin myocardial walls, e.g. DCM patients [69] or in chronic myocardial infarction, but also in patients with fatty infiltration of the left ventricle where fat causes T_1 bias [374].

14.4 Conclusion

This thesis has identified the unmet clinical need for reliable RV imaging methods that allow for detection and localisation of diffuse fibrosis. This is particularly important for CHD patient cohorts such as rTOF, where diffuse fibrosis can predict adverse events in clinical outcome [67].

Two methods have been presented that for the first time allow for *in vivo* microstructural and parametric T₁ mapping in the challenging RV myocardium, using the excellent blood and fat suppression provided by STEAM sequences. Both the STEAM-SASHA and interleaved spiral STEAM DT-CMR sequences have shown to provide good reproducibility in cohorts of 10 healthy volunteers. The DT-CMR sequence was also shown to have utility in providing *ex vivo* data from the hearts of both healthy and diseased subjects which will provide clinicians with higher resolution data to study the cardiac microstructure. With both STEAM-SASHA and interleaved spiral STEAM DT-CMR sequences showing control (septal) values in line with more widely applied and validated LV methods, the work conducted here is an important initial step towards the non-invasive investigation of diffuse fibrosis in the RV of rTOF and other patient groups.

This thesis has further shown that higher resolution interleaved spiral methods can provide DT-CMR values in the RV similar to those obtained using the more established lower resolution single shot EPI methods. This can be seen as important first step of the adaption of these methods to imaging the challenging RV myocardium, providing higher resolution DT-CMR maps with reduced partial voluming. However, this work has also shown that, despite the improved spatial resolution, the interleaved spiral methods still require more technical development before they can adequately replace the standard single shot EPI methods in the RV. The more complex artefact patterns and the more challenging motion registration have to be addressed to fully take advantage of the benefits that interleaved spiral sampling patterns provide.

The T₁ work has shown that the novel STEAM-SASHA sequence can provide excellent blood and fat suppression, therefore avoiding partial volume effects common in MOLLI sequences. While it has shown to be less precise when compared to the MOLLI sequence, the results from the STEAM-SASHA technique are consistent with improved accuracy over MOLLI. Including the initial demonstration in a rTOF patient, the STEAM-SASHA sequence has shown potential for the detection of diffuse fibrosis in future.

The biggest challenge that was identified for the future of RV microstructural/parametric mapping is the need for more accurate image registration methods. The rigid motion registration algorithms used at present are clearly limited in the more mobile and heterogeneous RV free wall.

In future the novel techniques shown in this work will provide clinical researchers with the first methods to identify and localise diffuse fibrosis in the RV of CHD (in particular rTOF) and inform clinical decisions that will improve outcomes.

15 References

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17 Conference Abstracts

CNN-based Off-resonance Correction in Cardiac Spiral MRI

Annual Meeting of the International Society for Magnetic Resonance in Medicine 2022

Wang S, Ferreira PF, Khalique Z, Gorodezky M, Roehl M, Pu J, Pennell DJ, Nielles-Vallespin S, Scott AD. Program number P267.

Right ventricular T₁ mapping using a novel STEAM-based approach: STEAM-SASHA

Annual Meeting of the International Society for Magnetic Resonance in Medicine 2021

Roehl M, Gatehouse PD, Ferreira PF, Nielles-Vallespin S, Babu-Narayan S, Pennell DJ, Firmin DN, Scott AD. Abstract 3606.

Optimising spiral diffusion tensor cardiovascular magnetic resonance for high-resolution ex vivo STEAM imaging on a clinical scanner

Annual Meeting of the International Society for Magnetic Resonance in Medicine 2021

Roehl M, Gatehouse PD, Ferreira PF, Nielles-Vallespin S, Babu-Narayan S, Pennell DJ, Firmin DN, Scott AD. Abstract 1326.

Correcting for T₂^{*} related blurring in spiral MR: A novel method compensating for spatial variations in T₂^{*}

Annual Meeting of the International Society for Magnetic Resonance in Medicine 2020

Roehl M, Gatehouse PD, Ferreira PF, Nielles-Vallespin S, Babu-Narayan S, Gorodezky M, Xue H, Kellman P, Pennell DJ, Firmin DN, Scott AD. Abstract 5584.

Correcting for the effects of spatially varying T₂^{*} in spiral cardiovascular magnetic resonance

Annual Meeting of the Society for Cardiovascular Magnetic Resonance 2020

Roehl M, Firmin DN, Gorodezky M, Ferreira PF, Babu-Narayan S, Gatehouse PD, Kellman P, Xue H, Pennell DJ, Nielles-Vallespin S, Scott AD. Program number P267.

Diffusion tensor cardiovascular magnetic resonance in a Langendorff perfused beating porcine heart

Annual Meeting of the International Society for Magnetic Resonance in Medicine 2019

Scott AD, Jackson T, Khalique Z, Gorodezky M, Pardoe B, Bruno D, Chowdhury RA, Ferreira PF, Nielles-Vallespin S, Begum L, Roehl M, Sarathchandra P, Rose JN, Doorly DJ, Pennell DJ, Ascione R, Silva R, Firmin DN. Program number Po404.

18 Papers

Development of a CMR compatible large animal isolated heart model for direct comparison of beating and arrested hearts

NMR in Biomedicine - Under revision

Scott AD, Jackson T, Khalique Z, Gorodezky M, Pardoe B, Begum L, Bruno D, Chowdhury RA, Ferreira PF, Nielles-Vallespin S, Roehl M, McCarthy K, Sarathchandra P, Rose JN, Doorly DJ, Pennell DJ, Ascione R, Silva R, Firmin DN.

Stochastic Deep Compressive Sensing for the Reconstruction of Diffusion Tensor Cardiac MRI.

Medical Image Computing and Computer Assisted Intervention – MICCAI 2018

Jo Schlemper, Guang Yang, Pedro Ferreira, Andrew Scott, Laura-Ann McGill, Zohya Khalique, Margarita Gorodezky, Malte Roehl, Jennifer Keegan, Dudley Pennell, David Firmin, Daniel Rueckert. https://doi.org/10.1007/978-3-030-00928-1_34

19 Grants

British Heart Foundation Non-Clinical PhD Studentship

Awarding Institution: *British Heart Foundation*

Purpose: *Funding for PhD stipend*

Grant No: *P62117*

Dean's Internship Award

Awarding Institution: *Imperial College London; National Heart and Lung Institute (NHLI)*

Purpose: *Granted for exceptional training and internship opportunities. In this case a two-week training at NIH under the supervision of Dr Peter Kellman and Dr Hui Xue.*