

Development of a high temporal resolution spiral 3D phase velocity mapping technique for analysis of regional myocardial mechanics

A thesis presented for the degree of
Doctor of Philosophy at Imperial College London

By

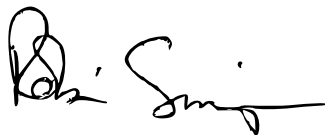
Robin Matthew Simpson

The Royal Brompton Hospital and National Heart and Lung Institute
Imperial College
180 Queen 's Gate, London SW7 2BZ

Supervised by Dr Jennifer Keegan and Prof David Firmin

I certify that this thesis, and the research to which it refers, are the product of my own work, and that any ideas or quotations from the work of other people, published or otherwise, are fully acknowledged in accordance with the standard referencing practices of the discipline.

Signed:

A handwritten signature in black ink, appearing to read "Rishi Singh". The signature is fluid and cursive, with the first name "Rishi" and the last name "Singh" clearly distinguishable.

Copyright

The copyright of this thesis rests with the author and is made available under a Creative Commons Attribution Non-Commercial No Derivatives licence. Researchers are free to copy, distribute or transmit the thesis on the condition that they attribute it, that they do not use it for commercial purposes and that they do not alter, transform or build upon it. For any reuse or redistribution, researchers must make clear to others the licence terms of this work.

Abstract

MRI is a powerful tool for imaging the heart, allowing the collection of anatomical and functional information non-invasively. Heart function is routinely assessed by global performance via ventricular masses and ejection fraction. Regional dysfunction, often a precursor of disease, can be hidden by apparently healthy global ventricular function and so there is a clear need for accurate and reproducible methods for measuring regional myocardial mechanics.

Tissue phase velocity mapping is the only MR technique which is capable of measuring motion over the entire cardiac cycle. Unfortunately current sequences are inefficient and do not fully exploit its full potential. This thesis presents the development of a new high temporal resolution sequence which uses spiral k-space trajectories to speed up the acquisitions, and implements retrospective cardiac gating to extend the technique over the entire heartbeat. Two sequence variations are developed and assessed.

The first uses a modified respiratory navigator algorithm to acquire high resolution data in ten healthy volunteers on two occasions, demonstrating very good reproducibility. Measurements in atrial systole have been made for the first time, providing information that previously was only seen from echocardiography. The second sequence variation uses a non-Cartesian SENSE reconstruction to allow the acquisition of similar resolution images within a short breath-hold. This sequence performs as well as the navigator gated sequence despite being

acquired in just thirteen heartbeats. Analysis tools have also been developed and colour plots have been used for the first time to present a large amount of data in an easily interpretable way.

By speeding up the acquisition of tissue phase velocity mapping data and by extending it over the entire cardiac cycle, the work presented in this thesis provides the potential to routinely acquire information about regional myocardial mechanics in clinical practice.

Acknowledgements

I am very grateful to all those people who have helped and supported me throughout the duration of this work. In particular to Dr Jennifer Keegan and Prof David Firmin for providing the direction and experience without which this thesis would not have been possible. My thanks also go to Heart Research UK for funding; to Dr Peter Gatehouse and the rest of the physics team at the Royal Brompton Hospital for all of the fruitful, tea-fueled discussions that have provided much needed inspiration and advice; to Steven Collins and Matthew Round for IT support and to the many others at the Royal Brompton who have made this time so enjoyable.

Finally, thanks to Sonia and my family for everything they have done for me.

Table of contents

List of Figures	17
List of Tables	22
1 Background	24
1.1 Cardiac Anatomy and function	24
1.1.1 Overview	24
1.1.2 Muscle structure	26
1.1.2.1 Myocytes	26
1.1.2.2 Left ventricle	29
1.1.2.3 Right ventricle	30
1.1.3 Function	30
1.1.3.1 Electrocardiogram	31
1.1.3.2 Phonocardiogram	33
1.1.3.3 Mechanics	33
1.1.4 The importance of measuring cardiac function	35
1.2 Global measures of cardiac function	35
1.3 Techniques to measure global cardiac function	40
1.3.1 Echocardiographic techniques	40
1.3.1.1 Tissue Doppler Imaging	42
1.3.1.2 Speckle tracking	44
1.3.2 Nuclear Cardiology	44
1.3.3 Computed Tomography	46

1.3.4	Magnetic Resonance	47
1.3.5	Limitations of global measures of cardiac function	49
1.4	Regional measures of cardiac function	50
1.4.1	Segmentation	50
1.4.2	Parameters	51
1.4.2.1	Strain	52
1.4.2.2	Strain-rate	53
1.4.3	Co-ordinate systems	54
1.4.3.1	Left Ventricle	54
1.4.3.1.1	Radial-Circumferential-Longitudinal	55
1.4.3.1.2	Principal	55
1.4.3.2	Right Ventricle	55
1.5	Methods of measuring regional cardiac function	56
1.5.1	Echocardiography	56
1.5.1.1	Tissue Doppler Imaging	56
1.5.1.2	Speckle tracking	59
1.5.2	Magnetic Resonance Imaging	60
2	MR methods of measuring regional myocardial mechanics	61
2.1	Tissue tagging	62
2.1.1	Introduction	62
2.1.2	Sequence design	62
2.1.3	Developments	65
2.1.3.1	C-SPAMM	65
2.1.3.2	Imaging variants	65
2.1.3.3	3D	66
2.1.4	Image analysis	66
2.1.4.1	Techniques	67
2.1.4.1.1	Tag following	67
2.1.4.1.2	Optical flow	67

	2.1.4.1.3	HARP	68
	2.1.4.1.4	FAST	72
2.1.5		Validation	72
	2.1.5.1	Phantoms	72
	2.1.5.2	Animals	72
	2.1.5.3	Healthy subjects	73
	2.1.5.4	Patients	73
2.1.6		Normal motion	74
2.1.7		Clinical application	74
	2.1.7.1	Circumferential strain	75
	2.1.7.2	Circumferential strain-rate	76
	2.1.7.3	Other strains	76
	2.1.7.4	Shortening	77
	2.1.7.5	Torsion/Rotation	77
2.2		Phase velocity mapping	78
	2.2.1	Introduction	78
	2.2.2	Sequence Design	79
		2.2.2.1 Initial implementation	81
		2.2.2.2 Developments	81
	2.2.3	Image Analysis	83
		2.2.3.1 Parameters	83
		2.2.3.1.1 Velocities	84
		2.2.3.1.2 Strain-rate	84
	2.2.4	Validation	84
		2.2.4.1 Phantoms	84
		2.2.4.2 Healthy subjects	85
		2.2.4.3 Patients	86
	2.2.5	Normal motion	86
	2.2.6	Clinical Application	87
		2.2.6.1 Strain-rate	87

2.2.6.2	Peak velocities	88
2.2.6.3	Time to peak velocities	88
2.3	DENSE	89
2.3.1	Introduction	89
2.3.2	Sequence Design	89
2.3.2.1	Implementations	92
2.3.2.2	Artefacts	94
2.3.3	Validation	95
2.3.4	Normal motion	97
2.3.5	Clinical Applications	98
2.4	SENC	99
2.4.1	Introduction	99
2.4.2	Sequence design	100
2.4.2.1	Implementations	104
2.4.3	Validation	106
2.4.4	Normal motion	107
2.4.5	Clinical applications	108
2.5	Comparisons	111
2.5.1	Need for improvements	115
3	Technique Development	118
3.1	Introduction	118
3.2	Sequence Development	119
3.2.1	Respiratory navigator	119
3.2.1.1	Background	119
3.2.1.2	Implementation	124
3.2.1.2.1	Modified navigator algorithm	126
3.2.2	Water excitation	129
3.2.2.1	Background	129
3.2.2.2	Implementation	132

3.2.3	Black blood pulse	133
3.2.3.1	Background	133
3.2.3.2	Implementation	135
3.2.3.3	Frequency of black blood pulses	137
3.2.3.3.1	Results	139
3.2.3.3.2	Conclusions	141
3.2.4	Velocity encoding	142
3.2.4.1	Background	142
3.2.4.1.1	Encoding strategies	145
3.2.4.1.2	Velocity compensation	146
3.2.4.1.3	Errors	146
3.2.4.1.3.1	Concomitant fields	146
3.2.4.1.3.2	Eddy currents	147
3.2.4.1.4	Background offsets	147
3.2.4.2	Implementation	148
3.2.5	Spiral trajectories	149
3.2.5.1	Background	149
3.2.5.1.1	Advantages of non-Cartesian trajectories	149
3.2.5.1.1.1	Radial	152
3.2.5.1.1.2	Spiral	153
3.2.5.1.2	Spiral imaging	153
3.2.5.1.3	Spiral design	153
3.2.5.1.4	Artefacts	155
3.2.5.2	Implementation	156
3.2.6	Coil sensitivity maps	159
3.3	Image Reconstruction	159
3.3.1	Re-order functor	161
3.3.2	Retrospective cardiac gating functor	162
3.3.2.1	Background	162
3.3.2.1.1	Prospective gating	162

3.3.2.1.2	Retrospective gating	163
3.3.2.2	Implementation	163
3.3.3	Regridding functor	165
3.3.3.1	Background	165
3.3.3.2	Implementation	166
3.3.4	Non-Cartesian SENSE gadget	167
3.3.4.1	Background	167
3.3.4.1.1	GRAPPA	168
3.3.4.1.2	SENSE	170
3.3.4.1.3	Non-Cartesian acceleration	171
3.3.4.2	Implementation	172
3.3.5	Phase map subtraction	173
3.3.5.1	Background	173
3.3.5.2	Implementation	174
3.4	Analysis	174
4	Navigator Gated Acquisitions	178
4.1	Methods	179
4.1.1	Sequence	179
4.1.2	Protocol	180
4.1.3	Analysis	182
4.2	Results	184
4.2.1	LV	184
4.2.1.1	Global velocity curves	185
4.2.1.2	Global Peak and TTP velocities	187
4.2.1.3	Regional velocities	191
4.2.1.4	Colour plots	196
4.2.1.5	Transmural velocities	201
4.2.1.6	Phantom offsets	203
4.2.1.7	Reproducibility	206

4.2.2	RV	212
4.3	Discussion	215
4.3.1	Data acquisition	215
4.3.2	Results	216
4.3.3	Reproducibility	218
4.3.4	RV	219
4.3.5	Limitations	220
4.3.6	Conclusion	221
5	Breath-hold acquisitions	222
5.1	Methods	223
5.1.1	Sequence	223
5.1.2	Protocol	225
5.1.3	Analysis	226
5.2	Results	227
5.2.1	LV	228
5.2.1.1	Global velocity curves	228
5.2.1.2	Global Peak and TTP values	230
5.2.1.3	Regional velocities	232
5.2.1.4	Colour plots	236
5.2.1.5	Transmural velocities	240
5.2.1.6	Phantom offsets	241
5.2.1.7	Stack of slices	244
5.2.2	Comparison with HighRes	245
5.2.3	RV	253
5.3	Discussion	255
5.3.1	Data acquisition	255
5.3.2	Data analysis	256
5.3.2.1	Breath-hold acquisitions	256
5.3.2.2	Comparison with navigator gated sequence . . .	257

5.3.2.3	RV	258
5.3.3	Limitations	258
5.3.4	Conclusion	259
6	Simulating the effect of natural heart rate variation	260
6.1	Validation of simulation method	261
6.1.1	Introduction	261
6.1.2	Validation	261
6.1.3	Results	263
6.1.3.1	Geometrically increasing phantom phase values	263
6.1.3.2	Random phantom phase values	263
6.1.4	Discussion	263
6.2	Simulation Method	267
6.2.1	Prospective gating	268
6.2.2	Retrospective gating	270
6.3	Missed triggers	270
6.3.1	Introduction	270
6.3.2	Methods	271
6.3.3	Results	271
6.3.3.1	Peaks curve	271
6.3.3.2	Curve based on real data	273
6.3.4	Discussion	274
6.4	Heart rate variation	275
6.4.1	Linear	276
6.4.1.1	Methods	276
6.4.1.2	Results	276
6.4.1.3	Discussion	279
6.4.2	Constant systole	279
6.4.2.1	Methods	279
6.4.2.2	Results	279

6.4.2.3	Discussion	282
6.4.3	Changing systole and diastole	283
6.4.3.1	Methods	283
6.4.3.2	Results	283
6.4.3.3	Discussion	286
6.4.4	Splitting the cardiac cycle based on diastolic intervals . .	286
6.4.4.1	Methods	286
6.4.4.2	Results	287
6.4.4.3	Discussion	290
6.4.5	Heart rate variation discussion	290
7	Discussion	292
7.1	Summary of findings	293
7.2	Limitations	295
7.3	Future work	296
7.3.1	Improvements to the technique	296
7.3.1.1	Background offset modelling	296
7.3.1.2	Improved segmentation	298
7.3.1.3	GRAPPA	299
7.3.1.4	Strain-rate	300
7.3.2	Future studies	302
7.3.2.1	Comparison with Echocardiography	302
7.3.2.2	Patient studies	303
7.4	Conclusion	307
	References	354
	Glossary of terms	355
A	Water excitation proof	358
B	Publications	361

C	Conference abstracts	362
C.1	Oral presentations	362
C.2	E-posters	363
C.3	Traditional posters	363
D	Copyright Permissions	365

List of Figures

1.1	Diagram of heart anatomy	25
1.2	Schematic diagram showing the blood flow through the heart . .	25
1.3	A single myocyte	27
1.4	Cell voltage, calcium level and contraction through the cardiac cycle	27
1.5	Dissection of ovine left ventricle	29
1.6	Wiggers Diagram	31
1.7	Conduction system in the heart	32
1.8	Dimensions used to calculate volumes	36
1.9	Example echocardiography apical view	40
1.10	Mitral annulus velocities measured with TDI	43
1.11	CT image	46
1.12	The AHA 17 segment model	51
1.13	RCL and Principal co-ordinate systems	54
1.14	Dyssynchrony measured with TDI	57
1.15	Displacement measured with speckle tracking	58
2.1	Tagging sequence diagram and example images	63
2.2	HARP k-space, magnitude and phase images with explanation of changes with deformation	69
2.3	Lowered E_{CC} in former and current smokers measured by HARP	75
2.4	Phase velocity mapping sequence diagram	79
2.5	Velocities measured in healthy volunteers with PVM	83

2.6	DENSE sequence diagram	90
2.7	The k-space echoes produced from a DENSE acquisition	94
2.8	Comparison between tagging and DENSE in mice	96
2.9	SENC sequence diagram	101
2.10	The effect of through plane strain on SENC tags	102
2.11	Inducible ischemia detection with SENC	110
2.12	Similarities between HARP and DENSE	112
3.1	Sequence diagram and looping structure	120
3.2	Example navigator trace	122
3.3	Comparison of navigator sequence diagrams	125
3.4	Images acquired with conventional and modified navigator algorithms	127
3.5	The effect of the modified algorithm on respiratory efficiency	128
3.6	The effect of a 1-3-3-1 water excitation	131
3.7	Water Excitation	133
3.8	The effect of a black blood pulse in Cartesian imaging	134
3.9	Black blood pulse	136
3.10	The benefits of using black blood pulses	137
3.11	Global longitudinal velocities from all three volunteers acquired with different blackblood frequencies	139
3.12	Images from different blackblood frequencies	139
3.13	Bloodpool signal magnitude over the cardiac cycle for different blackblood frequencies	140
3.14	Bipolar velocity encoding gradient	142
3.15	Example Cartesian, radial and spiral trajectories	152
3.16	Spiral readout	156
3.17	The effect of spiral duration on off resonance artefacts	158
3.18	The reconstruction pipelines	161
3.19	The retrospective reconstruction algorithm	164

3.20	GRAPPA reconstruction	169
3.21	Conjugate Gradient SENSE reconstruction	172
3.22	Screenshot of the GUI during analysis	175
4.1	Example navigator images	184
4.2	Global velocity-time curves for all ten volunteers.	185
4.3	Normalised global velocity-time curves for all ten volunteers. . .	186
4.4	Mean $\pm$ SD peak and time-to-peak velocity values	187
4.5	Regional velocity-time curves for one volunteer	191
4.6	Regional longitudinal, radial and circumferential velocity-time curves in the mid slice for all volunteers	193
4.7	Longitudinal colour overlays from a single volunteer	194
4.8	Radial colour overlays from a single volunteer	195
4.9	Circumferential colour overlays from a single volunteer	195
4.10	Colour plots for average velocities over the subjects	196
4.11	Longitudinal colour plots for three individual volunteers	198
4.12	Radial colour plots for three individual volunteers	199
4.13	Circumferential colour plots for three individual volunteers . . .	200
4.14	Global background offsets for all ten volunteers	203
4.15	Through plane background offsets	204
4.16	In plane background offsets	205
4.17	Bland-Altman plots for peak velocity values in the basal slice . .	207
4.18	Bland-Altman plots for peak velocity values in the mid slice . . .	208
4.19	Bland-Altman plots for peak velocity values in the apical slice . .	208
4.20	Bland-Altman plots for TTP longitudinal values for the two mea- surements in the mid slice in all volunteers	209
4.21	Bland-Altman plots for TTP velocity values in the basal slice . .	210
4.22	Bland-Altman plots for TTP velocity values in the mid slice . . .	211
4.23	Bland-Altman plots for TTP velocity values in the apical slice . .	211
4.24	Longitudinal RV velocity-time curves for all volunteers	212

4.25 Average Peak and TTP values for LV and RV. Mean $\pm$ SD values are shown for all parameters.	214
4.26 Examples of heart rate variation in three volunteers	218
5.1 Example images	227
5.2 R2 velocity time curves	228
5.3 R3 velocity time curves	229
5.4 Mean peak and TTP velocity values for R2 and R3	230
5.5 Regional velocity-time curves in the 6 mid slice regions for all volunteers	233
5.6 Longitudinal colour overlays	234
5.7 Radial colour overlays	234
5.8 Circumferential colour overlays	235
5.9 Colourplots averaged over all volunteers	236
5.10 Longitudinal colourplots for three volunteers	237
5.11 Radial colourplots for three volunteers	238
5.12 Circumferential colourplots for three volunteers	239
5.13 Background offsets over the cardiac cycle	241
5.14 Regional background offsets in the Z direction.	242
5.15 Regional background offsets in X and Y	243
5.16 Velocity time curves from a stack of nine slices acquired in two volunteers	244
5.17 Mean $\pm$ SD values for R2, R3 and HighRes acquisitions	245
5.18 Bland Altman plots for basal peak velocities	247
5.19 Bland Altman plots for mid slice peak velocities	248
5.20 Bland Altman plots for apical slice peak velocities	249
5.21 Bland Altman plots for apical slice TTP velocities	250
5.22 Bland Altman plots for the mid slice TTP velocities	251
5.23 Bland Altman plots for apical slice TTP velocities	252
5.24 Longitudinal RV velocity-time curves in all volunteers	253

5.25	Average Peak and TTP values for LV and RV	254
6.1	The simulated phantom used for validation	262
6.2	Simulated phase images for geometric series	264
6.3	Simulated phase images for random series	265
6.4	The two input curves used for simulations.	267
6.5	Schematic showing how the simulations are carried out	269
6.6	The effect of 0 to 3 missed triggers on the peaks curve for various heart rates.	272
6.7	Effect of missed triggers on real data curve	273
6.8	Missed triggers for <i>in vivo</i> vs simulated data	275
6.9	Effect of linear stretching on the peaks curve	277
6.10	Effect of linear stretching on real data curve	278
6.11	Effect of stretching diastole only on the peaks curve	280
6.12	Effect of stretching diastole only on real data curve	281
6.13	The effect of double scale stretching on the peaks curve	284
6.14	The effect of double scale stretching on the real data curve	285
6.15	Method of splitting cycle based on diastolic intervals	286
6.16	The effect of stretching based on diastolic intervals on the peaks curve	288
6.17	The effect of stretching based on diastolic intervals on the real data curve	289
7.1	Possible segmentation of stationary tissue in a single volunteer . .	296
7.2	Example modelling results compared with phantom background measurements	297
7.3	Example strain rate plots	301
7.4	Example HCM colourplots	304
7.5	Peak and TTP values for DCM patients and healthy volunteers . .	305
7.6	Colourmaps acquired in two DCM patients compared with a healthy volunteer	306

List of Tables

2.1	Comparison of tagging with DENSE and SENC results	98
2.2	Comparison of the advantages and disadvantages of the four MR techniques	114
3.1	Ratio of maximum bloodpool signal with different blackblood frequencies to the maximum signal with no blood suppression. .	140
3.2	Parameters for spiral design	158
4.1	Navigator sequence details	180
4.2	Peak and TTP mean $\pm$ SD values in all three slices	190
4.3	Transmural peak velocities in all three slices	202
4.4	Reproducibility of Peak and TTP measurements	206
4.5	Intra-study reproducibilities for the mid slice	212
4.6	Peak and TTP mean $\pm$ SD values in the RV	213
4.7	Reproducibility of peak and TTP mean $\pm$ SD values in the mid slice of the RV	213
5.1	Breath-hold sequence details	224
5.2	Peak and time to peak values for R2 and R3 acquisitions	231
5.3	Transmural peak velocities in all three slices. Any significant differences between layers are also shown in the final two columns.	240
5.4	Statistical comparison of measurements made with the different sequences	246
5.5	Peak and TTP mean $\pm$ SD values in the RV	253

6.1	Effect of missed triggers on peaks curve	271
6.2	Effect of missed triggers on real data peaks	274
6.3	Effect of linear stretching on the peaks curve	277
6.4	Effect of linear stretching on real data curve	278
6.5	Effect of stretching diastole only on the peaks curve	280
6.6	Effect of stretching diastole only on real data curve	281
6.7	The effect of double scale stretching on peak velocities in the peaks curve	284
6.8	The effect of double scale stretching on the peak velocities mea- sured with the real data curve	285
6.9	The effect of stretching based on diastolic intervals on the peak velocities of the peaks curve	288
6.10	The effect of stretching based on diastolic intervals on the real data curve	289
7.1	Peak velocities in DCM patients	305

Chapter 1

Background

1.1 Cardiac Anatomy and function

1.1.1 Overview

The human heart is a muscular organ, about the size of a fist and weighing 250-350 grams. It has a complex internal structure (see Figure 1.1) and functions as an extremely stable pump, capable of beating 2 to 3 billion times within a normal lifetime.

The heart is split into two sides, referred to as left and right. The muscular left heart pumps blood at high pressure, supplying the whole body with oxygen and nutrients. Meanwhile the right heart works at much lower pressures allowing the blood to pick up oxygen as it passes through the lungs before returning to the left side. Each half of the heart is further divided into an atrium and a ventricle. The atria act as entrance halls to the heart, where the blood accumulates until the atrio-ventricular valves (tricuspid in the right heart, mitral in the left) open, admitting it into the pumping ventricles.

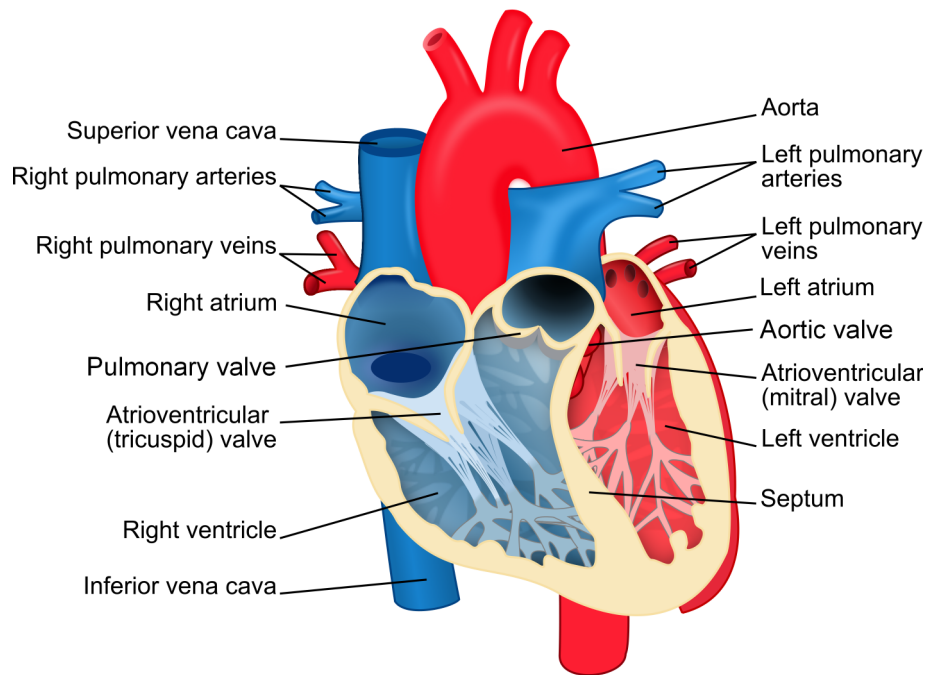


Figure 1.1: Diagram of heart anatomy (en.wikipedia.org/wiki/File:Heart_diagram-en.svg)

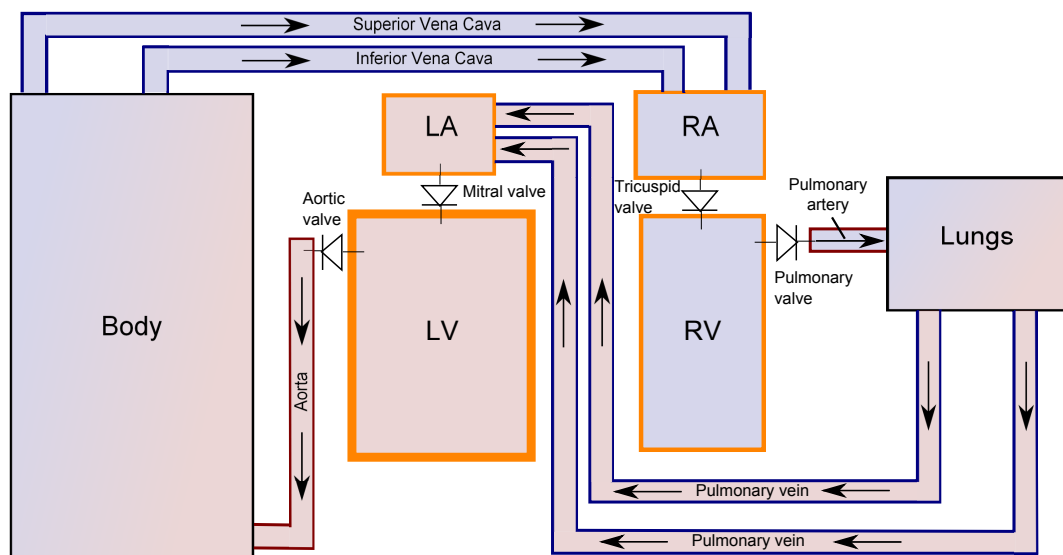


Figure 1.2: Schematic diagram showing the blood flow through the heart. LV = left ventricle, RV = right ventricle, LA = left atrium, RA = right atrium.

In total there are four valves found within the heart which are all vital to its function - without them the heart would not be able to produce pressure and hence no blood would be pumped. The valves work passively, the pressure of blood in one or the other direction working to open or close them as necessary. The tricuspid and mitral valves separate the right and left atria from their respective ventricles, opening as the ventricles relax (to allow the entrance of fresh blood ready to be pumped in the next contraction) and then closing as the ventricles contract (stopping the blood from returning into the atria). As the tricuspid and mitral valves close, the pulmonary and aortic valves open, directing the blood from the right ventricle (RV) into the pulmonary artery (which carries it to the lungs) and from the left ventricle (LV) into the aorta (from which it is distributed around the body). A schematic diagram showing the path of blood through the circulatory system is shown in Figure 1.2. In order to pump the blood around this path, the heart has evolved a complicated muscle structure, which is described in the following section.

1.1.2 Muscle structure

1.1.2.1 Myocytes

Muscle is composed of cells known as myocytes which contract in a single direction (see Figure 1.3). In compacted muscle within the heart, these myocytes are collected into muscle fibres, with all myocytes within a fibre having a similar orientation. The contraction and relaxation of myocytes is driven by their polarisation and depolarisation.

The polarisation of cells is determined by the concentration of positive ions within them. This is in turn controlled by ion pumps (which actively remove specific ions from the cell), and ion channels in the cell membrane (which can selectively allow specific ions to pass into, or out of, the cell and which can

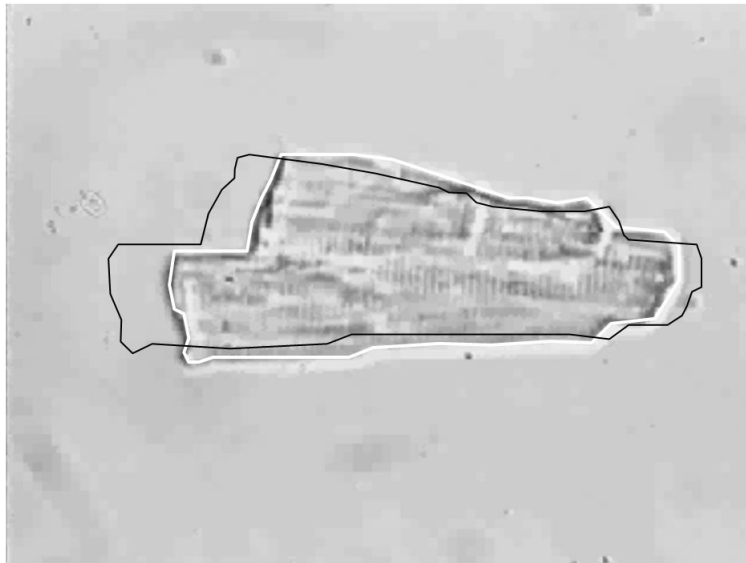


Figure 1.3: A single, contracted, myocyte (uncontracted outline shown in black). Myocytes contract in a single direction (here left to right) while simultaneously thickening in the other directions. In this case the cell contracts by around 14% while counter thickening by around 7% of its diameter (from Professor Sian Harding, Imperial College).

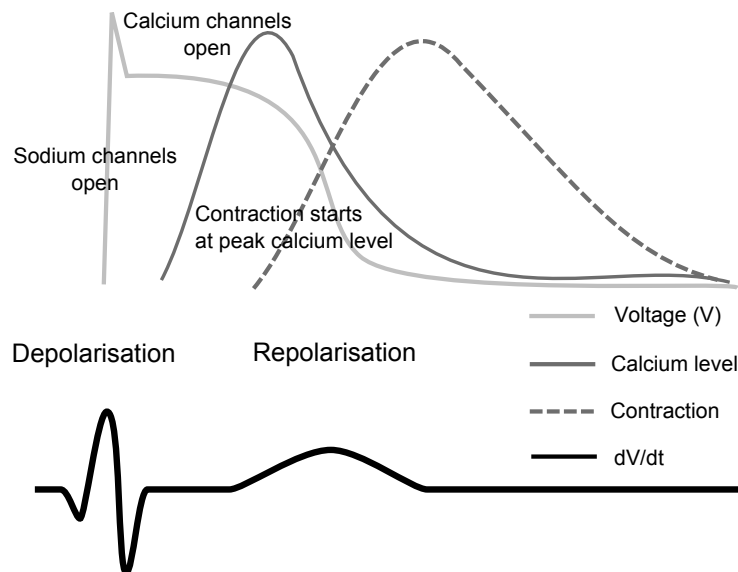


Figure 1.4: Diagram showing voltage across cell membranes, calcium levels and myocyte contraction through the cardiac cycle.

be open or closed depending on the voltage across the cell membrane). The ions involved in the polarisation of cells are sodium (Na^+), calcium (Ca^{2+}) and potassium (K^+).

At rest Na^+ and Ca^{2+} have a greater concentration outside the cell than inside, whereas for K^+ the opposite is true. This causes a resting voltage of -80 to -90mV across the cell membrane. At resting voltage levels, the K^+ channels are open, allowing K^+ ions to move across the cell membrane, while ion pumps remove Na^+ and Ca^{2+} from the cell. Two opposing forces act on the potassium ions: the electrical repulsion of other positively charged ions outside the cell pushes K^+ ions into the cell, while the higher concentration of K^+ inside the cell forms a concentration gradient which acts to repel incoming K^+ ions. In normal ventricular cells, a state of K^+ equilibrium is reached at resting voltage, which persists until an external stimulus is provided.

At certain sites within the heart there exist pacing cells in which the voltage slowly increases (the mechanism of this increase is not fully understood). When the voltage in these cells reaches -70mV the sodium channels open, leading to rapid influx of Na^+ into the cell. This influx increases the voltage further until the calcium channels also open. This process is known as depolarisation. As well as changing the voltage in the cell, the calcium ions drive the cell contraction. The increased level of positive calcium and sodium within the cell changes the potassium equilibrium level, forcing K^+ ions out of the cell. After contraction the calcium and sodium channels close again and the pumps begin removing Na^+ and Ca^{2+} from inside the cell, while the potassium slowly returns into the cell - this is known as re-polarisation. The timing of this process can be seen in Figure 1.4.

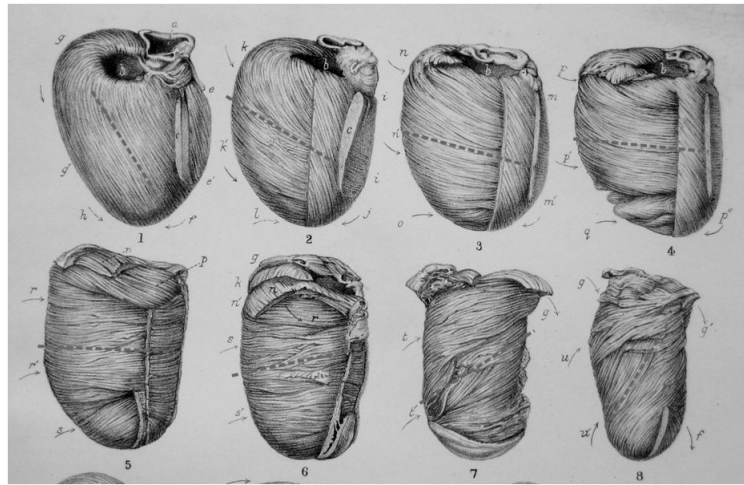


Figure 1.5: Detailed drawings of the dissection of an ovine left ventricle. As layers of muscle are stripped away, the general orientation of muscle fibres can be seen to change (dotted lines). From Pettigrew (1864) (<http://www.jstor.org/stable/108877?seq=57>) - dotted lines added.

1.1.2.2 Left ventricle

The LV is the main pumping chamber of the heart and therefore has the thickest walls (around 8 to 10 mm). It has an approximately circular cross section which is largest at base and reduces towards the apex. The walls are mostly made of compacted muscle, with a small amount of trabeculation (fibrous muscle tissue separate from the myocardial wall). To produce the complicated motion of the heart from muscle fibres contracting in a single direction requires a complicated fibre organisation. As can be seen in Figure 1.5, the fibres are effectively arranged in a sheet which wraps around the LV forming several layers of muscle - the outer epicardium, the thick myocardium and the inner epicardium. In a short axis view, the direction of general fibre orientation changes from around -70° at epicardium to $+70^\circ$ at endocardium (angles measured relative to the circumferential axis) (Sands et al., 2008). It is this arrangement which allows the LV to contract as it does purely from the shortening of myocytes. The inner and outer layers provide shortening in a longitudinal direction, whilst the mid-

dle layer allows simultaneous circumferential shortening, reducing the cross sectional area of the LV cavity.

1.1.2.3 Right ventricle

The RV works at much lower pressures than the LV and hence the compacted muscle layer in the RV free wall is much thinner than in the LV (around 4mm wall thickness), with a larger amount of trabeculated muscle. Although its geometry is more asymmetrical than the left ventricle (it forms a crescent moon shape in cross section) it similarly has its largest cross section at base.

The structure of the left and right ventricles as described above allows the heart to pump blood efficiently. However the timing of the contraction of the chambers of the heart is also vital to its performance and is explained in the following section.

1.1.3 Function

Figure 1.6 shows a Wiggers diagram which relates the timing of pressure, volume and electrical changes through the heart cycle. The time evolutions of aortic, atrial, and ventricular pressure, ventricular volume, the ECG and the phonocardiogram (recording of heart sounds) are shown and the various stages of the heart cycle are marked. Systole and diastole are broadly defined as the periods of LV contraction and relaxation respectively. The shapes of the curves are explained in the following sections.

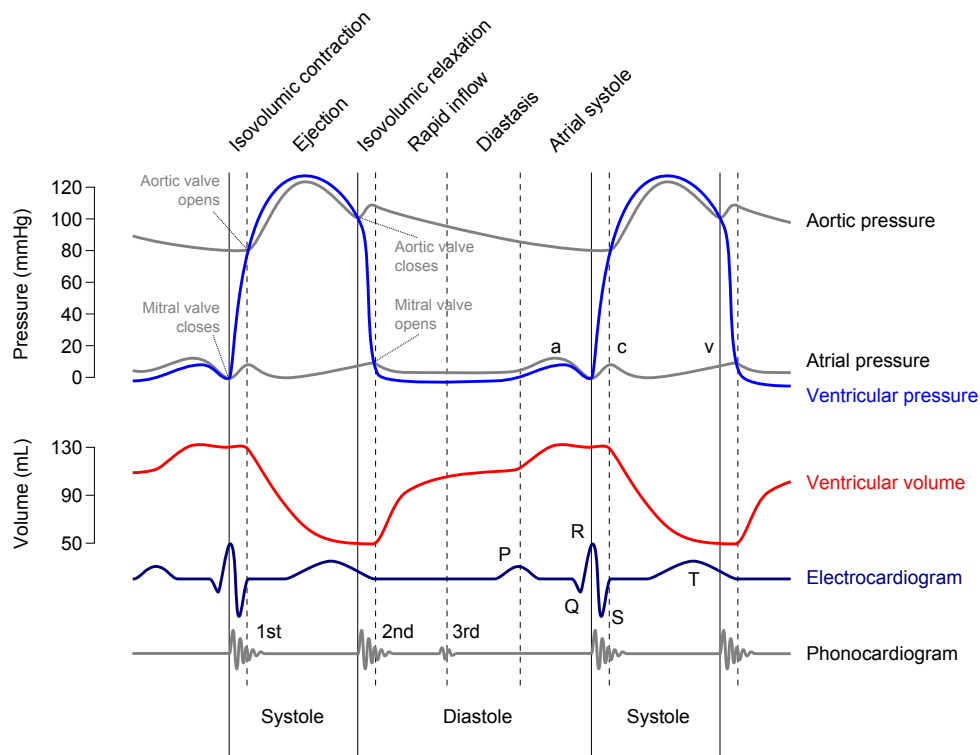


Figure 1.6: Wiggers Diagram showing the time evolution of pressure, volume, electrocardiogram (ECG) and phonocardiogram through the cardiac cycle (en.wikipedia.org/wiki/File:Wiggers_Diagram.svg)

1.1.3.1 Electrocardiogram

The electrocardiogram measures the electrical activity of the heart muscle using electrodes placed on the skin. The ECG detects and amplifies the electrical changes that occur on the skin due to the polarisation and depolarisation of myocytes (see Section 1.1.2.1) within the heart muscle during the heart cycle.

The depolarisation of pacing cells causes an injection of ions into neighbouring cells, providing the external stimulus for normal ventricular cells to depolarise and contract. This sets off a chain reaction, causing a wave of polarisation and contraction throughout the heart muscle. However a contraction which simply

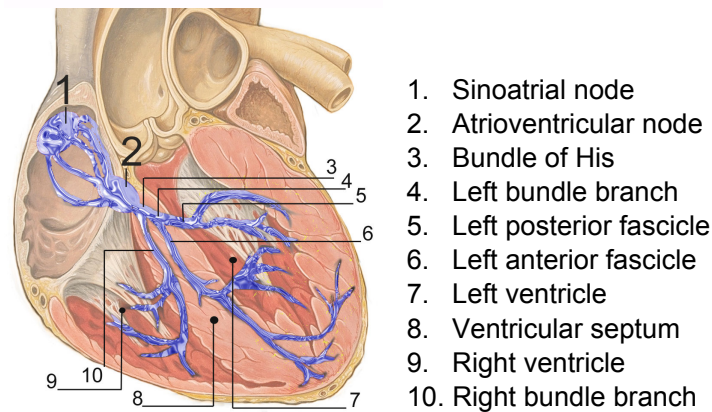


Figure 1.7: Conduction system in the heart (modified from http://en.wikipedia.org/wiki/File:RLS_12blauLeg.png)

spreads symmetrically outwards from pacing sites would not allow the heart to pump effectively. A series of conduction pathways within the heart transport the pacing signal quickly from one area of the heart to another, allowing the heart to transfer blood between its chambers and around the body efficiently.

The primary pacemaker of the heart is an area with a high concentration of pacing cells known as the sinoatrial node. As can be seen in Figure 1.7, it is located in the right atrium, explaining why the atria contract before the ventricles. A conduction pathway transfers the signal to the atrioventricular node, which then delays the signal before passing it on through the bundle of His into the right and left bundle branches (the left bundle branch further splits into anterior and posterior fascicles) and eventually into the myocardium where waves of contraction are initiated.

This sequence of depolarisation and re-polarisation across the whole heart causes the changes in electrical activity which are measured on the surface of the body

by the ECG. The bottom of Figure 1.4 shows the time derivative of the voltage across a single cell membrane. Comparing with the ECG trace in Figure 1.6, many similar features can be seen. Specifically the strong QRS complex (as marked on Figure 1.6) is caused by the rapid depolarisation of the many ventricular cells, while their slower re-polarisation causes the smaller T-wave. The smaller atria contract before the ventricles, causing the small P-wave peak before the QRS complex. The re-polarisation of the atria is hidden by the stronger QRS complex. The timing and magnitude of these features can be used to infer a lot about how the heart is functioning globally.

1.1.3.2 Phonocardiogram

A phonocardiogram measures the sounds made by the heart. As can be seen in Figure 1.6 the two main heart sounds coincide with the closing of the mitral and aortic valves. The presence of abnormal heart sounds can indicate valvular problems, while comparison with simultaneous ECG measurement can provide other useful information about global heart function.

1.1.3.3 Mechanics

The pressures and volume shown in Figure 1.6 are closely linked with the mechanics of the contracting chambers of the heart. The heartbeat is generally considered to start at the beginning of ventricular systole, however linking with the above discussion of electrophysiology it is clearer to start at the initial pacing of the heart which occurs just before atrial systole (marked P on the ECG trace). Contraction is triggered from the sinoatrial node which is situated at the top of the right atrium (see Figure 1.7) so the atria contract first, causing the P wave in the ECG and forcing blood into the ventricles. Since the aortic and pulmonary valves are closed, this increases the volume in the ventricles. The contraction of

the left atrium accounts for about 20-30% of left ventricular filling in healthy hearts (Leong et al., 2010). While the atria contract the propagation of the electrical signal is delayed at the atrioventricular node which allows the blood to flow into the ventricles before they start to contract. This accounts for the flat section of the ECG between P and Q.

When the ventricles begin to contract the mitral and tricuspid valves are forced closed by the backwards pressure of the blood, causing the first heart sound on the phonocardiogram. This marks the beginning of ventricular systole (often referred to simply as systole). There is a short period of isovolumic contraction during which the pressure in the ventricles sharply increases until the aortic and pulmonary valves are forced open and then blood can escape. The ventricular contraction occurs earliest at the apex and in the longitudinal direction, with the base being pulled down towards the apex. Radial contraction also occurs in the LV, reducing the cross-sectional area and maximising the amount of blood that is ejected.

Once the ventricles have contracted, the aortic and pulmonary valves close, leading to the second heart sound, and the beginning of ventricular diastole. Meanwhile the ventricular myocytes are re-polarising and relaxing, leading to the T wave on the ECG. A short period of isovolumic relaxation occurs during which the pressure in the ventricles drops sharply until the pressure in the atria (which are filling with blood delivered from the pulmonary veins and venae cavae) is enough to force open the mitral and tricuspid valves. Then follows a period of rapid inflow of blood into the ventricles. During this rapid inflow, the ventricles relax. Again the majority of the relaxation occurs in the longitudinal direction and is stronger at base than at apex. The cross section of the ventricles increases and the left ventricle also twists with opposite directions of circumferential motion occurring at base and apex.

Once the ventricles have relaxed the heart is primed for the next heart beat to

begin and a period of rest occurs which is known as diastasis. Diastasis lasts until the next heart beat is stimulated by the pacing cells in the sinoatrial node, at which point the process begins again.

1.1.4 The importance of measuring cardiac function

The normal functioning of the heart is a complicated process with electrophysiology, muscle structure, anatomy, blood flow and valve mechanics all having vital roles to play in order for the heart to pump effectively. It is therefore not surprising that heart disease is very common. In fact diseases of the heart and circulatory system are the main cause of death in the UK, accounting for almost 191000 deaths each year - one in three of all deaths. It is also the most common cause of premature death (death before the age of 75), accounting for 28% of those in men and 20% in women. As well as the obvious human cost of heart disease, it also has major economic consequences. In the UK in 2006, heart disease cost the NHS £14.4 billion. This is without taking into account the economic cost of illness in those of working age. The above statistics are from the British Heart Foundation coronary heart disease statistics report, 2010 (Scarborough et al., 2010).

The benefits of being able to detect abnormal heart function are obvious, potentially allowing diagnosis and follow up of many cardiac diseases. Several parameters of heart function are commonly used to make an assessment and they are each discussed in detail in the next section.

1.2 Global measures of cardiac function

Global ventricular function is commonly assessed by measuring left ventricular volumes. There are several methods available to do this. Some methods

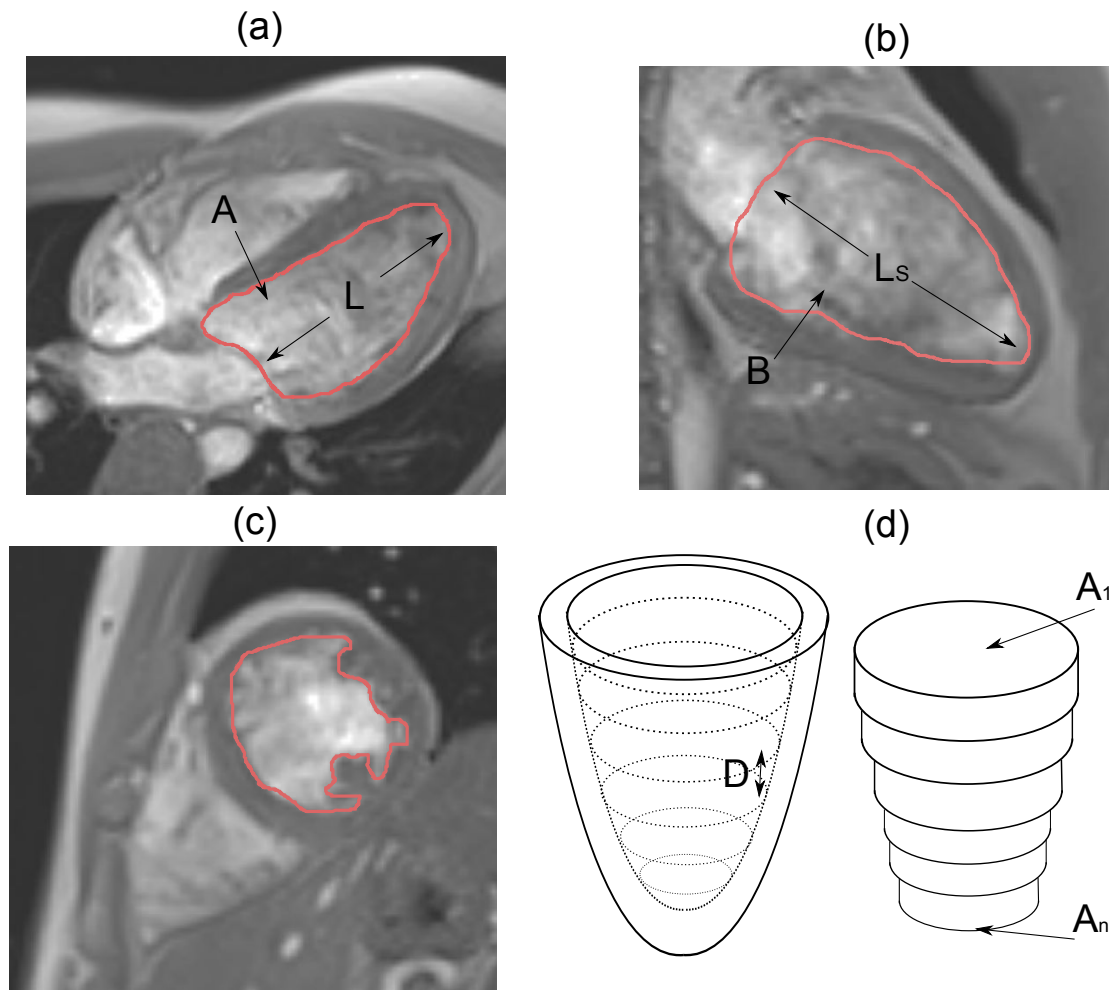


Figure 1.8: Dimensions used to calculate left ventricular volumes: (a) Horizontal long axis (four chamber) view. (b) Vertical long axis (two chamber) view. (c) Short axis view. (d) Rule of disks.

make large assumptions about ventricular geometry, thereby approximating the volume with relatively few measurements, while others use fewer geometrical assumptions to obtain more accurate volume measurements, but require more initial measurements and hence are more time consuming. However these more time consuming methods will be much more accurate, particularly in abnormal hearts where geometric assumptions may be less reliable.

A very simple method of estimating LV volume is to cube the diameter of the ventricle imaged in a short axis plane (effectively assuming a cube-shaped cavity). While this is not very accurate as a measure of absolute volume, it requires only a single measurement and in normal hearts will give a reasonable estimation. A more accurate assumption is to model the LV as an ellipsoid. In this case, the volume can be estimated from a single four chamber view (see Figure 1.8 (a)). The cross sectional area (A) can be traced from this view and the length of the ventricle (L) can be measured. The volume (V) can then be calculated as

$$V = \frac{0.85 \times A^2}{L}. \quad (1.1)$$

This approximation can be made more accurate by acquiring both vertical and horizontal long axis planes (Figure 1.8 (a) and (b)). The two perpendicular areas (A and B) are measured and the smaller of the two ventricular lengths (L_s) can then be used in the formula

$$V = \frac{0.85 \times A \times B}{L_s} \quad (1.2)$$

These equations are approximations to the volume of an ellipsoid which in general is

$$V = \frac{4}{3}\pi abc \quad (1.3)$$

where a, b and c are the three axes of the ellipsoid (we will treat c as the common minor axis i.e. $c = \frac{L}{2}$). This can be rewritten

$$V = \frac{4}{3} \frac{(\pi ab)(\pi bc)}{\pi b} \quad (1.4)$$

and since πpq is the area of an ellipse with axes p and q we can rewrite this as

$$V = \frac{4}{3} \frac{A \times B}{\pi \frac{L}{2}} = \frac{8}{3\pi} \frac{A \times B}{L} \quad (1.5)$$

so

$$V \approx \frac{0.85 \times A \times B}{L}. \quad (1.6)$$

as before.

Finally, the rule of discs can be used to measure ventricular volumes (Figure 1.8 (c) and (d)). A stack of n contiguous short axis slices of slice thickness D covering the LV are needed for this calculation. The area of the i th slice (A_i) is measured and the volume is then calculated by

$$V = D \times \sum_{i=1}^n A_i \quad (1.7)$$

The accuracy of this calculation is determined by the slice thickness (or the number of slices acquired) and how well the endocardial borders are defined (similarly for the other methods). The advantage of this technique is that no geometric assumptions are made and so it can also be applied to abnormal LVs or to the asymmetrical RV. It is possible to use Simpson's rule just using a long and a short axis view (bi-plane Simpson's rule) although this assumes an ellipsoidal cross section and so is less accurate than using a stack of slices. While determination of volumes using Simpson's rule or volumetric imaging has been shown to be both highly accurate and highly reproducible (Sakuma et al., 1993), studies comparing the quicker methods described above with more comprehensive methods such as Simpson's rule have found poor agreement (Chuang et al., 2000). For this reason, Simpson's rule from a stack of slices is widely used to

assess ventricular volumes using Magnetic Resonance Imaging (MRI) both in research and in clinical practice.

If the blood pool volume is measured both at end systole and end diastole, the stroke volume can be calculated as the difference between the two, estimating the amount of blood which is ejected in each heartbeat. Similarly the ejection fraction can be calculated as the stroke volume divided by the maximum volume of each ventricle. LV volume can be used to provide information for selection of therapies and time of intervention (Bonow et al., 1991; Carabello, 1997; Pfeffer et al., 1992), and in combination with ejection fraction can be used to predict prognosis in ischemic and non-ischemic cardiomyopathies (Cohn et al., 1993; Pfeffer et al., 1992; Wong et al., 1993). Ejection fraction is the most commonly used parameter measured during an echocardiogram (Lang et al., 2005), showing that it is often used as an early indicator for cardiac dysfunction.

By simultaneously measuring the endo- and epicardial borders in a stack of contiguous slices, the ventricular mass can be estimated. This helps to assess the health of the myocardium, particularly in hypertrophic cardiomyopathy (HCM) where ventricular mass has been identified as a predictor of cardiac mortality and morbidity (Lorell and Carabello, 2000).

For each of the above parameters of global ventricular function there are several imaging modalities which can measure them with various degrees of accuracy. These modalities and the measurements that they can make are described below.

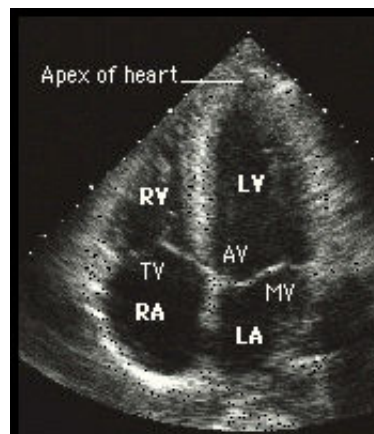


Figure 1.9: Example echocardiography apical view (en.wikipedia.org/wiki/File:Apical_4_chamber_view.gif). The valves and chambers of the heart are labelled. LV = left ventricle, RV = right ventricle, LA = left atrium, RA = right atrium, MV = mitral valve, AV = aortic valve, TV = tricuspid valve.

1.3 Techniques to measure global cardiac function

1.3.1 Echocardiographic techniques

The basic concept which underpins all echocardiographic techniques is the reflection of sound waves from matter. High frequency pressure waves are produced in a transducer (the frequency of the waves is above 20kHz, which is why the technique is also known as ultrasound) and reflect from the heart walls or blood, back to the transducer which detects them. Either a single transducer is used to scan a single line through the body (A-mode) or a linear array is used to image a 2D plane (B-mode) (see Figure 1.9).

The time between the emission and detection of the waves is used to infer the position of the various reflective tissues and hence build up a picture of

anatomy. A- and B-mode echoes can be used in combination with M-mode (motion mode) in which a series of pulses are emitted and received in quick succession to image motion in real time (high temporal resolution is possible with frame rates of up to 100/second). Spatial resolution is determined separately in the axial and lateral directions. Axial resolution is determined by the wavelength of the acoustic waves whereas lateral resolution is determined by the width of the beam. Both resolutions are typically of the order of 1mm.

Echocardiographic, or cardiac ultrasound, equipment is relatively cheap and portable (recently a smartphone compatible ultrasound device was approved by the FDA for use in the US), and is therefore a widely available imaging modality. No ionising radiation is used so multiple examinations can be performed, making it ideal for monitoring disease. However the technique is limited by the need for clear acoustic windows (ultrasound cannot image through bone) which leads to poor image quality in around 10% of patients (Sicari et al., 2008). Comprehensive assessment of the entire heart is also not possible for this reason.

Echocardiography can be used to measure ventricular volumes with some of the methods described in Section 1.2. As mentioned above, the accuracy of the measurement depends on the method used to calculate volumes as well as the modality used for imaging. For example the ejection fraction measured in a cohort of 52 patients with the cubic assumption with A-mode was $39 \pm 22\%$, whereas for the same volunteers using B-mode and bi-plane Simpson's rule ejection fraction (EF) was $31 \pm 5\%$ (Bellenger et al., 2000).

In general the accuracy of echocardiography measurements of ventricular volumes is not good, with poor delineation of endocardial borders leading to underestimation of volumes (Gutierrez-Chico et al., 2005). More recently it has become possible to acquire three dimensional images using echocardiography (allowing the use of Simpson's rule from a stack of slices). A 2D matrix of transducers can be used in an obvious extension of the linear array used to

acquire 2D images. In a systematic review and meta analysis assessing the performance of three-dimensional echo-cardiography to measure ventricular volumes and ejection fraction (Dorosz et al., 2012) the pooled bias for end systolic volume, end diastolic volume and ejection fraction were $-19 \pm 34.2\text{ml}$, $-10.1 \pm 29.7\text{ml}$ and $-0.6 \pm 11.8\%$ for three-dimensional echo and $-48.2 \pm 55.9\text{ml}$, $-27.7 \pm 45.7\text{ml}$ and $0.1 \pm 13.9\%$ for two dimensional echo respectively. Three dimensional echocardiography is therefore significantly more accurate than two-dimensional echocardiography for measuring volumes (when compared with MRI) and more precise for volumes and ejection fractions. However it still has wide limits of agreement and consistently underestimates ventricular volumes.

Similar conclusions can be drawn about left ventricular mass measurements with echocardiography. M-mode measurements of LV mass are systematically overestimated and have wide limits of agreement, while measurements made with a three dimensional technique were much more accurate, with intraobserver (two assessments by the same observer, one month apart), interobserver (two assessments by different observers, one month apart) and test-retest (two assessments by the same observer, less than 24 hours apart) variabilities of 9%, 12% and 6% respectively (Takeuchi et al., 2008).

1.3.1.1 Tissue Doppler Imaging

A technique within echocardiography which is capable of assessing global LV function is tissue Doppler imaging (TDI). When waves reflect from a moving object, their frequency is changed. In TDI, the frequency of reflected waves (f) is measured and used to infer the velocity of the blood or tissue being imaged (v) using the formula for the Doppler effect

$$v = c \left(\frac{f_0}{f} - 1 \right) \quad (1.8)$$

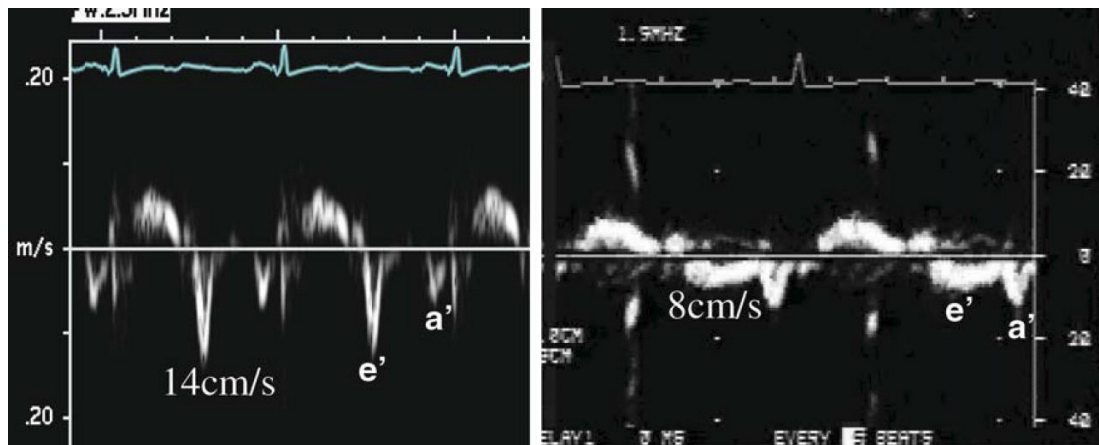


Figure 1.10: Mitral annulus velocities measured with TDI. From Nagueh et al. (2009). On the left a healthy example is shown with peak early diastolic velocity (e') of 14cm/s, whereas this peak is lowered in disease on the right, also changing the ratio e'/a' .

where c is the velocity of the sound waves and f_0 is the emitted frequency. There are two types of TDI, known as continuous and pulsed. Continuous wave Doppler has the transducer constantly emitting and receiving waves, allowing very high temporal resolution. In contrast by sending out short bursts of ultrasound waves (pulse wave Doppler), a picture of anatomy can be built up using the fact that waves reflected far away from the transducer will be detected later than waves reflected close to the transducer, as with normal M-mode echocardiography.

As well as the disadvantages inherent with all echocardiographic techniques, TDI only measures the component of velocity aligned with the ultrasound beam and so is highly dependent on the availability of acoustic windows. For continuous wave Doppler the received signal is a sum of all the reflected signals within the beam and so no depth information can be determined. This is not the case for pulse wave Doppler, a major advantage. Pulse wave TDI typically has a temporal resolution of 3-4ms.

As well as for measuring blood flow velocities, pulsed wave TDI can be used for measuring the velocity of myocardium as it moves through the cardiac cycle. The velocity of the mitral annulus is used to assess global ventricular function (Nagueh et al., 2009). Peak systolic (S), diastolic (D) and late diastolic/atrial systolic (AS) mitral velocities can be measured, as well as the ratio of diastolic and atrial diastolic peak velocities (see Figure 1.10). Mitral annular velocities give information about LV relaxation and can provide information which allows the prediction of LV filling pressure (Van de Veire et al., 2008).

1.3.1.2 Speckle tracking

A recent development in echocardiography is speckle tracking which uses the characteristic interference patterns caused by the acoustic waves to track tissue through time (Leitman et al., 2004). While this technique was developed to measure regional function (see Section 1.5.1.2), the fact that tissue can automatically be tracked through time has lead to interest in its ability to also assess global function without time consuming manual segmentation. Another advantage of this technique is that the speckles caused by the interference are properties of the tissue being tracked, so that measurements made with speckle tracking are angle independent. Measurements of LV volumes and EF made with the technique have shown good correlation with MRI ($R=0.95$, 0.95 and 0.88 for end diastolic volume, end systolic volume and ejection fraction respectively) and with 3D echocardiography ($R = 0.95, 0.97$ and 0.92), although ejection fractions showed an 8% underestimation (Nishikage et al., 2009).

1.3.2 Nuclear Cardiology

Nuclear cardiology uses an injection of radioactive isotopes to assess function. Typically ECG gated acquisitions are carried out, imaging different portions

of the cardiac cycle over a period of five to ten minutes. Average blood pool images are then created for different parts of the cardiac cycle and volumes or ejection fractions are then calculated (typically 16 frames through the cardiac cycle are reconstructed). This is known as multigated acquisition (MUGA) or radionuclide ventriculography (RVG).

As well as the radioactive materials, a detector is needed, although mobile gamma cameras allow the use of nuclear cardiology at bedside. However, the use of ionising radiation means that repeated scanning is undesirable and since the volume of blood is measured directly, ventricular masses cannot be measured.

Despite the disadvantages, RVG is the most widely accepted method of assessing ejection fraction during cancer treatment (Altena et al., 2009) and reproducibility is better than both two dimensional echocardiography and three dimensional echocardiography (intra and inter observer variability for 2D echo was 6.4% and 10.4%, for 3D echo was 3.7% and 8.3% and for MUGA was 2.4 and 3.9% respectively) (de Geus-Oei et al., 2011).

Ventricular volumes and EF can also be measured with gated single photon emission computed tomography (SPECT). Technetium 99 is injected into the blood and can be imaged as it is taken up in the myocardium, providing measurements of perfusion. SPECT examinations are not carried out with the sole purpose of measuring ventricular volumes but ventricular volumes are measured as an adjunct to a perfusion scan (Manning and Pennell, 2010), showing very good reproducibility ($R=0.99$ for end diastolic and end systolic volumes) (Iskandrian et al., 1998). SPECT images are typically low resolution (around 1cm) and take a long time to acquire (15-20 minutes).

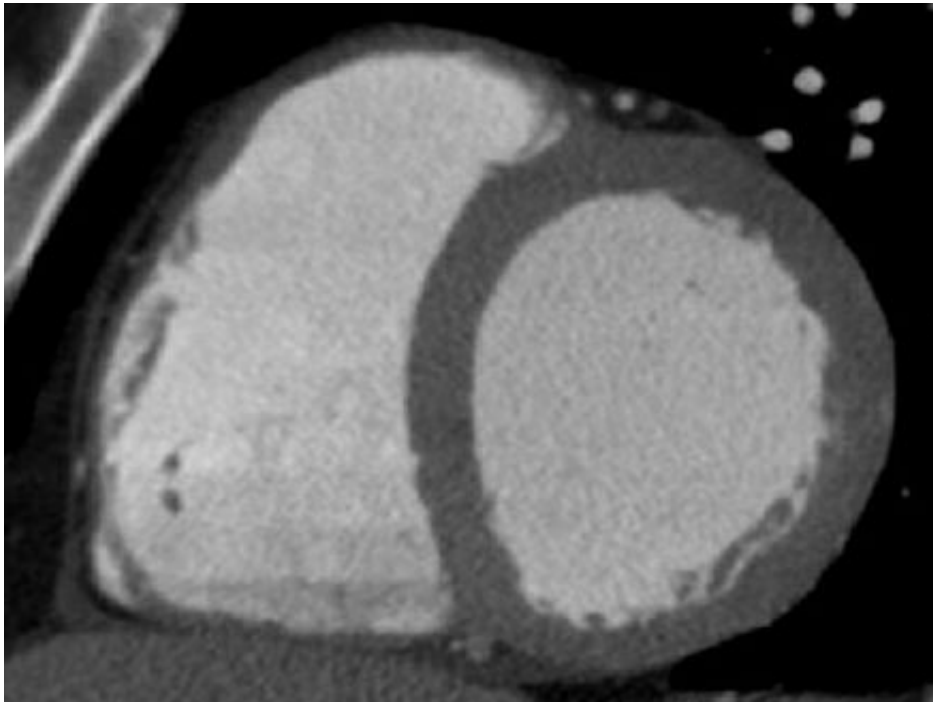


Figure 1.11: Example short axis CT reformat which can be used to measure volumes via Simpson's rule. From Orakzai et al. (2006).

1.3.3 Computed Tomography

Multi detector computed tomography (MDCT) uses a large series of X-ray images from various angles around a single axis to produce three dimensional image volumes (see Figure 1.11). Dynamic information is acquired although with low temporal resolution (around 100-300ms).

Computed tomography uses ionising radiation and potentially harmful contrast agents and so volumes are measured with this technique only for additional dynamic information when patients are undergoing coronary angiography. However as set out in an excellent review article, several studies have compared MDCT measurements of function with results from other modalities, and have assessed the reproducibility of the technique (Orakzai et al., 2006).

A strong correlation has been found in 52 patients for measurements of end-systolic volume, end-diastolic volume, ejection fraction and myocardial mass between MDCT and MRI ($R > 0.66$ for all, average differences 10.6ml, 15.1ml, 1.8% and 8.2g respectively) (Heuschmid et al., 2006) and good agreement was also found in another study of 50 patients ($1.1 \pm 8.6\text{ml}$ $R=0.99$, $-0.35 \pm 15.2\text{ml}$ $R=0.97$, $-1.2 \pm 4.6\%$ $R=0.96$ and $2.5 \pm 15.0\text{ml}$ $R=0.96$ respectively in 50 patients (Yamamuro et al., 2005)). Comparisons have also been made with echocardiography showing good agreement with 2D echo for measurements of ejection fraction ($R=0.96$, mean difference $-0.02 \pm 3.9\%$) in forty five patients with coronary disease (Schuijf et al., 2005).

Interobserver variability for measuring end-systolic volume, end diastolic volume, ejection fraction and myocardial mass was 7.0%, 6.9%, 5.7% and 9.3% respectively in forty one patients (Yamamuro et al., 2005). Since volumetric imaging is performed, reproducibility was still high in patients with LV dysfunction or dilatation where two dimensional techniques would potentially have to use inaccurate geometrical assumptions (Orakzai et al., 2006).

1.3.4 Magnetic Resonance

MRI uses the fact that hydrogen nuclei are spin $\frac{1}{2}$ particles and hence have magnetic moment

$$\mu = \frac{e}{2m} \mathbf{S} \quad (1.9)$$

where e is the charge on an electron, m is the mass of the hydrogen nucleus and $\mathbf{S}$ is the spin angular momentum. When an external magnetic field $\mathbf{B}$ is applied (field strength B_0), the spins align either parallel or anti-parallel with the field lines (spin up or spin down states). Since the parallel state has slightly lower energy, more align parallel than anti-parallel leading to a net magnetisa-

tion in the direction of the field. A semi classical picture is generally used to describe MRI within which the spin angular momentum causes a torque τ on the hydrogen atom

$$\tau = \mu \times \mathbf{B} \quad (1.10)$$

causing precession around the magnetic field direction at the Larmor frequency (ν)

$$\nu = \frac{\gamma B}{2\pi} \quad (1.11)$$

where γ is the gyromagnetic ratio ($\frac{e}{2m}$). The frequency of precession is proportional to the field strength so by applying additional magnetic field gradients, the frequency of precession can be made to be dependent on position in the scanner. By measuring the strength of signal with different frequencies of precession, the relative density of spins at different positions along a linear gradient can be inferred. In this way an image can be produced. With different combinations of linear gradients and radio-frequency pulses, the spins can be manipulated in many ways, allowing Magnetic Resonance (MR) the greatest flexibility and versatility of all the imaging modalities discussed. No ionising radiation is used which allows repeated scanning to be performed, and the technique is not limited by acoustic windows allowing comprehensive assessment of the entire heart.

In order to create an accurate image, a strong but highly homogeneous magnetic field is needed. An MR scanner capable of producing this field is large and expensive and so MR is not widely available or portable. MR collects data by moving through k-space, acquiring different spatial frequencies. This is a slow method of acquiring data which makes real time imaging difficult; unlike echocardiography, the majority of cine images acquired with MR are re-

constructed from data acquired over several heartbeats. The accuracy of measurements can therefore be affected by a variable heart rate. It also means that an MR examination tends to take longer than an equivalent echocardiography exam.

The accuracy of MRI measurements of ventricular volumes has been established for some time and MR is now considered the reference standard for measuring global cardiac function non-invasively. Simpson's rule applied to a high resolution stack of slices (0.8 x 0.8 x 10mm) acquired in 15 excised left ventricles showed excellent accuracy for measurements of volume ($R=0.997$) (Rehr et al., 1985) and similar accuracy has been shown in vivo (Longmore et al., 1985). The interstudy reproducibility is also excellent, as shown in a study of 20 healthy subjects, 20 patients with heart failure and 20 patients with hypertrophy where the coefficient of variabilities of end-systolic volume, ejection fraction and ventricular mass were significantly better than that of 2D echocardiography (4.4% to 9.2% vs 13.7% to 20.3%, $p < 0.001$ for end systolic volume, 2.4% to 7.3% vs 8.6% to 19.4%, $p < 0.001$ for ejection fraction, 2.8% to 4.8% vs 11.6% to 15.7% $p < 0.001$ for mass) with a trend for end diastolic volume (2.9% to 4.9% vs 5.5% to 10.5%, $p = 0.17$) (Grothues et al., 2002).

Because of the flexibility of MRI it can also be used to measure right ventricular volumes. Reproducibility of RV measurements from short axis slices is good (14.1% for end systolic volume, 6.2% for end-diastolic volume, 8.3% for ejection fraction and 8.7% for RV mass) (Grothues et al., 2004) which allows measurement of left and right ventricular volumes from a single dataset.

1.3.5 Limitations of global measures of cardiac function

Although global measures of cardiac function can clearly be affected by pathology, in the early stages of disease regional wall motion may be abnormal while

global function remains within the normal range. This could either be due to compensatory motion of other regions, or because the regional effect is too small to significantly alter global function.

For this reason, several of the above imaging modalities have been developed to measure regional heart function. This obviously requires higher spatial resolution than is necessary to estimate global function, and often complicated post processing is necessary. The parameters used to characterise regional wall motion are described in the following section.

1.4 Regional measures of cardiac function

Before discussing the assessment of regional wall motion it is necessary to describe how the myocardium of the left ventricle can be consistently split into separate regions.

1.4.1 Segmentation

In 2002 the American Heart Association (AHA) produced a scientific statement which aimed to provide a method for regional myocardial segmentation which could be applied across different imaging modalities (Cerqueira et al., 2002). The result was the 17 segment model of the LV which can be seen in Figure 1.12, along with a mid-ventricular short axis slice. This model splits the LV into three levels along the long axis (basal, mid and apical). The basal and mid levels are further split into 6 sections (1-6 and 7-12), whereas the smaller apical level is split into four (13-16). The 17th segment is the apical cap.

Segmentation of the RV is more difficult because of its asymmetric shape and the thinness of the free wall. Consequently there is as yet no corresponding

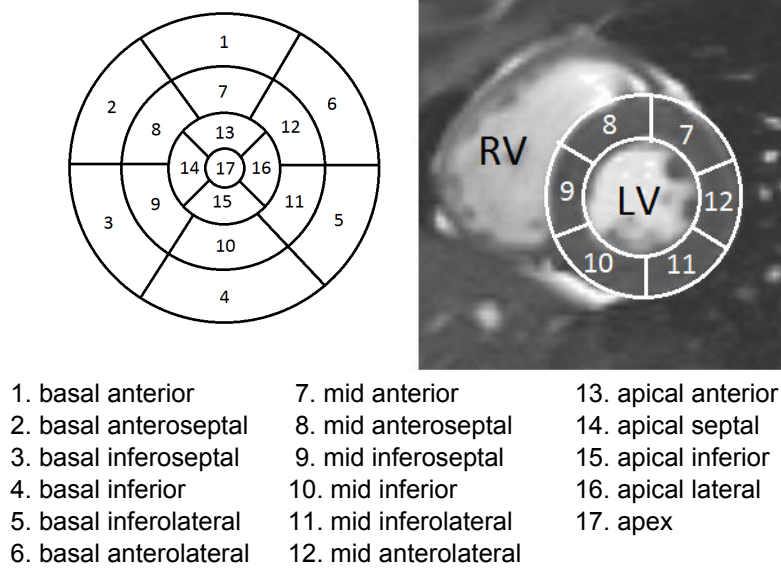


Figure 1.12: The AHA 17 segment model

scientific statement for segmentation of the RV.

1.4.2 Parameters

There are various qualitative and quantitative parameters which can be used to characterise motion. Regional function can be assessed qualitatively using wall motion scores. The motion of the myocardium in each segment can be compared visually with normal motion and areas of abnormal motion can be identified. In conjunction with a low dose of stress agent this can be used to detect viable myocardium (Dendale et al., 1995), while a high dose of agent can be used to detect ischemia (Nagel et al., 1999). However qualitative parameters are highly observer dependent and therefore not ideal for measuring function.

Quantitatively there are several parameters which can be measured directly. The most basic of these is tissue displacement which can be measured by techniques within echocardiography (speckle tracking) and MRI (tagging and DENSE).

Recently speckle tracking algorithms developed for echocardiography have also been applied to images acquired with MRI (feature tracking) (Maret et al., 2009) although it is not clear whether this is valid as the speckles which arise in echocardiography are not found in MRI. Velocities can also be measured directly both by echocardiography (Tissue Doppler Imaging) and MRI (phase velocity mapping), allowing regional measurements of peak and time to peak velocities which can characterise both healthy and diseased motion. With these parameters care must be taken to separate bulk motion from regional motion of the myocardium.

Strain and strain rate are derived quantitative parameters which can be used to analyse active contraction and relaxation of the myocardium. The definitions of strain and strain-rate are to be found in the following sections.

1.4.2.1 Strain

Strain is a measure of deformation and is defined as the fractional change in length of an object relative to its original length. Unlike displacement, strain measures relative motion between two areas of the myocardium and hence can distinguish between active and passive motion. It can be defined in either the Lagrangian or Eulerian frames of reference. In the Lagrangian frame of reference, one dimensional strain at time t ($E_L(t)$) is defined as

$$E_L(t) = \frac{L(t) - L(0)}{L(0)} \quad (1.12)$$

where $L(t)$ is the length of the object at time t and requires knowledge of the original length $L(0)$ which is constant over time. Alternatively, Eulerian (or natural) strain (E_E) can be defined as the integral of the instantaneous Eulerian strain (dE_E), i.e.

$$E_E(t) = \int dE_E(t) \quad (1.13)$$

where the instantaneous Eulerian strain is defined as the infinitesimally small amount of deformation occurring over an infinitesimally small time interval dt , i.e.

$$dE_E(t) = \frac{L(t + dt) - L(t)}{L(t)} \quad (1.14)$$

In this formulation, the reference length is the length at the time of measurement (which varies with the time of measurement). For Lagrangian strain, displacements are calculated at specific material points in the myocardium using the deforming myocardium itself as a reference, while for Eulerian strain the reference frame is fixed in space. Lagrangian strain represents the tissue strain at a specific location in the myocardium (at a material point) which moves as the heart contracts while Eulerian strain represents the tissue strain at a specific location in space.

The coordinate systems used are referred to as material and spatial coordinate systems respectively. In practical terms, this difference in reference frame and co-ordinate system means that a positive Eulerian strain will be smaller than the Lagrangian equivalent and conversely a negative Eulerian strain will be larger than the Lagrangian equivalent.

1.4.2.2 Strain-rate

Strain-rate ($\dot{E}$) is the time derivative of strain. Hence it similarly can distinguish between active and passive motion. The equation for strain rate is

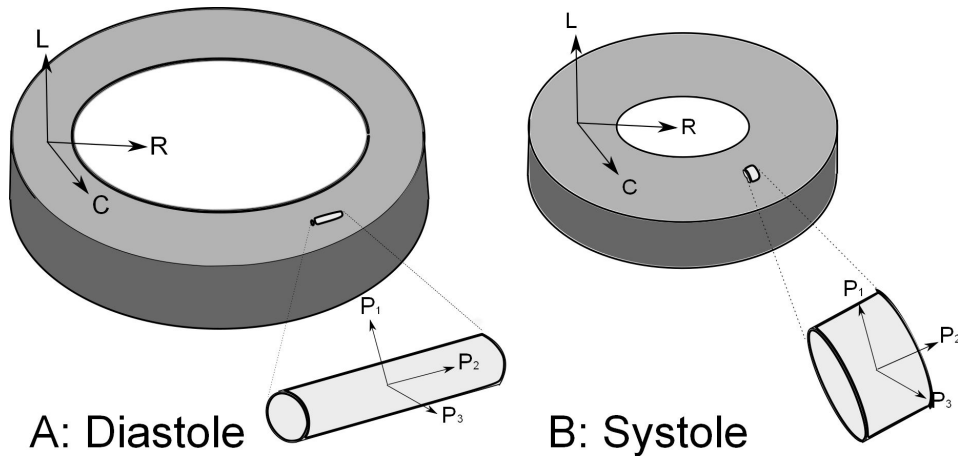


Figure 1.13: The radial-circumferential-longitudinal and Principal coordinate systems. Reproduced with permission from (Simpson et al., 2013b).

$$\dot{E} = \frac{dE}{dt} = \frac{d}{dt} \left(\frac{L(t) - L(0)}{L(0)} \right) = \frac{1}{L(0)} \frac{dL(t)}{dt} = \frac{v_2 - v_1}{L(0)} \quad (1.15)$$

where v_1 and v_2 are the velocities at each end of L , and so can be derived from velocity measurements.

1.4.3 Co-ordinate systems

As well as segmenting the myocardium into different regions, a coordinate system needs to be defined so that the three directional motion of the heart can be split into components for analysis or visualisation.

1.4.3.1 Left Ventricle

There are two main coordinate systems that are used to describe motion in the LV: the radial-circumferential-longitudinal (RCL) and the Principal systems. They are described below and can be seen in Figure 1.13.

1.4.3.1.1 Radial-Circumferential-Longitudinal The RCL coordinate system uses the long and short axes of the LV to define a cylindrical coordinate system. The longitudinal direction is aligned with the long axis, while polar coordinates are used to define the radial and circumferential directions in the perpendicular short axis plane. For example, thickening of the myocardium in the radial direction can clearly be seen between diastole and systole in Figure 1.13.

1.4.3.1.2 Principal The Principal coordinate system is mostly used to decompose three dimensional strain (see Section 1.4.2.1) into three components. The first direction (P_1) is defined as the direction in which the greatest length increase occurs (corresponding to the maximum positive strain). As can be seen in Figure 1.13 this is likely to be perpendicular to the general orientation of muscle fibres (as fibres contract they get shorter and fatter). The second principal direction (P_2) is defined as the direction of greatest length *decrease* and is therefore likely to lie parallel to fibre orientation. The third direction (P_3) is defined as orthogonal to the first two. This relationship between principal directions and fibre orientation mean that this coordinate system is sometimes referred to as the ‘Fibre-Cross-Fibre’ system.

1.4.3.2 Right Ventricle

It is clear that the RCL system cannot directly be used for the RV (for example there is no obvious way to define a radial direction). However the longitudinal axis of the heart can be used to define one direction, with the remaining motion being decomposed into the components parallel and perpendicular to the RV free wall at each point (analogous to radial and circumferential directions in the LV).

1.5 Methods of measuring regional cardiac function

In order to measure regional cardiac function higher spatial resolution is needed than for global measures. Hence there are fewer modalities that can be used to assess regional function than there are for global measures of function - only echocardiographic and magnetic resonance techniques are used to make quantitative measurements, although wall motion scores from gated SPECT have been shown to independently predict cardiac death in a large cohort of patients (Kapetanopoulos et al., 2007).

1.5.1 Echocardiography

1.5.1.1 Tissue Doppler Imaging

As explained in Section 1.3.1.1, TDI is used to measure the velocity of blood or tissue. While measuring mitral annulus velocities gives information about global function, regional myocardial velocities can also be assessed (Van de Veire et al., 2008). However only portions of the myocardium which can be accessed through the available acoustic windows can be assessed, which limits how comprehensive TDI can be for measuring regional myocardial velocities over the entire ventricle.

There are two modes of TDI which can be used; pulsed wave or colour-coded (Sutherland et al., 1993). Pulsed-wave TDI measures the velocity of a single spatial volume over time, while colour-coded TDI superimposes colour-coded velocities onto 2 dimensional grey-scale images. Velocity-time curves can then be extracted from any position in the image. While colour-coded TDI velocities underestimate velocities when compared with pulsed wave velocities measured

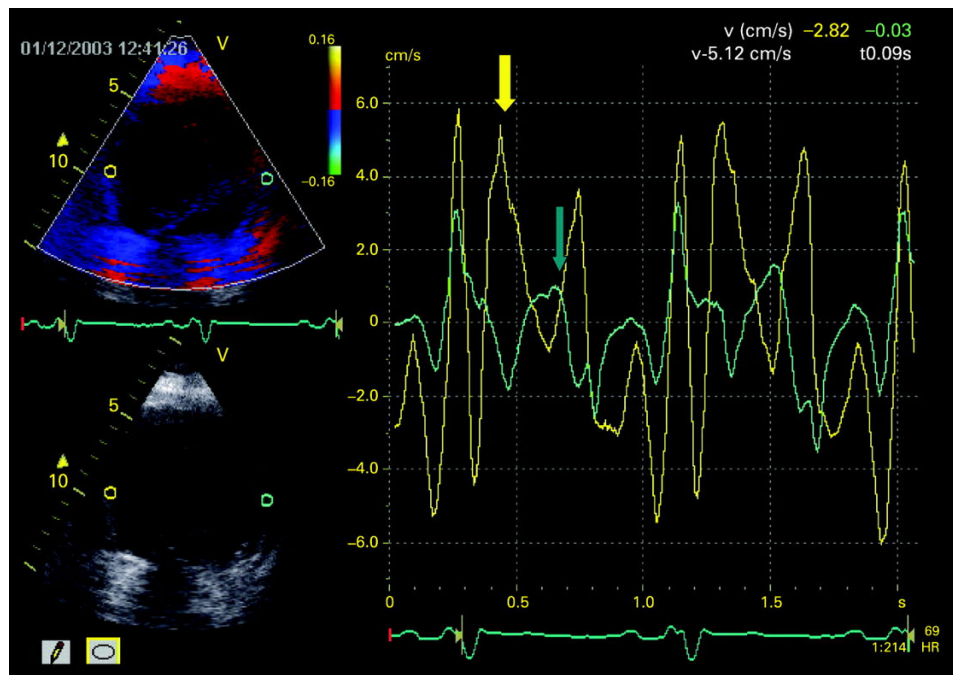


Figure 1.14: Septal (yellow) and lateral (green) velocities measured with TDI showing intraventricular dyssynchrony. From Van de Veire et al. (2008).

in the same segment by 10-20% (Kukulski et al., 2000), the ability to measure velocities over a large portion of the LV in a single scan significantly reduces imaging time.

A study on 60 patients found that a peak systolic velocity less than 5.5cm/s was 96% sensitive and 81% specific at detecting abnormal segments of myocardium (Katz et al., 1997). Regional myocardial velocities measured with TDI have been used to analyse intra-ventricular dyssynchrony in order to predict the response to cardiac resynchronisation therapy (see Figure 1.14); significantly higher dyssynchrony was found in responders when compared with that found in non-responders ($87 \pm 49\text{ms}$ vs. $35 \pm 20\text{ms}$, $p < 0.01$) (Bax et al., 2004). The detection of myocardial contraction and relaxation abnormalities with TDI in preclinical diagnosis of cardiomyopathy also shows great promise for future understanding of preclinical changes in structure and function in these condi-

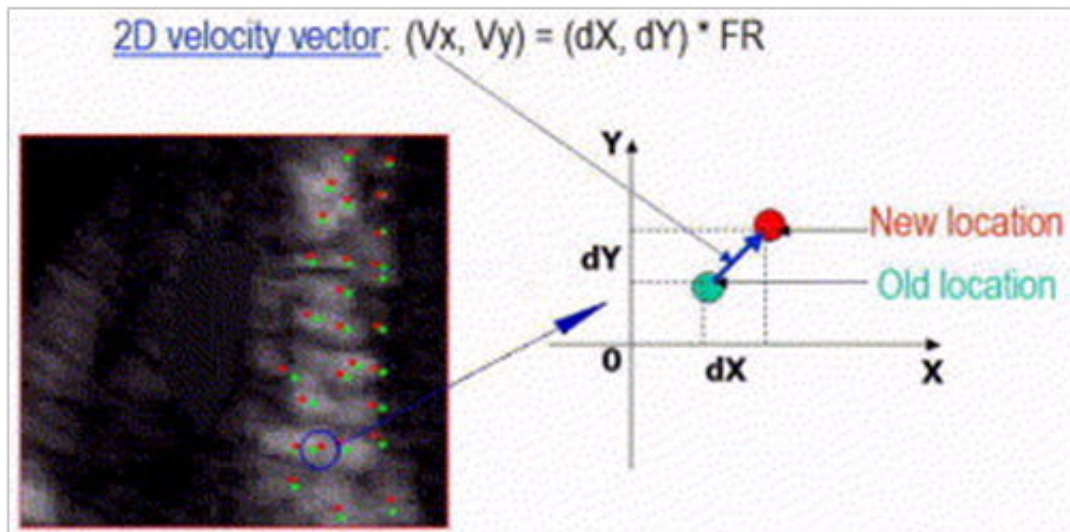


Figure 1.15: Displacement measured with speckle tracking. Green dots indicate the positions of speckles at one time point, red speckles indicate the positions of speckles at a later time point (left). Displacement between pairs of red and green dots can then be measured (right) and velocity or strain can then be calculated. FR = frame rate. From Leitman et al. (2004)

tions (De Backer et al., 2005; Nagueh et al., 2001).

TDI can also be used to calculate strain-rate (Stoylen et al., 1999) via the spatial gradient of measured velocities (i.e. Equation 1.15). These strain-rates can then be integrated over time to produce strain measurements (Urheim et al., 2000), although the propagation of errors through the integration can lead to unreliable results. Strain-rates measured with TDI have been shown to be superior to simple velocity measurements for detecting inducible ischemia under dobutamine stress (Voigt et al., 2004) and can potentially differentiate between hypertrophy caused by hypertension and hypertrophy caused by HCM (Kato et al., 2004).

1.5.1.2 Speckle tracking

Although speckle tracking can be used to measure LV volumes and hence calculate global parameters of motion (see Section 1.3.1.2), its main strength lies in its ability to quickly calculate regional strain values. The distance between speckles can be measured at a series of time points and so the Lagrangian strain of the tissue between them can be calculated using Equation 1.12 (see Figure 1.15). Speckle tracking is performed by manually delineating the endocardial border, which is then tracked automatically. The changing distances between tracked points are used to calculate strain.

Speckle tracking has been used to quantify abnormalities in contraction for patients undergoing cardiac resynchronisation therapy (Gorcsan and Tanaka, 2011). It has also been found to be superior to both 2D echo and TDI for assessing myocardial viability (Hoffmann et al., 2002) and it shows potential for measuring left ventricular torsion, showing good correlation with sonomicrometry ($R=0.94$, $p<0.001$) (Helle-Valle et al., 2005). Initial experiments with speckle tracking show that it is a promising technique for future analysis of regional myocardial mechanics, however it has not yet been accepted as a clinical technique (Van de Veire et al., 2008).

Despite the high temporal resolution and availability of echocardiographic techniques, their use for measuring regional myocardial mechanics will always be limited by the fact that they cannot comprehensively measure three directional velocities over the entire ventricle. TDI can only measure velocities parallel to the direction of the transducer and while this is not the case for strain measured by speckle tracking, the technique is still restricted to those areas of the ventricle which can be seen through acoustic windows.

1.5.2 Magnetic Resonance Imaging

Unlike echocardiographic techniques, MRI is not limited to acoustic windows and so has the potential to comprehensively measure myocardial mechanics over the whole heart. There are four main techniques within MRI which are capable of providing regional information about myocardial motion. These are tissue tagging, phase velocity mapping (PVM), displacement encoding with stimulated echoes (DENSE) and strain-encoded imaging (SENC). The four techniques are explained in detail in Chapter 2. The explanation concentrates mostly on sequence design, describing the initial implementations of the techniques, as well as technical developments in the following years. Validation and any clinical applications are also described.

Chapter 2

MR methods of measuring regional myocardial mechanics

Much of this Chapter is based on the extensive review article Simpson et al. (2013b), published in the Journal of Magnetic Resonance Imaging as part of this project. The sequences for the four methods within MR which can be used to measure regional myocardial mechanics (tissue tagging, phase velocity mapping, DENSE and SENC) are described in detail. A summary of the main validation and clinical application studies is then presented to show the potential of each technique. The techniques are then compared with each other to highlight their strengths and weaknesses. Definitions for the parameters which are used to measure regional mechanics can be found in Section 1.4.

2.1 Tissue tagging

2.1.1 Introduction

Tissue tagging techniques for the assessment of myocardial motion were first developed more than 20 years ago (Axel and Dougherty, 1989; Zerhouni et al., 1988). They consist of a preparation (or encoding) phase where lines or a grid of magnetic saturation (tags) are imposed on the myocardium at one time point (usually immediately after the R wave) followed by an imaging phase which shows the deformation of the tags through the cardiac cycle. While visually appealing, the quantitative analysis of the tag deformation is complicated and can require time consuming post processing, although more recent phase based analysis techniques have greatly speeded up the process.

Tissue tagging has been used extensively in a clinical context and is currently the most widely applied MR assessment of regional myocardial function. It has been shown to have potential clinical application for many conditions including coronary artery disease (CAD) (Edvardsen et al., 2006a; Kraitchman et al., 2003; Rosen et al., 2006b), myocardial infarction (Kramer et al., 1993; Marcus et al., 1997; Nagel et al., 2000b), dilated cardiomyopathy (DCM) (Kanzaki et al., 2006; Nelson et al., 2000; Young et al., 2001), HCM (Ennis et al., 2003; Rüssel et al., 2011; Young et al., 1994), LV hypertrophy (Edvardsen et al., 2006b) and ventricular dyssynchrony (Nelson et al., 2000).

2.1.2 Sequence design

The first tagging implementation used slice-selective radio frequency (RF) pulses to selectively saturate a few parallel bands in the heart followed by imaging in systole (Zerhouni et al., 1988). Subsequently, a 1-1 spatial modulation of magnetisation (SPAMM) preparation (Axel and Dougherty, 1989) was developed

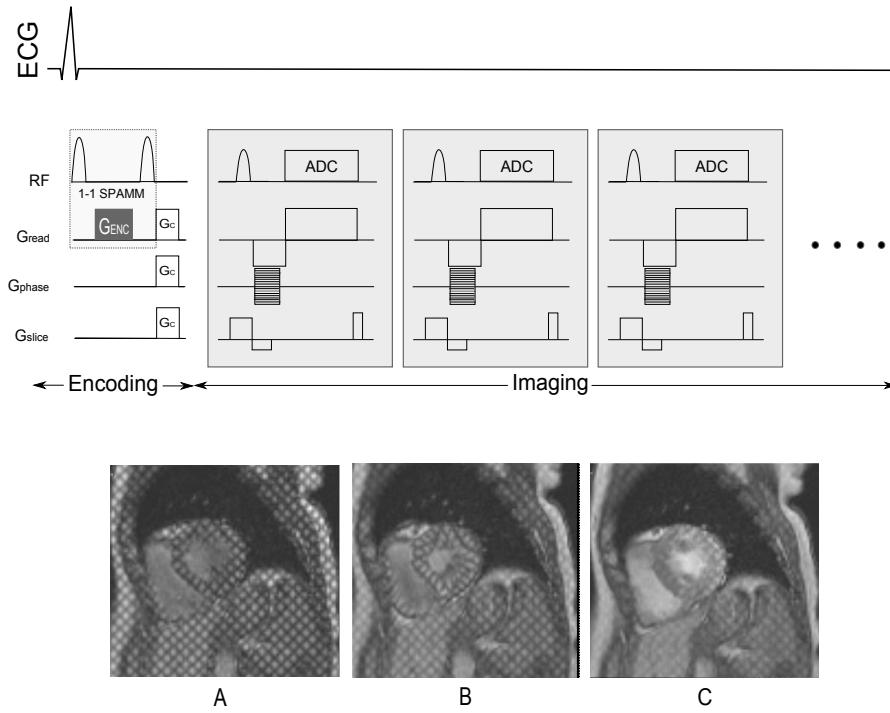


Figure 2.1: Top: Tagging sequence diagram showing 1-1 SPAMM tagging preparation (encoding) followed by a standard imaging sequence. Bottom: Tagged images at progressively later times after the R-wave. The tags deform with the myocardium but also fade through time. G_{ENC} =encoding gradient, G_C =crusher gradient, ADC=analogue to digital converter. Reproduced with permission from Simpson et al. (2013b).

to efficiently saturate parallel planes throughout the imaging volume and was combined with a cine imaging sequence (see Figure 2.1) so that the deformation of these saturated planes (or tags) could be visualized throughout the cardiac cycle. 1-1 refers to the fact that both RF pulses in the preparation module have the same flip angle, which for initial implementations was 45 degrees (resulting in a total flip angle of 90 degrees). In SPAMM, some (or in the case of a 90° pulse, all) of the longitudinal magnetisation is tipped into the transverse plane, sinusoidally modulated by an encoding gradient along the readout direction, G_{ENC} , then tipped back into the longitudinal direction. Immediately after the SPAMM preparation (at $t=0$), the longitudinal magnetization, M , varies as a

function of distance, x , along the direction of the encoding gradient

$$M(x, t = 0) = M_0 \cos(k_{ENC} x) \quad (2.1)$$

where M_0 is the equilibrium longitudinal magnetization, $k_{ENC} = \gamma \int G_{ENC}(t) dt$, where $\int G_{ENC}(t) dt$ is the area under the gradient lobe (the zeroth moment) and γ is the gyromagnetic ratio.

The tag separation is determined by G_{ENC} , and is typically 4-8mm. During the cardiac cycle, the signal in the tag lines increases due to T1 recovery. The longitudinal magnetisation at time t can therefore be expressed as:

$$M(x, t) = M_0 \cos(k_{ENC} x) e^{-\frac{t}{T_1}} + M_0 (1 - e^{-\frac{t}{T_1}}) \quad (2.2)$$

The resulting tag fading generally limits the use of tagging to the first two thirds of the cardiac cycle, although longer T1 times at higher magnetic field strengths increase tag persistence and allow tagging to be used over a greater portion of the cardiac cycle (Gutberlet et al., 2005; Kramer et al., 2006).

By using a series of RF pulses with relative amplitudes distributed according to binomial coefficients (high-order SPAMM), sharper tags are possible, which are easier to analyse (Axel and Dougherty, 1989). The density of the tags can also be made variable, allowing more sensitive motion estimation (McVeigh and Bolster, 1998). An alternative tagging scheme uses delays alternating with nutations for tailored excitation (DANTE) tagging (Mosher and Smith, 1990) which allows greater flexibility in the tag specification than SPAMM. However, all of these techniques need a longer preparation time than the original 1-1 SPAMM. A tagging scheme producing radial tags (perhaps a more natural tag geometry for the left ventricle) has also been developed (Bolster et al., 1990; Nasiraei-Moghaddam and Finn, 2013) but not widely applied, possibly due to the long

encoding modules (although the more recent work has reduced this issue) and complicated post processing.

2.1.3 Developments

2.1.3.1 C-SPAMM

Complementary SPAMM (C-SPAMM) (Fischer et al., 1993) was developed to improve tag contrast. A conventional 1-1 SPAMM acquisition using 90° RF pulses is followed by one where the second RF pulse in the tagging preparation is inverted. By subtracting the two datasets, the non-modulated magnetization resulting from T1 recovery is removed and the tag contrast is greatly improved, which allows more of the cardiac cycle to be analysed, although the scan time is doubled. An incrementing flip angle in the imaging module further improves tag contrast through the cardiac cycle.

2.1.3.2 Imaging variants

Tag preparation can be used with a variety of imaging sequences to enable 2D motion assessment in a single breath-hold. While the most commonly used sequence is segmented gradient echo (Shehata et al., 2009), balanced steady state free precession (bSSFP) has been implemented and has been shown to increase signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR) and tag persistence (Herzka et al., 2003; Markl et al., 2004; Zwanenburg et al., 2003). Spiral imaging (Ryf et al., 2004a), echo-planar imaging (EPI) with incremental flip angles (Sampath et al., 2003) and undersampled projection reconstruction (Peters et al., 2001) have also been used and typically result in increased SNR at the expense of some artefact.

As with all imaging techniques, there is a trade-off between spatial resolution, temporal resolution and acquisition duration. Typical parameters for a SPAMM tagged acquisition are $1.6 \times 1.6\text{mm}$ spatial resolution and 32ms temporal resolution acquired in a fourteen heartbeat breath-hold (Rosen et al., 2006a). Parallel imaging has also been applied to allow tagged acquisitions in as little as five cardiac cycles (Pai and Axel, 2006) at the expense of SNR. For higher spatial and temporal resolution, free breathing studies with navigator gating have been performed (Pai and Axel, 2006). At 3T images have increased SNR (103%) and CNR (19%) (Gutberlet et al., 2005), with the increased myocardial T1 also resulting in increased tag persistence.

2.1.3.3 3D

The motion of the myocardium is three-dimensional and measuring deformation within a single 2D image plane ignores any through-plane motion. Slice-following techniques have been proposed to deal with this problem (Fischer et al., 1994; Rogers et al., 1991) and work by saturating slices either side of the tagged slice of interest and increasing the imaging slice thickness so that it encompasses the tagged slice at the extremes of its motion. However, a 3D model of cardiac motion is required if the full motion of the myocardium is to be analysed. This has been achieved using a fully 3D tagged dataset, acquired during a series of breath-holds over 30-40 minutes (Ryf et al., 2002), but the usual method is to combine short and long axis tagged images and interpolate to build a 3D displacement field (Young et al., 1994).

2.1.4 Image analysis

While tagged images are visually appealing and allow an immediate qualitative estimate of myocardial motion, quantitative analysis may be complicated

and time consuming. The main stages of analysis of tagged images, as outlined in the detailed review of tagging by Axel et al. (2005), are image preparation, boundary surface extraction (segmentation), tag tracking and 3D motion reconstruction. The tag tracking is performed by tracking the dark tag lines or intersections as intensity minima (Amini et al., 1998; Guttman et al., 1994; Park et al., 1996; Young et al., 1995). Alternatively, motion information may be obtained directly from the tagged images without extracting the tag features by using optical flow techniques (Prince and McVeigh, 1992) or phase based analysis (Osman et al., 1999).

2.1.4.1 Techniques

2.1.4.1.1 Tag following Algorithms such as FindTags (Guttman et al., 1994) or SPAMMVU (Axel et al., 1992) typically work by manually or semi-automatically identifying the tag locations in one image and then using that image as a template to find the most probable location of tags in adjacent images (Axel et al., 2005). The tag trajectories can then be used to compute deformation fields, which in turn can be used to extract motion parameters (Amini et al., 2001; Frangi et al., 2001) such as displacement or strain. Early techniques involving fully manual segmentation of the images took a long time to analyse (5 hours to analyse 5 slices at 5 time points (Kraitchman et al., 1995)) and while semi-automated methods greatly reduced this time, it was still too long for clinical application. In addition data can only be extracted from pixels which lie on tag lines (and hence the accuracy of these techniques is improved with finer tag spacing) and analysis is highly dependent on image quality.

2.1.4.1.2 Optical flow Optical flow techniques attempt to follow pixels from frame to frame via a constant brightness constraint. Put simply, these techniques identify the brightness of a pixel and then look for a nearby pixel in

the next image which has a similar intensity. As previously discussed, the tags fade through the cardiac cycle and in early work this was modeled to produce a more robust technique (variable brightness optical flow) (Dougherty et al., 1999; Prince and McVeigh, 1992). More recently, optical flow methods have been presented which extend the technique into three dimensions (Xu et al., 2010). An advantage of optical flow methods over tag following is that the resolution is not limited to the tag spacing.

2.1.4.1.3 HARP harmonic phase (HARP) analysis follows pixels from frame to frame via a constant phase constraint. Expanding the cosine term in Equation 2.2 in terms of complex exponentials, the longitudinal magnetization at time t after tagging is given by:

$$M(x, t) = M_0(1 - e^{-\frac{t}{T_1}}) + \frac{M_0}{2}e^{-\frac{t}{T_1}}e^{-ik_{ENC}x} + \frac{M_0}{2}e^{-\frac{t}{T_1}}e^{ik_{ENC}x} \quad (2.3)$$

Equation 2.3 shows that there are three distinct echoes in k-space. The first term is a central peak which has no tagged component (known as the T1 echo); the other two are off-centre peaks responsible for the tags.

In HARP analysis (Osman et al., 1999), one of the off-centre peaks is isolated by a bandpass filter. An inverse Fourier Transform of this isolated peak results in a complex image, the magnitude reconstruction showing low resolution anatomical information and the phase reconstruction showing discontinuities at the approximate positions of the original tags (Figure 2.2 A). HARP analysis is based on the phase invariance property of tissue over time. The tissue phase is determined by the tagging preparation and thereafter remains constant, allowing tissue to be tracked by tracking regions of constant phase (Figure 2.2 B). After phase unwrapping, the Eulerian strain is calculated as the spatial gradient of the phase at each point in the HARP phase image, or Lagrangian strain can be calculated by tracking points of constant phase through a time-series

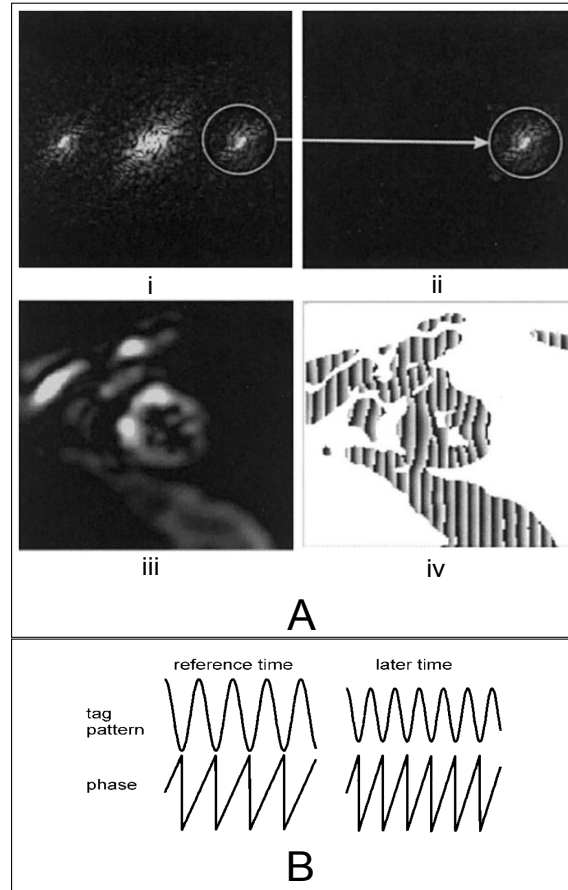


Figure 2.2: A: i) K-space for a tagging acquisition. The tag information is found in the off-centre peaks one of which is isolated for basic HARP processing (ii). This leads to a low resolution magnitude image (iii) and a phase image (iv) which can be used to track tissue since its phase is constant through time. B: The phase invariance property of material points in HARP processing. A sinusoidal tag pattern and its corresponding harmonic phase at reference time is shown on the left. At a later time (right) the tags decay in amplitude due to tag fading and change frequency because of deformation. The range of phase does not change but the phase slope does. A is reproduced with permission from Sampath et al. (2003), B is from Osman and Prince (2000) ©2000 IEEE.

of HARP images. Contours of equal phase can be overlaid on magnitude images to produce deforming grids similar to conventional tagging (but with any tag spacing) for better visualisation (Osman and Prince, 2000, 2004). HARP processing is typically ten times faster than conventional tag following analysis techniques.

The shape and size of the filter used to isolate the selected spectral peak strongly affects the resolution of the final image (see magnitude image in Figure 2.2 A) and can also potentially cause artefacts. Early investigations showed that an elliptical filter with a Gaussian edge minimised error (Osman et al., 2000) although its effectiveness decreases over time in the cardiac cycle as the central T1 recovery echo increases as the tags fade.

Phase wrapping causes difficulties in HARP analysis as there are many points in each image with the same phase. However, using a distance constraint and local unwrapping (Osman et al., 1999) any point within the image can be tracked, not just those points which lie on tag lines or intersections. Unlike conventional tagging analysis, this can be done very quickly, an un-optimised algorithm taking just 2 minutes to produce strain at 48 points through 20 time frames when the same analysis using FindTags (Guttman et al., 1994) took an hour (Osman et al., 1999).

While conventional tagging can benefit from long high-order SPAMM or DANTE tagging preparations to produce fine tag lines, this results in an increased number of k-space peaks which makes it more difficult to isolate a single peak for HARP analysis and reduces SNR. A 1-1 SPAMM tagging sequence is therefore generally used. HARP analysis of CSPAMM images has been shown to be more robust to artefacts than SPAMM images and, because the central T1 recovery peak is eliminated, less sensitive to the choice of k-space filter (Kuijjer et al., 2001). Although the scan time is doubled, C-SPAMM images have increased SNR which may be further improved by subtracting the positive and negative

peaks in k-space (Ryf et al., 2004b). This peak combination HARP also results in the removal of any phase errors (caused by B_0 inhomogeneities, chemical shift, flow etc.) which are the same for the two peaks.

An imaging sequence capable of producing real-time HARP images by using a gradient-echo EPI sequence with incrementing RF flip angles to compensate for tag fading has been developed (Sampath et al., 2003). This is achieved by only acquiring a small region of k-space around the position of the selected spectral peak. Horizontally and vertically tagged images are acquired in alternate heartbeats and the low-resolution magnitude images are displayed in real time, with up to 20 frames per heartbeat, each taking approximately 40ms to acquire. HARP strain images can be produced offline at a rate of four per second.

For a 2D tagging acquisition, the displacements measured using HARP analysis are a 2D projection of 3D motion into the imaging plane (Osman et al., 1999). However by acquiring both long and short axis views, 3D motion can be reconstructed (Pan et al., 2005). A technique known as zHARP has also been developed which is capable of tracking the 3D displacement of all points within a single image plane (Abd-Elmoniem et al., 2005). In this technique, two C-SPAMM data sets are acquired over two breath-holds - one with tags in the x-direction and one with tags in the y-direction - which have equal but opposite through-plane phase encoding. By using all four of the resulting k-space peaks, HARP images for motion in x, y and z can be calculated. This technique is much faster than other 3D HARP methods as it does not require the acquisition of long axis images and it also reduces the issue of registration errors inherent in building a 3D model from short and long axis images acquired over multiple breath-holds. Application of zHARP to imaging in pigs found that it is capable of identifying infarcts and their neighbouring regions (Soleimanifard et al., 2012).

2.1.4.1.4 FAST Fourier Analysis of Stimulated Echoes (FAST) is a new processing technique for SPAMM tagged data which provides measurements of LV twist (a parameter that has been shown to be important in several pathologies) with minimal user interaction (Reyhan et al., 2012). This is achieved by roughly masking the LV in FAST images so that only tagged data remains in the image, before carrying out the Fourier transform (FT). The resulting k-space can then be automatically analysed to measure twist. The technique has good intrascan and moderate interscan reproducibility (Reyhan et al., 2013). However it is a very new technique and it yet to be implemented by any groups other than the developers.

2.1.5 Validation

2.1.5.1 Phantoms

Studies on phantoms with known strains have shown that it is possible to measure the position of tags to within 0.1mm, allowing highly accurate and precise measurements of myocardial strain (McVeigh and Zerhouni, 1991). Further phantom studies have shown tagging to be a reliable method of measuring axial and azimuthal shear (Young et al., 1993) and strain (Moore et al., 1994).

2.1.5.2 Animals

Measurements of systolic wall thickening with tagging have been validated against implanted fiducial markers in dogs with both normal and ischemic myocardium. A correlation of 0.95 between measurements made with the two methods was found (Lima et al., 1993). Circumferential shortening measurements have also been validated using sonomicrometry (Yeon et al., 2001). Both methods were capable of distinguishing between remote and ischemic segments,

although tagging measurements were slightly higher in the remote regions ($p = 0.033$). Tagging measurements of end and late systolic shortening correlated well with sonomicrometry ($p=0.84$ and $p=0.88$ respectively, $p<0.001$ for both).

2.1.5.3 Healthy subjects

A tagging study using tag tracking analysis on 31 healthy volunteers has shown that measurements of E_3 and E_{CC} have a higher precision than those of E_{RR} and E_1 (Moore et al., 2000). E_{CC} , E_2 and E_2 -direction from HARP analysis (see Figure 1.13 for definitions) are in good agreement with tag tracking in both healthy volunteers and patients (Garot et al., 2000) with pooled analysis from two independent observers showing good reproducibility. Real-time HARP (Sampath et al., 2003) and 3D HARP (Pan et al., 2005) also agree well.

2.1.5.4 Patients

Analysis of strain measurements by 3 independent observers on data from the multi-centre Multi-Ethnic Study of Atherosclerosis (MESA) study have assessed the reproducibility of HARP analysis (Castillo et al., 2005), and found agreement to be highest in systole (pooled systolic strain E_{CC} inter- and intraobserver agreement $R=0.82$ and $R=0.69-0.76$) and lower in diastole due to reduced tag contrast ($R=0.69$ and $R=0.58-0.62$). The most reproducible measurement was found to be peak systolic circumferential strain ($R=0.84$ and 0.89 for inter and intra observer reproducibility respectively) and a direct relationship between image quality and reproducibility was observed.

2.1.6 Normal motion

E_{CC} and E_{CC} -rate are the most commonly quoted parameters of wall motion and have been shown to be one of the most robust measurements possible from tagging studies (Castillo et al., 2005; Moore et al., 2000). Many studies have been undertaken to characterize normal heart motion using tissue tagging, some of which (20 articles and 8 technical papers from 1991-2003) have been meticulously compiled to produce confidence intervals for standard deformation parameters in an excellent review article by Petitjean (Petitjean et al., 2005). Age-related changes in regional myocardial motion have also been studied using tagging (Oxenham et al., 2003) and have shown clinically relevant changes in motion.

2.1.7 Clinical application

Tissue tagging is the most widely accepted MR technique for measuring regional myocardial motion and because of this, it has been used in large scale clinical trials. In the multi-center MESA trial, for example, peak systolic mid-wall E_{CC} was calculated in 1184 asymptomatic participants using HARP analysis of tagged images and enabled a risk factor analysis of LV function. The clinical relevance of tagging has been discussed in detail in several excellent review articles (Axel et al., 2005; Götter et al., 2006; Shehata et al., 2009). It is capable of measuring a number of clinically relevant parameters, as outlined below.

2.1.7.1 Circumferential strain

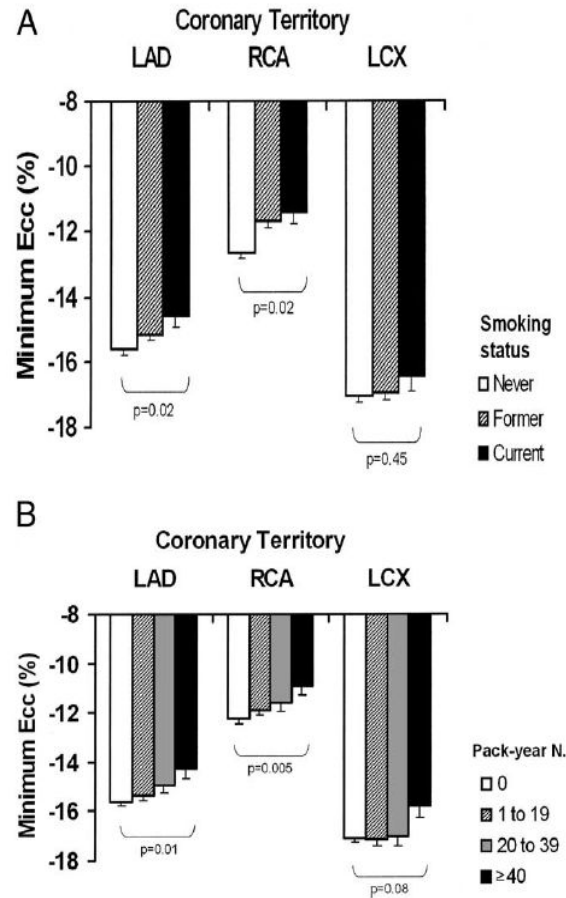


Figure 2.3: The effect of smoking on minimum E_{CC} measured by HARP in MESA. E_{CC} is lowered both in former and current smokers (A). The effect increases with the amount of cigarettes smoked (B). Reproduced with permission from Rosen et al. (2006a)

As discussed above, circumferential strain and strain rate are the most reproducible (Garot et al., 2000) parameters derived from tagging acquisitions and have the highest precision. The MESA study showed that reduced peak systolic E_{CC} correlates with increased diastolic blood pressure in coronary territories with coronary artery disease (Rosen et al., 2006b). Smoking also caused re-

duced peak E_{CC} , with the size of the reduction increasing with greater cigarette consumption (Rosen et al., 2006b) (see Figure 2.3). Reduced peak systolic E_{CC} was also related to coronary artery calcification (potentially providing a link between coronary atherosclerosis and incipient regional dysfunction (Edvardsen et al., 2006a)) and reduced coronary perfusion reserve (Rosen et al., 2006a).

Peak systolic E_{CC} has also been shown to be lowered in the anterior and lateral regions of the heart in patients with HCM (Ennis et al., 2003) and in a small cohort of patients with Duchenne muscular dystrophy, tissue tagging has shown reduced midventricular and basal E_{CC} compared to 9 age-matched volunteers, despite the patients having preserved LV volumes and ejection fractions (Ashford et al., 2005).

2.1.7.2 Circumferential strain-rate

Both systolic and early diastolic E_{CC} rates may be measured from tagging studies, provided that the tags persist. Diastolic E_{CC} -rate was reduced in asymptomatic MESA study patients with LV hypertrophy, indicating that reduced E_{CC} -rate could be a precursor to clinical heart disease (Edvardsen et al., 2006b). Peak systolic E_{CC} -rate was also reduced in areas of coronary artery calcification (Edvardsen et al., 2006a). It has also been shown that increased carotid wall stiffness is strongly related to reduced diastolic and systolic E_{CC} -rate (Fernandes et al., 2008). In patients with HCM, early diastolic E_{CC} -rate has also been shown to be reduced in all regions (Ennis et al., 2003).

2.1.7.3 Other strains

In patients with infarcts, the principal strains have been found to alter and re-orient both in adjacent and remote myocardium (Marcus et al., 1997). E_1 is also reduced in the basal septum and anterior walls in patients with HCM (Young

et al., 1994). In a study of patients with DCM, spatial strain variance at the time of maximal shortening has been shown to be an index for dyssynchrony (Nelson et al., 2000).

2.1.7.4 Shortening

Early tagging studies quoted results in terms of shortening instead of strain. Shortening is the difference in length of an object between two time points (i.e. similar to Equation 1.14 but with no division by the original length). Reduced circumferential and longitudinal shortening has been found in adjacent compared to remote myocardium in patients with myocardial infarction (Kramer et al., 1993) with the difference persisting for up to 6 months after infarction. In patients with DCM the septum was found to lengthen during systole whereas it shortens in healthy motion (Young et al., 2001). After partial left ventriculectomy, tagging studies showed that septal function recovered (Setser et al., 2003). Septal longitudinal and circumferential shortening is also reduced in patients with HCM (Young et al., 1994).

2.1.7.5 Torsion/Rotation

Reduced systolic apical rotation, along with delayed and prolonged diastolic untwisting has been demonstrated in infarcted hearts (Nagel et al., 2000b). In patients with aortic valve stenosis, systolic rotation is reduced at the base but increased at the apex (Nagel et al., 2000a). Peak systolic torsion is reduced at base and apex in DCM (Kanzaki et al., 2006) whereas torsion is increased in HCM (Young et al., 1994), and increased torsion has been shown to be a potential precursor to HCM in healthy mutation carriers (Rüssel et al., 2011). Due to its clinical potential a paper has been produced which aims to standardise the measurement of torsion (Young and Cowan, 2012).

2.2 Phase velocity mapping

2.2.1 Introduction

Phase velocity mapping (Bryant et al., 1984; Nayler et al., 1986; van Dijk, 1984) (also known as phase mapping, phase contrast velocity mapping or phase contrast imaging) was first applied to measuring myocardial velocity nearly twenty years ago (Karwatowski et al., 1994b; Pelc et al., 1994). A bipolar gradient is used to encode velocity directly into the phase of the signal. The technique is widely available as a standard sequence on most clinical scanners and has quick post-processing, however it is prone to motion artefacts and phase distortion. Phase velocity mapping is widely used clinically to measure blood flow and has been shown to be useful for measuring myocardial motion in myocardial infarction (Arai et al., 1999; Markl et al., 1999), heart failure (Delfino et al., 2008b), LV hypertrophy (Jung et al., 2006b), HCM (Beache et al., 1995), DCM (Föll et al., 2009), coronary artery disease (CAD) (Karwatowski et al., 1994a,b; Schneider et al., 2001) and ventricular dyssynchrony (Delfino et al., 2008b). Phase velocity mapping is the technique that has been used to measure regional myocardial mechanics in this thesis. It is briefly introduced below but is explained in more detail in Chapter 3.

2.2.2 Sequence Design

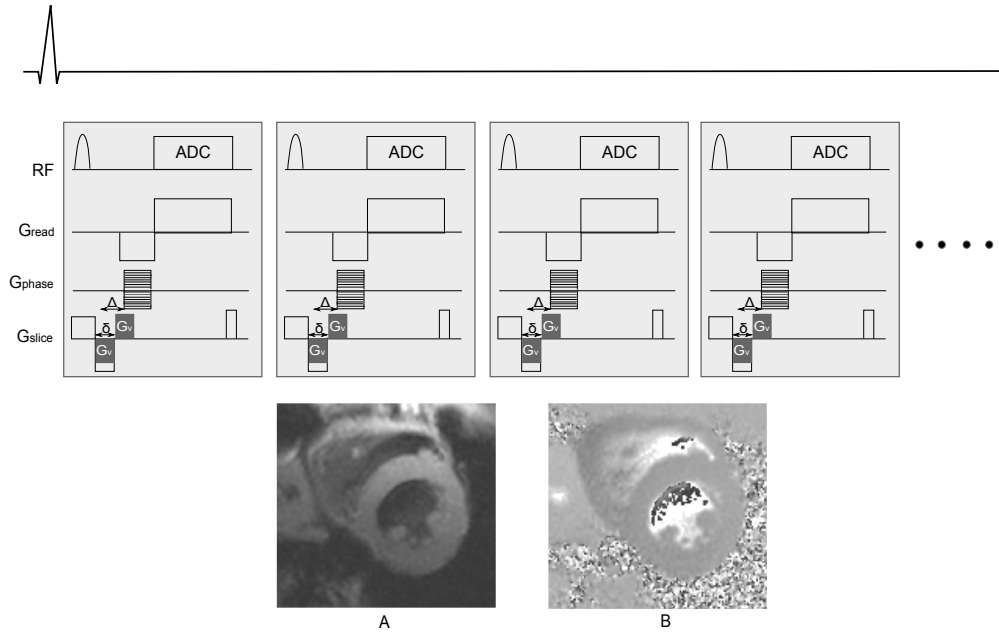


Figure 2.4: Top: Phase velocity mapping sequence diagram showing through plane velocity encoding. Reference acquisitions and acquisitions for other directions of velocity encoding can either be interleaved within the same heartbeat or can be acquired in separate heartbeats. Bottom: Magnitude image (A) and phase map (B) for the longitudinal direction of velocity encoding. Reproduced with permission from (Simpson et al., 2013b).

A bipolar gradient of magnitude G_v along the desired direction of velocity encoding causes a phase shift

$$\phi = \gamma G_v v \delta \Delta \quad (2.4)$$

where v is the velocity of material being imaged along the direction of encoding, γ is the gyromagnetic ratio, δ is the gradient duration and Δ is the time between the positive and negative gradient lobes (see Figure 2.4). The bipolar gradient

is incorporated into the imaging sequence, normally being combined with the rephasing lobes so as to reduce the sequence echo and repeat times.

Equation 2.4 shows that the phase shift is directly proportional to the velocity in the direction of the encoding gradient, however velocities which result in phase shifts outside of the range $\pm\pi$ are aliased causing analysis problems. Some of these issues can be overcome by phase unwrapping (Yang et al., 1996).

The largest velocity that can be measured without aliasing is known as the VENC which is controlled by altering the amplitude and duration of the encoding gradients. For myocardial phase velocity mapping, the required VENC is small (typically 15-25cm/s) and requires relatively high amplitude gradients. By repeating the sequence with velocity encoding in in-plane and through plane directions, 3-directional myocardial velocities can be measured. In addition to acquisitions in each direction of velocity encoding, a reference (non flow encoded) acquisition is also required to correct for any uncontrolled phase errors. The different velocity encodings can either all be acquired consecutively in the same heartbeat or in separate heartbeats. The first technique has significantly lower temporal resolution than the second but results in a shorter scan time and removes any potential registration issues.

Phase errors caused by Maxwell or concomitant gradients can be calculated and corrected for precisely and automatically in software (Bernstein et al., 1998). Phase shifts due to eddy currents can be more troublesome and result in background phase shifts in stationary tissues. Identifying points of stationary tissue (in the chest wall, liver and back for example) may allow this background phase to be modelled and corrected, but if stationary tissue is not present on all sides of the heart it may not be possible to model accurately. In such cases, the acquisition of a second dataset with the same parameters as the first in a large static phantom may be necessary to allow the phase errors to be subtracted (Chernobelsky et al., 2007). Beat-to-beat variations in blood flow in the heart

result in ghosting of blood signals in the phase encoding direction and errors in myocardial velocity measurements. A ‘black-blood’ pre-saturation pulse is generally included in the pulse sequence to reduce this (Drangova et al., 1997; Hennig et al., 1998).

2.2.2.1 Initial implementation

One of the first applications of phase velocity mapping to measure myocardial velocities used an unsegmented gradient echo sequence over 192 heartbeats, each line of data being acquired twice and averaged to reduce respiratory motion artefacts (temporal resolution 25ms, spatial resolution 1.4-2mm, through-plane velocities) (Karwatowski et al., 1994b; Pelc et al., 1994).

2.2.2.2 Developments

Segmented imaging techniques have been applied, allowing the measurement of one directional velocities within a breath-hold (for example temporal resolution 37-87ms with view sharing, spatial resolution 2.7x1.3mm in a 17-29 heart-beat breath-hold (Petersen et al., 2006)). The temporal resolution can be improved by acquiring different encoding directions in different heartbeats, however this increases the duration of the scan such that it cannot be performed in a breath-hold. Respiratory gating using navigators has been implemented to allow 3-directional velocity encoding with improved temporal and spatial resolution although at the expense of increased acquisition durations (Delfino et al., 2006; Jung et al., 2006a). Temporal resolution has also been improved by using view sharing techniques (Foo et al., 1995; Markl and Hennig, 2001), optimised GRAPPA (Peng et al., 2010) and k-t BLAST Lutz et al. (2011).

The motion of the heart is intrinsically three dimensional. 3D velocity information is normally obtained by encoding velocity in three orthogonal directions

and acquiring a stack of 2D short-axis images. However, acquisitions of 3D data with 3-directional velocities at each point have also been carried out (Kvitting et al., 2004; Lutz et al., 2012; Selskog et al., 2002) allowing velocities to be extracted from any point in the myocardium without the need for prior slice positioning. However scan times are long (30-40 minutes) and no respiratory motion compensation has been applied.

2.2.3 Image Analysis

2.2.3.1 Parameters

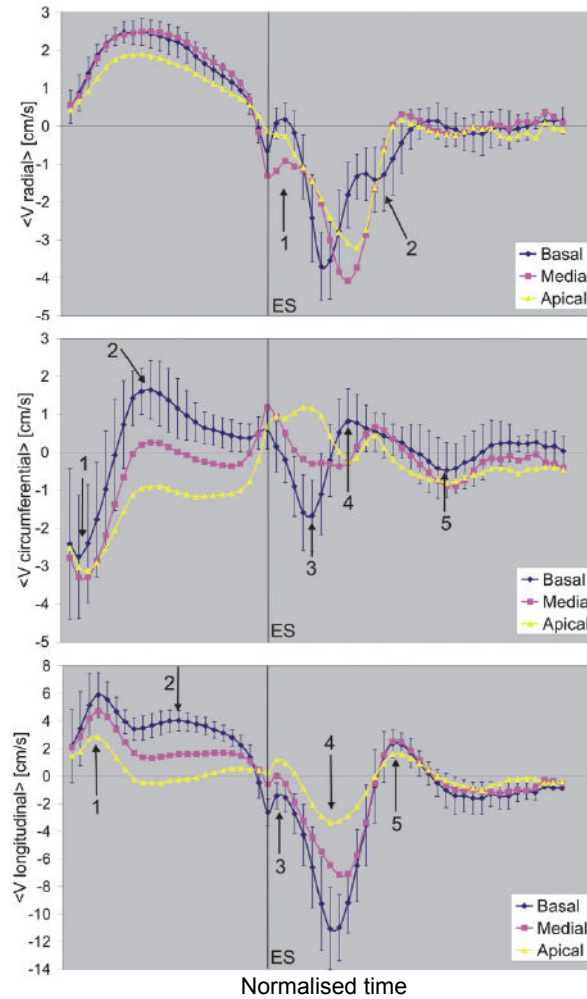


Figure 2.5: Velocities measured in 12 healthy volunteers with PVM. Longitudinal, radial and circumferential velocities are shown from basal, mid and apical slices. Times are normalised to end systole (ES) as shown by the vertical line. The mean velocity values at each normalised time point are shown and for the basal slice SD values are indicated by error bars. Interesting features of motion are indicated by arrows. Reproduced with permission from Jung et al. (2006a).

2.2.3.1.1 Velocities Most studies using phase velocity mapping analyse the velocities directly as they can be obtained with a minimum of image processing and are more accurate than other derived parameters (Hennig et al., 1998; Jung et al., 2006a; Karwatowski et al., 1994b). The acquired x, y and z velocities (relative to the image plane) are generally converted to radial, circumferential and longitudinal velocities based on the geometry of the left ventricle. Example normal global (averaged over the entire myocardial slice being imaged) radial, circumferential and longitudinal velocities averaged over basal, mid and apical slices can be seen in Figure 2.5. Many differences between slices can be seen, for example basal and apical circumferential velocities are in opposite directions in early diastole (point 3 in the middle graph) and longitudinal velocities are higher at base than apex (points 1 and 4 on the last graph).

2.2.3.1.2 Strain-rate Strain-rate is determined from phase velocity mapping images by calculating the spatial derivatives of the velocities at each pixel (Wedeen, 1992). A method to calculate strain-rate in all three directions from a single slice position has also been developed (Robson and Constable, 1996), exploiting the information about the range of velocities present in a voxel encoded in the magnitude of the signal from that voxel. Strain can be calculated from trajectories, obtained by integrating velocities with respect to time (Zhu et al., 1997), however this is not often done as errors can propagate through the integration to an unacceptable level, and the processing time is long.

2.2.4 Validation

2.2.4.1 Phantoms

Phase velocity mapping was validated for measuring blood flow in the first studies (Bryant et al., 1984) and exactly the same technique is used for measur-

ing myocardial mechanics. However validation studies have been performed specifically to validate the technique for measuring tissue velocities to assess the effect of using lower VENC values and the effect of blood flow on myocardial velocities. In a rotating phantom the average absolute error between measured and actual velocities was 0.13 ± 0.17 cm/s which corresponds to 0.65% of the velocity-encoding range (Arai et al., 1999), and in an oscillating phantom, measured and theoretical velocities were highly consistent (Markl and Hennig, 2001).

A phantom capable of both longitudinal and circumferential motion has also been developed (Delfino et al., 2008b) and phase velocity mapping was shown to be capable of accurate measurements (mean differences were -0.15 ± 2.8 cm/s and 0.06 ± 1.38 cm/s in the longitudinal and circumferential direction). Time-to-peak velocities were measured with accuracy corresponding to less than one time frame (9.4 ± 24.4 ms and 1.0 ± 20.3 ms difference between measured and actual values in the longitudinal and circumferential directions respectively, temporal resolution 35 ms).

2.2.4.2 Healthy subjects

Radial strain measured with phase velocity mapping has been validated against strain calculated from changes in myocardial thickness on bSSFP images in healthy volunteers (Delfino et al., 2008a). However, while this study showed good agreement between the mean peak radial strains ($38.0 \pm 6.2\%$ vs $38.1 \pm 5.4\%$), Bland-Altman analysis showed large limits of agreement (mean difference between techniques $-0.18 \pm 18.3\%$) possibly because the velocity data must be integrated over time to calculate strain which results in increased noise. Radial velocities in 29 healthy volunteers (Jung et al., 2004) measured with phase velocity mapping and TDI have shown excellent agreement ($R=0.97$).

2.2.4.3 Patients

Normalised septal velocities in 18 patients with hypertensive heart disease showed excellent agreement with TDI measurements ($R=0.89$) (Paelinck et al., 2005). Similarly, agreement between TDI and phase velocity mapping for the assessment of longitudinal septal velocities over the cardiac cycle and time to peak longitudinal velocity in healthy volunteers and patients with dyssynchrony have been excellent ($R = 0.87$ and $R = 0.97$ respectively), although in this study, MR measured velocities consistently exceeded those measured by TDI, possibly because of the angle dependence of TDI measurements (Delfino et al., 2006).

2.2.5 Normal motion

Investigations into the reproducibility of phase velocity mapping have shown that the coefficient of variation for repeated measurements of septal peak velocity is 11% and time-to-peak velocity is 5.7%, the corresponding values for TDI being 13.1% and 9.1% respectively (Delfino et al., 2006). Intra- and interobserver variabilities of lateral radial velocity measured from the same data by 3 independent observers were (mean $\pm$ standard deviation (SD)) 0.15 ± 0.18 cm/s (averaged over the observers) and 0.16 ± 0.23 cm/s respectively (Jung et al., 2004).

Phase velocity mapping has been used to investigate the function of fibre orientation in the determination of heart motion and architecture (Buckberg et al., 2006; Jung et al., 2006b). Transmural, epicardial and endocardial strain and strain rates have been computed in healthy volunteers by Delfino, who was first to report an endocardial-epicardial strain-rate gradient in the human heart (Delfino et al., 2008a).

A database of normal 3D systolic and diastolic endocardial and epicardial velocities based on data from 96 healthy volunteers was produced by Petersen (Pe-

tersen et al., 2006) and Föll undertook a detailed study of the motion of the left ventricle in 58 subjects (Föll et al., 2009). This study used correlation analysis and a schematic visualisation model to discover age-related changes in regional left ventricle myocardial velocities. The most recent work in this area is able to perform very detailed regional analysis of the left ventricle motion (Codreanu et al., 2010), revealing complicated motion and suggesting how the anatomy and positioning of the heart may explain its complex mechanics. There is also potential for assessing arterial stiffness by investigating the effect of the aortic reflected pulse pressure wave on myocardial velocities (Codreanu et al., 2011b).

2.2.6 Clinical Application

Phase velocity mapping has been used in several clinical studies to quantify regional myocardial motion and detect regional abnormalities in patients with various conditions, mostly by detecting differences in peak velocities at various stages in the cardiac cycle between patients and healthy volunteers. The clinically relevant parameters that tissue phase mapping can measure are outlined below.

2.2.6.1 Strain-rate

Strain rate can be calculated from velocity data using its spatial derivative. The heterogeneity of strain-rates has been shown to increase in patients with HCM compared with healthy volunteers during diastole, with regional diastolic strain-rate correlating with wall thickness (Beache et al., 1995). Early diastolic radial strain-rate has also been shown to be a parameter capable of identifying areas of infarcted myocardium in canine hearts (Arai et al., 1999).

2.2.6.2 Peak velocities

Reduced diastolic peak longitudinal and radial velocities have been found in the septal and lateral regions of 28 patients with heart failure compared with 17 healthy volunteers, with diastolic longitudinal velocities being the most affected (Delfino et al., 2008b). Motion patterns during diastole were found to be prolonged and peak velocities reduced in 2 patients with LV hypertrophy (Jung et al., 2006a), and in a study of 58 healthy volunteers and a single patient with DCM, age caused significant differences in peak and time-to-peak velocities in the radial and longitudinal directions. Marked regional differences were also observed between the patient and age-matched normals (Föll et al., 2009). Maximum long axis velocity is reduced in patients with CAD compared with healthy volunteers and further reduced in patients with CAD and previous infarction (125mm/s in healthy volunteers (n=19), 99mm/s in CAD without infarction (n=21), 80mm/s in CAD with infarction (n=26)) (Karwatowski et al., 1994b). Regional diastolic radial velocities are also reduced in patients with CAD (Schneider et al., 2001). Patients suffering from myocardial infarction show significantly reduced radial velocities and dyskinetic regions are easily identified (Markl et al., 1999). More recently left ventricular remodelling after coronary artery bypass surgery was investigated with PVM and despite increased apical contraction (2.4 ± 0.2 cm/s compared with 3.1 ± 0.2 cm/s, $p=0.03$), no increase in peak diastolic velocities were seen (Codreanu et al., 2011a).

2.2.6.3 Time to peak velocities

In patients with dyssynchrony, the time-to-peak systolic velocity in the lateral wall is increased in the longitudinal (99 ± 17 ms in volunteers, 198 ± 83 ms in patients) and radial (168 ± 51 ms in volunteers, 224 ± 66 ms in patients) directions, as is time-to-peak diastolic velocity in the longitudinal (507 ± 34 ms in volun-

teers, 613 ± 112 ms in patients) and radial (478 ± 34 ms in volunteers, 530 ± 50 ms in patients) directions (Delfino et al., 2008b).

2.3 DENSE

2.3.1 Introduction

DENSE, first developed in 1999, encodes in-plane tissue displacement directly into the phase of an image (Aletras et al., 1999b). This is achieved by using three RF pulses to generate a stimulated echo along with encoding and decoding gradients. However, because the sequence is based on a stimulated echo, the technique has intrinsically low SNR and, like tagging, T1 recovery makes analysis of myocardial motion over the entire cardiac cycle difficult.

DENSE is not yet widely applied in a clinical context, however in initial studies it has been shown to have potential use in the areas of myocardial infarction (Aletras et al., 2006), ventricular dyssynchrony (Spottiswoode, 2006) and non-ischemic cardiomyopathy (Feng et al., 2009).

2.3.2 Sequence Design

The original DENSE sequence (Figure 2.6) is a stimulated echo acquisition mode (STEAM) sequence which consists of a 1-1 SPAMM tagging section which modulates the longitudinal magnetisation in an in-plane direction using an encoding gradient G_{ENC} , followed by a mixing time T_M (approximately 100ms) and an imaging section which includes a gradient to refocus the phase of stationary spins (known as the decoding gradient). STEAM sequences can be used to reduce the effect of T_1 recovery by storing the magnetisation along the longitudinal direction. This enables the use of a long mixing time, which allows large

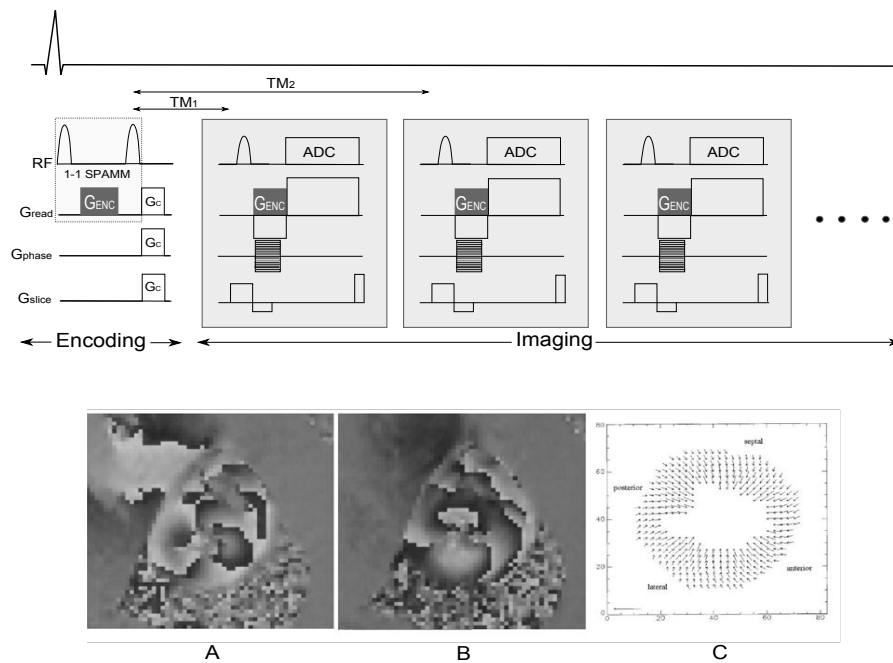


Figure 2.6: Top: The cine-DENSE sequence diagram showing an initial 1-1 SPAMM tagging module followed by a modified imaging sequence. TM_i is the mixing time for the i th acquired cardiac phase. G_{ENC} = encoding gradient, G_C = crusher gradient. Reproduced with permission from Simpson et al. (2013b). A and B show DENSE phase images for the two in plane directions of encoding which can then be combined to produce a displacement map, shown in C. Reproduced with permission from Aletras et al. (1999a).

displacements to be encoded (resulting in good phase contrast) with relatively small gradients which reduces signal loss through intravoxel phase dispersion.

The initial encoding stage is the same as that used for conventional tagging (Equations 2.1 and 2.2). After the third RF pulse (which forms part of the imaging sequence and has flip angle α), the transverse magnetisation, $M_T(x, t)$, is given by

$$M_T(x, t) = M_0 \sin \alpha (1 - e^{-\frac{t}{T_1}}) + M_0 \sin \alpha \cos(k_{ENC} x) e^{-\frac{t}{T_1}} \quad (2.5)$$

where $k_{ENC} = \gamma \int G_{ENC}(t)dt$ where $\int G_{ENC}(t)dt$ is the zeroth moment of the encoding gradient lobe. After the mixing time the region of interest has moved a distance Δx . The effect of the decoding gradient (which also has magnitude G_{ENC}) is to add an additional phase of $k_{ENC}(x + \Delta x)$ to the signal:

$$M_T(x, t) = M_0 \sin \alpha (1 - e^{-\frac{t}{T_1}}) e^{-ik_{ENC}(x+\Delta x)} + M_0 \sin \alpha \cos(k_{ENC}x) e^{-\frac{t}{T_1}} e^{-ik_{ENC}(x+\Delta x)}. \quad (2.6)$$

Expanding the cosine term by using complex exponentials we get:

$$M_T(x, t) = M_0 \sin \alpha (1 - e^{-\frac{t}{T_1}}) e^{-ik_{ENC}\Delta x} e^{-ik_{ENC}x} + \frac{M_0}{2} \sin \alpha e^{-ik_{ENC}x\Delta x} + \frac{M_0}{2} \sin \alpha e^{-\frac{t}{T_1}} e^{-ik_{ENC}\Delta x} e^{-i2k_{ENC}x}. \quad (2.7)$$

Equation 2.7 shows that the acquired k-space will contain three distinct echoes. From left to right they are known as the T_1 recovery echo (found at $k = k_{ENC}$), the stimulated echo (STE) (found at $k = 0$) and the stimulated anti-echo (STAE) (found at $k = 2k_{ENC}$) (also known as the conjugate echo). Note that the effect of the decoding gradient has been to shift the three echoes by an amount k_{ENC} relative to their positions in a simple SPAMM tagging acquisition where the echo centres are at $k = -k_{ENC}$, $k = 0$ and $k = +k_{ENC}$ (Equation 2.3, Figure 2.2 Ai).

For DENSE imaging, the required displacement information is contained within the STE (as for this echo, the phase is directly proportional to displacement). Equation 2.7 also shows that DENSE imaging has inherently low SNR as the magnitude of the STE is proportional to only half of the original longitudinal magnetisation. The entire sequence can be repeated with encoding in an

orthogonal direction in order to get a 2D displacement for each pixel (See Figure 2.6). While the STE is, by design, compensated for phase errors resulting from B_0 inhomogeneities and chemical shift during both encoding and decoding, a phase correction scan is required to compensate for any changes which occur between the two (Aletras et al., 1999a).

2.3.2.1 Implementations

The original implementation of DENSE acquired an image at a single time-point in the cardiac cycle and was slow as the imaging module was a cardiac and respiratory gated un-segmented acquisition (spatial resolution $1 \times 1.9\text{mm}$, 4.3 minutes per image) (Aletras et al., 1999b). However, the acquisition duration was subsequently reduced to a 24 heartbeat breath-hold using a multi-shot segmented echo planar imaging scheme (spatial resolution $2.5 \times 2.5\text{mm}$) (Aletras et al., 1999a), thereby also eliminating artefacts due to respiratory motion. A mixed echo train acquisition (meta-DENSE) has also been developed to reduce the imaging time further (12-14 heartbeats) (Aletras and Wen, 2001), however signal loss occurs along the pulse train due to imperfect refocusing pulses.

Cine DENSE imaging has also been performed, using a fast imaging sequence such as an EPI sequence (Kim et al., 2004b) or a spiral readout trajectory (Zhong, 2007). Using EPI, a temporal resolution of 60ms with spatial resolution of $2.7 \times 2.7\text{mm}$ has been acquired in a 19 heartbeat breath-hold, whereas a spiral readout achieved temporal resolution of 34ms with spatial resolution of $2.8 \times 2.8\text{mm}$ in a 19 heartbeat breath-hold with improved SNR and reduced ghosting and flow artefacts compared to a fly-back EPI readout.

In the sav-DENSE technique, the imaging sequence is applied without displacement decoding and the STE and STAE echo are combined to increase SNR by a factor of $\sqrt{2}$ (Kim et al., 2004a). The CANSSEL (Cosine AND Sine acquisitions to

Eliminate artefact generating echoes) acquisition scheme has been introduced to eliminate both STAE and T1 recovery echoes. This requires 4 acquisitions each with a different version of the 1-1 tagging sequence: $(90^\circ)_x$ and $-(90^\circ)_x$, $(90^\circ)_x$ and $(90^\circ)_x$, $(90^\circ)_x$ and $(90^\circ)_y$, $(90^\circ)_x$ and $-(90^\circ)_y$ (Epstein and Gilson, 2004). These data sets can be combined by addition and subtraction to remove both the STAE and T1 echoes. Using this scheme, a smaller encoding gradient can be used (as the STAE does not need to be shifted out of the k-space window), resulting in reduced intravoxel dephasing, and the suppression of the STAE is also more complete than is possible by shifting it out of the k-space window. However, the study duration is extended by the need for the additional acquisitions.

While the multiple acquisitions in the above methods for removing unwanted echoes increase the scan time, the increased SNR achieved allows parallel imaging to be used (Aletras et al., 2005). A balanced n-dimensional encoding scheme has also been investigated (Zhong et al., 2009) and has been found to substantially reduce phase noise variance as well as any directional bias in the phase noise. This technique is equally applicable to phase contrast MRI.

Fast cine-DENSE is the collective name for a series of improvements made by Kim and Kellman (Kim and Kellman, 2007) to incrementally improve the SNR and acquisition efficiency of DENSE acquisitions. This was achieved by using a bSSFP imaging sequence at 3T with sav-DENSE. The combined effect was to improve SNR by 65%, acquiring images with 3.6×3.6 mm spatial resolution and 35ms temporal resolution in a 24 heartbeat breath-hold. The implementation of time adaptive SENSE (TSENSE) parallel imaging enabled the same resolution to be achieved in half the time, while still achieving an SNR improvement of 28%. Fast cine-DENSE has been found to be insensitive to the level of B_0 variation found clinically (Feng et al., 2009) with excellent agreement being found between simulated deformation models and the results of DENSE analysis.

2.3.2.2 Artefacts

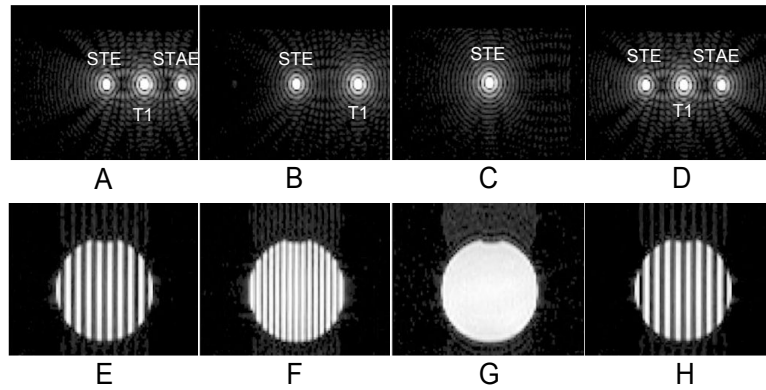


Figure 2.7: K-space (A-D) and images (E-H) for variations of DENSE imaging. A and E show all three echoes as in a standard DENSE acquisition, leading to tagging artefacts with frequencies of k_{ENC} and $2k_{ENC}$. The STAE can be removed by choosing a large enough value of k_{ENC} (B/F), leaving a tagging artefact of a single frequency. A C-SPAMM acquisition allows the subtraction of the T1 echo (C/G), removing the tagging artefact. For comparison D shows the k-space of a standard HARP acquisition, which is used for sav-DENSE. From Kim et al. (2004b).

The STAE and the T1 recovery echo cause unwanted banding artefacts and various methods have been developed to remove them (Figure 2.7 A/E). The STAE can be removed by using a sufficiently large displacement encoding to shift it outside of the range of k-space sampled for imaging (Figure 2.7 B/F). Alternatively, both the T1 recovery echo and the STAE can be removed by through-plane crusher gradients (Aletras et al., 1999a; Zhong et al., 2006) although this increases intravoxel dephasing and results in reduced SNR. The T1 recovery echo has also been eliminated by an inversion recovery technique which nulls the signal for a particular T1, although banding artefact will still be present from tissue with other T1 values (Aletras and Wen, 2001).

Another approach to artefact reduction is to use RF cycling in the form of complementary spatial modulation of magnetization (C-SPAMM) where a second

data set is acquired with the phase of the second RF pulse in the SPAMM module inverted (Aletras and Arai, 2004; Gilson et al., 2004). Subtraction of the two datasets increases the SNR, while the T1 recovery echo is removed regardless of T1 value, although this is at the expense of doubling the acquisition duration (Figure 2.7 C/G). A simple k-space filter, centred on $k = k_{ENC}$, can be used to suppress any residual T1 signal (Kim et al., 2004b).

2.3.3 Validation

The accuracy of DENSE displacement measurements has been validated in several studies. In the original DENSE implementation, a phantom rotation of 10.28° was measured by DENSE as $10.54^\circ \pm 0.36^\circ$ (Aletras et al., 1999a), while high resolution DENSE with C-SPAMM in mice found mean squared errors in x and y displacement measurements of 0.0034 and 0.0013mm^2 respectively (Aletras and Arai, 2004) (compared to an average systolic myocardial displacement in mice of $0.42 \pm 0.04\text{mm}$). The CANCEL acquisition scheme has been shown to measure through plane motion in a rotating cylindrical phantom more accurately than SPAMM or C-SPAMM (Epstein and Gilson, 2004). The introduction of slice following has allowed a through plane tracking accuracy of $0.46 \pm 0.32\text{mm}$ for a typical range of myocardial motion in humans (Spottiswoode et al., 2008).

Fast cine DENSE image analysis has low intra- and interobserver variability for both E_{CC} and E_2 measurements (Feng et al., 2009). The implementation of parallel imaging has been shown not to affect measurements of E_2 , with the mean difference between non-accelerated and accelerated sequences in 6 healthy volunteers being 0.00 with limits of agreement of -0.04 to 0.04 (Kim and Kellman, 2007).

A good correlation ($R = 0.90$) has been found between high resolution single

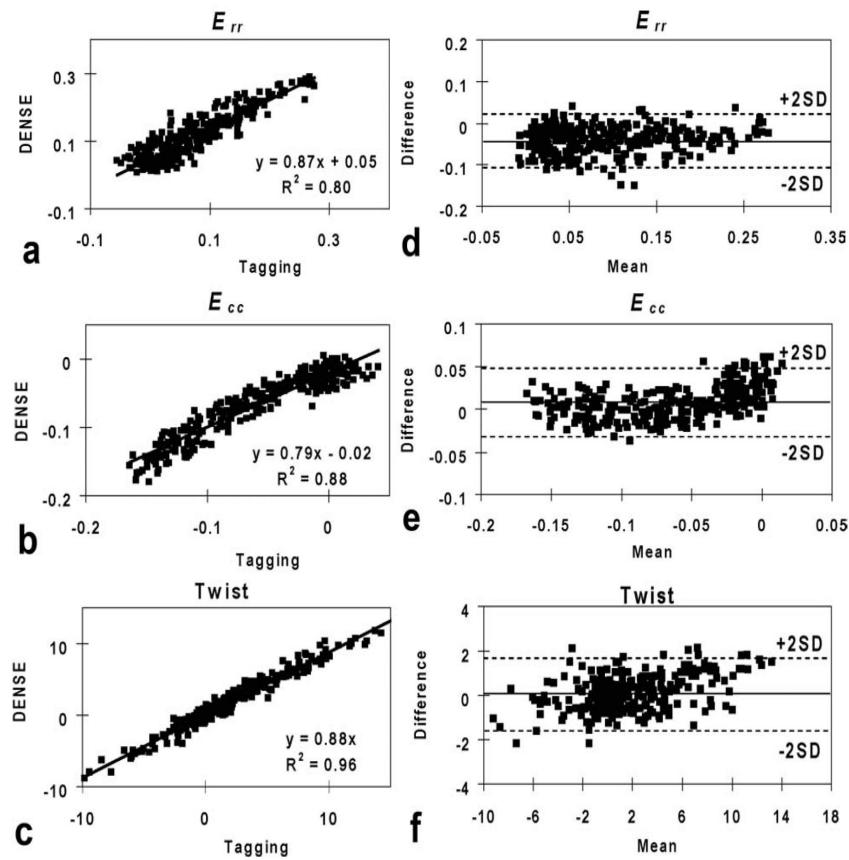


Figure 2.8: Comparison between E_{RR} (a), E_{CC} (b) and twist (c) measurements from DENSE and tagging in mice (Zhong and Yu, 2010). The difference in E_{CC} measurements between the two techniques can be seen to increase as the measured value increases towards zero.

phase C-SPAMM DENSE and tagging measurements of E_{CC} in mice (Gilson et al., 2004). In a further study, twist, radial strain and circumferential strain measured by cine-DENSE in mice correlated well with HARP analysis ($R = 0.96$, $R = 0.80$, $R = 0.88$ respectively) of the same images before complex subtraction (Zhong and Yu, 2010) although DENSE measurements were underestimated by $\sim 10\%$. Towards the peak E_{CC} values, the differences between HARP and DENSE increased (Figure 2.8).

E_{CC} measurements through the cardiac cycle from cine-DENSE have also been

shown to correlate well with tagged studies in healthy volunteers ($R = 0.87$) with the mean difference and limits of agreement being 0.014 and -0.06 to 0.09 respectively (Kim et al., 2004b) in this population where the typical E_{CC} value was 0.1. More recently, fast cine-DENSE has also shown good agreement ($R = 0.92$) with conventional tagging for both E_{CC} (mean difference 0.01, limits of agreement 0.07 to -0.04) and E_2 (mean difference 0.03, limits of agreement 0.08 to -0.03) measurements (Feng et al., 2009) in healthy subjects and in a heterogeneous group of patients with a prior history of cardiac disease (the typical value of both E_{CC} and E_2 in this study being 0.15). Sav-DENSE has also shown good correlation with tagging in E_{CC} measurements ($R = 0.92$) (Kim et al., 2004a).

3D DENSE has been achieved during free breathing using slice following with a respiratory navigator (Zhong et al., 2010). Results were in good agreement with both 2D DENSE and historical 3D tagging results. A method of computing automated measures of mechanical dyssynchrony using the Fourier transform of regional strain has been validated against time-to-peak parameters measured with tissue tagging (Budge et al., 2012). While this method discriminates well between different patient groups, correlations with tagging, although significant, were low ($R = -0.62$, $p = 0.03$).

2.3.4 Normal motion

In its original form, DENSE had sufficient resolution to detect transmural strain variation across the LV at end-systole (Aletras et al., 1999a). Measurements of E_{CC} and E_{RR} with 2D DENSE in 12 volunteers found that E_{CC} decreases throughout systole to a minimum of approximately 0.2 while E_{RR} increases throughout systole to a maximum of approximately 0.40 (Kim et al., 2004b), in agreement with tagging results. Measurements of 3D trajectories using slice following in 6 healthy volunteers found end-systolic E_{CC} and E_{RR} of -0.16 ± 0.02

Segment	End-systolic Tagging (n=10)	End-systolic DENSE (n=12)	Peak Tagging (n=75)	Peak SENC (n=75)
Basal anterior	-22 ± 2	-18 ± 2	-22 ± 2.4	-20.3 ± 1.9
Basal (antero)septal	-21 ± 3	-20 ± 3	-21.5 ± 2.8	-20.7 ± 2.9
Basal inferoseptal	-21 ± 3	-15 ± 2	-	-
Basal inferior	-16 ± 2	-17 ± 2	-20.9 ± 2.9	-20.2 ± 2.3
Basal (infero)lateral	-18 ± 1	-17 ± 5	-21.9 ± 2.5	-20.3 ± 2.5
Basal anterolateral	-19 ± 2	-19 ± 4	-	-
Mid anterior	-23 ± 2	-18 ± 2	-24.2 ± 2.8	-21.3 ± 2.3
Mid (antero)septal	-24 ± 3	-20 ± 3	-22.2 ± 2.9	-20.7 ± 2.2
Mid inferoseptal	-22 ± 3	-18 ± 1	-	-
Mid inferior	-18 ± 2	-16 ± 3	-19.5 ± 3.2	-19.8 ± 2.7
Mid (infero)lateral	-20 ± 3	-20 ± 4	-22.6 ± 2.7	-21.2 ± 2.6
Mid anterolateral	-21 ± 2	-22 ± 4	-	-
Apical anterior	-27 ± 2	-19 ± 3	-23.7 ± 3.1	-22.1 ± 2.3
Apical (antero)septal	-25 ± 2	-20 ± 2	-22.3 ± 3.1	-20.4 ± 2.4
Apical inferoseptal	-23 ± 2	-	-	-
Apical inferior	-21 ± 4	-19 ± 2	-19.9 ± 3.5	-19.8 ± 2.7
Apical (infero)lateral	-25 ± 3	-21 ± 3	-21.1 ± 3.9	-20.3 ± 2.4
Apical anterolateral	-26 ± 2	-	-	-

Table 2.1: Comparison of tagging with DENSE and SENC results. Percentage values are given. The first column is from Kuijer et al. (2002), the second column is from Epstein and Gilson (2004), the third and fourth columns are from Spottiswoode et al. (2008).

and 0.21 ± 0.08 respectively. The difference between the 2D and 3D results are attributed to the through plane component of strain. Measurements of end-systolic E_{CC} and E_2 in all 16 segments of the LV have also been made with fast DENSE (Feng et al., 2009) (Table 2.1).

2.3.5 Clinical Applications

DENSE has not yet been widely accepted as a clinical tool and the number of clinical studies is limited. Pre-clinical studies in mice have shown that E_{CC} and E_{RR} measured with DENSE can detect infarcted myocardium (Gilson et al., 2004, 2005) while more recently cine DENSE was used to show that stress induced significant increases in radial and circumferential strains and torsion in peak systole (Zhong and Yu, 2010).

In studies on individual patients, DENSE has demonstrated the potential for

detecting reduced deformation in myocardial infarction (Aletras et al., 2005), delayed onset of strain in LV-RV dyssynchrony (Spottiswoode, 2006), abnormal septal motion following pericardiectomy (Spottiswoode et al., 2008) and reduced E_{CC} and E_2 in non-ischemic cardiomyopathy (Feng et al., 2009).

In a DENSE study on 16 patients with hypertension, CAD or diabetes, segmental E_{CC} measurements were classified according to whether they were above or below a threshold value. Using adaptive post-processing techniques, DENSE agreed with the classifications made by echocardiography with a sensitivity of $87.7\% \pm 4.0$ and specificity of $87.7\% \pm 4.0$ (Wen et al., 2008).

2.4 SENC

2.4.1 Introduction

SENC is a relatively new technique, having been described for the first time in 2001 by Osman et al (Osman et al., 2001). Unlike conventional tagging where the tag planes are oriented perpendicular to the imaging plane, in SENC imaging tag planes are initially orientated parallel to the imaging plane. However the tags still fade due to T1 recovery and SENC cannot analyse the whole cardiac cycle. Through-plane strain is directly related to the pixel intensity in the resulting images and very little post-processing is needed. SENC measures through-plane strain, therefore longitudinal strain (E_{LL}) can be determined from a short axis image plane and circumferential strain (E_{CC}) from a long axis image plane. Radial strain cannot be measured. SENC has not yet been applied in a clinical context, however initial studies have shown it to be a potential diagnostic tool of the future for myocardial infarction (Neizel et al., 2010; Oyama-Manabe et al., 2011), CAD (Korosoglou et al., 2009) and RV function in pulmonary hypertension (Shehata et al., 2010).

2.4.2 Sequence design

The SENC imaging sequence consists of a 1-1 SPAMM tagging section with gradient strength G_{ENC} , which sinusoidally modulates the longitudinal magnetisation in the through-plane direction (z) (analogous to Equation 2.1), followed by an imaging section in which a through-plane demodulating or tuning gradient G_T is incorporated into the slice rephasing gradient (Figure 2.9). The frequency of the tags is then $k_{ENC} = \gamma \int G_{ENC}(t)dt$. This terminology has been used here to emphasize the similarity between SENC and conventional tagging or DENSE. However most of the SENC literature refers to the encoding gradient G_{ENC} as a tagging gradient G_{TAG} , and the tagging frequency as w_{TAG} rather than k_{ENC} (similarly the tuning frequency is known as w_T rather than k_T).

Through-plane stretching or compression of the slice causes the local tag frequency (initially equal to k_{ENC}) to change with time (see Figure 2.10). The time dependent frequency at each point is referred to as $\nu(t)$ and the Eulerian through-plane strain at the time of imaging (t) is simply calculated as

$$E(t) = \frac{k_{ENC}\nu(t)}{\nu(0)} \quad (2.8)$$

The determination of strain in SENC imaging is therefore reliant on determining the altered tissue tag frequency $\nu(t)$. As with conventional tagging, during the cardiac cycle the modulated magnetisation decays and a non-modulated magnetisation increases due to T1 recovery so the magnetisation at time t is the same as Equation 2.3 except with $k_{ENC}x$ replaced with $\nu(t)z$:

$$M(x, t) = M_0(1 - e^{-\frac{t}{T_1}}) + \frac{M_0}{2}e^{-\frac{t}{T_1}}e^{-i\nu(t)z} + \frac{M_0}{2}e^{-\frac{t}{T_1}}e^{i\nu(t)z} \quad (2.9)$$

During imaging, a tuning gradient along z , $G_T(t)$, is applied to demodulate the magnetisation. The intensity of the image acquired is:

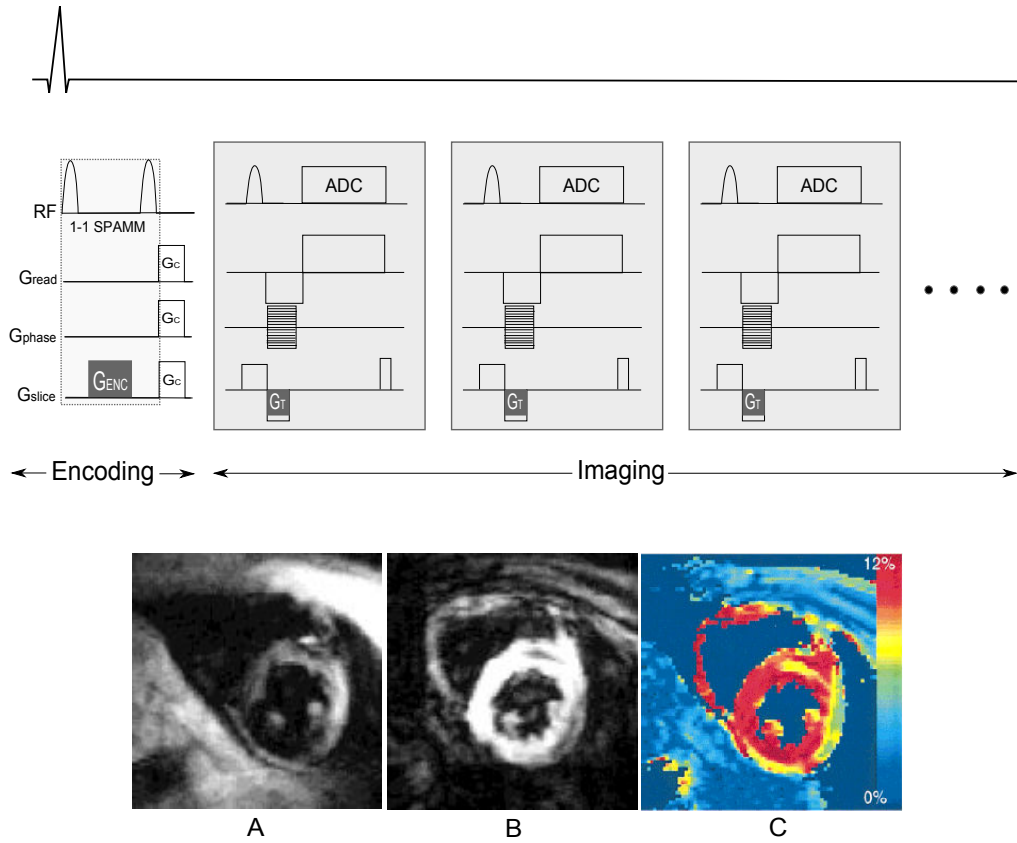


Figure 2.9: Top: Sequence diagram for SENC showing a through plane 1-1 SPAMM module followed by a modified imaging sequence. G_{ENC} = encoding gradient, G_T = tuning gradient. Bottom: SENC images showing low tuning (A), high tuning (B) and strain (C) images. Top reproduced with permission from Simpson et al. (2013b), bottom images reproduced with permission from Osman et al. (2001)

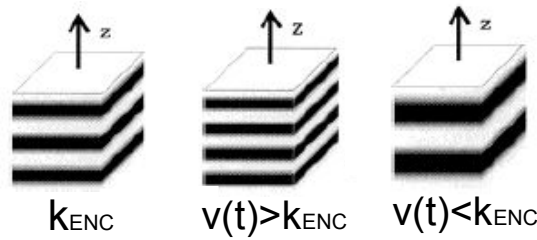


Figure 2.10: The effect of through plane strain on SENC tags. Initially the tag frequency is determined by k_{ENC} (left). If the tissue is then compressed the frequency $\nu(t)$ is greater than k_{ENC} (middle), whereas if the tissue is stretched $\nu(t)$ is less than k_{ENC} (right). From Osman et al. (2001)

$$I(t, k_T) = \int_{-\infty}^{\infty} M(z, t) f(z) e^{-ik_T z} dz \quad (2.10)$$

where $f(z)$ is the slice profile and k_T is the demodulating or tuning frequency, $k_T = \gamma \int G_T(t) dt$. By using equations 2.9 and 2.10, we can rewrite the intensity as

$$I(t, k_T) = M_0(1 - e^{-\frac{t}{T_1}})F(k_T) + \frac{M_0}{2}e^{-\frac{t}{T_1}}F(k_T + \nu(t)) + \frac{M_0}{2}e^{-\frac{t}{T_1}}F(k_T - \nu(t)) \quad (2.11)$$

where $F(k)$ is the Fourier Transform of $f(z)$ evaluated at frequency k (the frequency profile). From Equation 2.11 we can see that the resulting image is a superposition of three images, each weighted by the FT of the slice profile evaluated at a specific frequency. However, if the demodulating frequency k_T is chosen to be close to $\nu(t)$, $F(k_T - \nu(t)) \approx F(0)$ is large compared to $F(k_T)$ and $F(k_T + \nu(t))$ since it approximates to the central lobe of a sinc pulse, centred on 0.

Hence, as long as the maximum strain is not too large (i.e. $k_T \approx \nu(t)$) the image intensity can be approximated as

$$I(t, k_T) \approx \frac{M_0}{2} e^{-\frac{t}{T}} F(k_T - \nu(t)) \quad (2.12)$$

The inherently low SNR of the technique is a result of the factor of two reduction in the equilibrium longitudinal magnetisation (as in DENSE).

To estimate the local tag frequency, $\nu(t)$, two images are acquired with different tuning frequencies, k_{LT} and k_{HT} , known as the low and high tuning frequencies respectively. $\nu(t)$ can then be estimated as the discrete approximation to the centre of mass of the image intensities acquired with the low and high tuning frequencies at time t ($I_{LT}(t)$ and $I_{HT}(t)$ respectively)

$$\nu(t) \approx \frac{k_{LT} |I_{LT}(t)| + k_{HT} |I_{HT}(t)|}{|I_{LT}(t)| + |I_{HT}(t)|} \quad (2.13)$$

This is only valid provided that k_{LT} and k_{HT} cover all values of strain in the image (Osman et al., 2001). Hence it is important to know the range of strains expected before the acquisition is carried out. In the high tuning image, tissue with high strain is bright while the low tuning image shows tissue with low strain (Figure 2.9). Having calculated $\nu(t)$ at each pixel using Equation 2.13, a strain map can be produced using Equation 2.8 with very little post-processing.

The values chosen for k_{LT} , k_{ENC} and k_{HT} depend on slice thickness (since the strain map is directly proportional to the FT of the slice profile (Equation 2.10)) and the expected strain. In the original implementation, $k_{LT} = k_{ENC} = 0.40 \text{ mm}^{-1}$ and $k_{HT} = 0.46 \text{ mm}^{-1}$, corresponding to strains in the range of 0 – 13%, which was suitable for the first 300ms of systolic contraction in normal hearts. Later studies have used different values depending on the slice thickness used (i.e. $k_{LT} = 0.30 \text{ mm}^{-1}$ and $k_{HT} = 0.40 \text{ mm}^{-1}$ covering 0 – 25% strain in a 10mm slice (Pan et al., 2006), $k_{LT} = 0.25 \text{ mm}^{-1}$ and $k_{HT} = 0.38 \text{ mm}^{-1}$ covering 0 – 25% strain in an 8mm slice (Ibrahim et al., 2007a)). The above calculation of strain assumes

that the initial tags are only compressed or stretched (as in Figure 2.10). In practice, strain gradients within the image plane may cause tags to be tilted which may affect the accuracy of the results. While this was taken into account in the original SENC reference, in healthy volunteers this tilting has been shown to be less than 15° (Osman et al., 2001) and it is consequently generally ignored.

2.4.2.1 Implementations

The original SENC sequence was implemented with segmented k-space gradient echo imaging to acquire a single systolic cardiac phase with a spatial resolution of $1.9 \times 3.8\text{mm}$ over two 16 heartbeat breath-holds, one for the low and one for the high tuning image. Since then, interleaved spiral imaging trajectories have been used to increase the acquisition efficiency (Hamdan et al., 2009; Neizel et al., 2009; Youssef et al., 2008) which, together with interleaving the tuning images so that they are acquired in the same cardiac cycle, results in cine imaging being performed with typical spatial resolution of $2 - 2.5 \times 2 - 2.5\text{mm}$ and temporal resolution of 15-25ms within a single 10-15 second breath-hold.

Fast-SENC has been developed to allow either real time imaging or imaging of the whole heart within a breath-hold (Pan et al., 2006). This has been achieved by using incrementing flip angles, a single-shot spiral readout trajectory, interleaving the two tuning images and using spatially-selective tagging to allow smaller fields of view without fold-over artefacts. Using this technique, real-time imaging can be performed with a spatial resolution of $4 \times 4\text{ mm}$ with the interleaving of the two tuning images having minimal effect on strain measurements, at least in healthy volunteers. Later work showed better image quality when acquiring three shorter, interleaved spiral trajectories per cardiac cycle, rather than a longer single-shot, due to decreased off resonance effects (Ibrahim et al., 2007a).

Fast-SENC has been combined with slice following (Fischer et al., 1994) to correct for tissue displacement in the through plane direction as the heart contracts and relaxes (Ibrahim et al., 2007a), the measured strain values being corrected for changes in slice thickness through the cardiac cycle. Slice-followed SENC consistently showed significantly different strain values to non-followed SENC, the differences being similar to those found between tagging and slice-followed tagging acquisitions. Despite this, the slice following technique has not been widely applied in subsequent studies, possibly due to increased noise.

A technique known as C-SENC combines conventional SENC imaging with T1 weighted viability imaging following gadolinium administration (Ibrahim et al., 2007b). Compared with a conventional SENC acquisition followed by a viability acquisition, the scan time is halved and the fact that the functional and viability images are acquired just milliseconds apart reduces misregistration issues. However, because of the presence of gadolinium, the T1 of myocardium is short and tag fading is rapid. C-SENC therefore cannot be used for a significant fraction of the cardiac cycle.

Although SENC only measures through plane strain, it can be combined with in-plane techniques to produce full 3D strain measurements. 3D strain maps of the myocardium have been produced by combining the SENC with 2D DENSE (Hess et al., 2009). SENC has also been combined with HARP to acquire radial, longitudinal and circumferential strains within a short axis slice in just six heartbeats (although the full strain tensor could not be calculated as longitudinal shear components could not be measured with this technique) (Garot et al., 2004).

2.4.3 Validation

Studies in healthy volunteers (Hamdan et al., 2009; Neizel et al., 2009) and patients (Garot et al., 2004; Korosoglou et al., 2009, 2010) have shown that peak circumferential and peak longitudinal strains measured by SENC imaging are highly reproducible with interobserver and interstudy interclass correlation coefficients ranging from 0.92 to 0.98 (all $p < 0.001$) (Hamdan et al., 2009). Peak circumferential strain and strain rate measured with fast-SENC also show low intra and inter-observer variability (Korosoglou et al., 2008) and good agreement with SENC imaging in the right ventricle ($R = 0.86$ for circumferential strain and 0.90 for longitudinal strain) (Shehata et al., 2010).

Several studies have been carried out to validate measurements from SENC imaging against those from conventional tagging. A comparison between conventional 3D tagged MRI (reconstructed from multiple short axis and long axis acquisitions) and SENC imaging in patients with myocardial infarction (Garot et al., 2004) found a correlation of $R = 0.75$ for pooled E_{11} values. However, while no systematic differences were seen between the two techniques, the limits of agreement were high relative to the absolute values of strain being measured (approx -5.8% to $+5.8\%$). In a more recent study of 75 healthy volunteers, poor correlation ($R = 0.3$) was found between the circumferential strain measured by tagging and SENC imaging (Neizel et al., 2009), with limits of agreement of -8.1% to 5.6% . The mean circumferential strain in this cohort was around 20%, consistent with the results of previous studies in healthy volunteers (Ibrahim et al., 2007a; Korosoglou et al., 2008). In this case, it was thought that the low correlation was possibly due to the limited variance of strain values in the study cohort. The authors also noted that peak circumferential strain values measured with SENC were higher than the corresponding peak values measured in tagging studies, possibly due to the higher temporal resolution achieved by SENC imaging.

In contrast to SENC, fast-SENC has been found to correlate well with tagging in both healthy volunteers and patients with heart failure (Korosoglou et al., 2008) (peak circumferential systolic strain: $R = 0.90$ and early circumferential diastolic strain rate: $R = 0.91$, $p < 0.001$ for both). However in a study comparing tagging and fast-SENC in the right ventricular free wall, no significant correlation was found for E_{CC} measurements in healthy volunteers with poor limits of agreement (mean difference $\pm 2SD = 0.8\% \pm 12.6\%$) (Shehata et al., 2010). This could potentially be due to the thickness of the RV being of a similar order to the tag spacing, making conventional tagging inaccurate for RV measurements. This observation is backed up by the fact that in patients with hypertrophied RVs, a statistically significant, though moderate, correlation was found ($R = 0.5$).

SENC has been compared to echocardiographic speckle tracking (see Sections 1.3.1.2 and 1.5.1.2) and both techniques could detect significant differences in motion between healthy and abnormal motion (defined by visual analysis). The two techniques performed similarly for measurements of peak circumferential and longitudinal strain, however speckle tracking allowed better distinction between normal and abnormal segments via circumferential strain analysis than SENC (Altiok et al., 2012). Peak E_{CC} measurements made with SENC were significantly higher than were measured with SPAMM at 3T (Sugimori et al., 2013) probably because of the higher spatial resolution of SENC.

2.4.4 Normal motion

SENC imaging is capable of reliable quantification of regional myocardial systolic and diastolic function, detecting slightly heterogeneous myocardial strain within LV segments, an observation that agrees well with tagged MRI results (Neizel et al., 2009) (Table 2.1). While peak systolic circumferential and longitudinal strain showed no age or gender related difference in this study of a

healthy subject group ($n = 75$), it was noted that the peak early diastolic circumferential strain rate was lowered amongst older volunteers. A study in 16 healthy subjects found peak E_{LL} and E_{CC} to be highest at apex (agreeing with earlier tagging studies (Kuijer et al., 2002; Moore et al., 2000)), and occurs earliest at base (Hamdan et al., 2009).

SENC has also been used to investigate normal RV motion, finding that peak systolic longitudinal strain values are highest at the apex and base, with a pronounced decrease in the mid ventricle, and maximal systolic circumferential strain showed the highest values at the apex. Peak systolic longitudinal and circumferential shortening occurred earliest at the apex (Hamdan et al., 2008). Peak E_{CC} values in 21 volunteers have been measured as $-20.4 \pm 2.9\%$, $-18.8 \pm 3.9\%$ and $-16.5 \pm 5.7\%$ in the basal, mid and apical segments respectively (Youssef et al., 2008).

2.4.5 Clinical applications

In patients following myocardial infarction, systolic and diastolic peak systolic E_{CC} and early diastolic E_{CC} -rate have been shown to provide similar accuracy for prediction of persistent severe myocardial dysfunction at follow-up compared with late gadolinium enhancement imaging (the current gold standard) and so to provide potential new parameters for the assessment of viability in patients after acute myocardial infarction (Neizel et al., 2010). Strain parameters derived from SENC imaging have also been shown to detect inducible ischemia in patients with known or suspected coronary artery disease during dobutamine high stress MRI and to provide incremental value to conventional wall motion analysis from cine acquisitions (Korosoglou et al., 2009). In particular, strain rate reserve (defined as the ratio of circumferential peak systolic strain rate during peak dobutamine stress to that at rest) was significantly ($p < 0.001$) related to coronary artery stenosis severity ($R = 0.75$) and a cut off of

1.64 was shown to be a highly accurate marker for the detection of significant ($\geq 50\%$) stenosis. A further study showed that SENC imaging could detect coronary artery disease (on a patient level) during intermediate stress with a similar diagnostic accuracy to cine wall motion analysis at peak dobutamine stress, potentially reducing the risk to patients by lowering the stress level needed for diagnosis (see Figure 2.11). Strain rate reserve was again shown to be a highly sensitive marker for the detection of inducible ischemia and showed significant decreases in the presence of even moderate stenoses of 40 to 60% (Korosoglou et al., 2010).

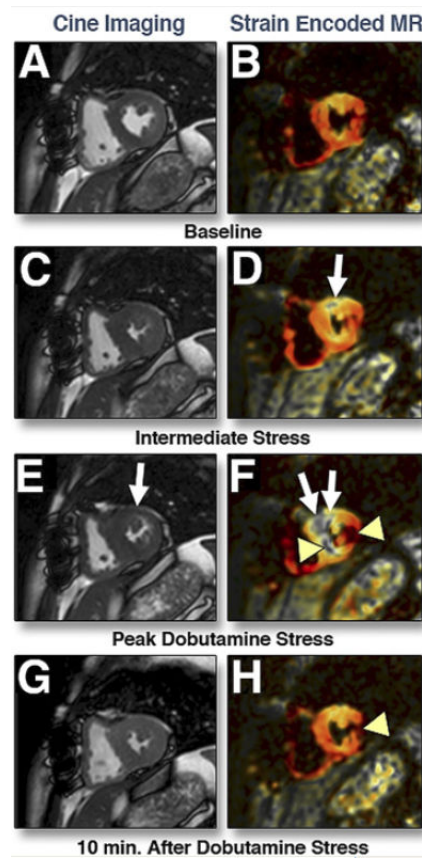


Figure 2.11: SENC imaging can detect inducible ischemia at lower stress levels than is possible for standard cine imaging. The colour scale represents pixel-wise through plane strain values with red representing high strain and grey representing low strain. At intermediate stress a clear strain defect can be seen in the SENC images (white arrow). Yellow arrow heads indicate signal voids. Reproduced with permission from Korosoglou et al. (2010).

Real-time fast-SENC has identified differences in peak systolic E_{CC} and early diastolic E_{CC} -rate between normal and dysfunctional segments in patients with heart failure (Korosoglou et al., 2008) and has been shown to be capable of identifying old myocardial infarction and differentiating subendocardial from transmural infarction (Oyama-Manabe et al., 2011) (reduced peak E_{CC} and E_{LL}). In the RV, it has been used to show a reduction in peak systolic E_{CC} at the base and reduced peak systolic E_{LL} at all levels in patients with pulmonary

hypertension compared with healthy volunteers (Shehata et al., 2010).

C-SENC identified similar infarct regions to late gadolinium enhancement (LGE) images ($90 \pm 4\%$ of the pixels identified as infarct in LGE were also identified as infarct by C-SENC) but with higher blood-infarct contrast to noise ratio (CNR was 30 ± 3.2 for C-SENC and $11 \pm 2.1\%$ for LGE) (Ibrahim et al., 2008).

2.5 Comparisons

While the techniques have been discussed separately, were developed separately, and produce images with very different appearances, HARP, DENSE and SENC are mathematically very similar. Each uses a 1-1 SPAMM tagging module to produce 3 peaks in k-space. In simple versions of HARP and DENSE either the left or right peak is then isolated for processing, although more sophisticated techniques combine both left and right peaks and may suppress or filter other peaks which would otherwise lead to artefact.

For HARP the selected peak is situated away from the centre of k-space, and phase reconstruction results in a distinctive tag-like phase variation across the image. For conventional DENSE, the decoding gradient shifts the selected peak to the centre of k-space which eliminates the tag-like appearance, and the image phase is directly proportional to displacement. Similarity between HARP and DENSE is highlighted further in the sav-DENSE variation which uses the exact HARP sequence of gradients (i.e. there is no decoding gradient) but which then treats each half of k-space separately (see Figure 2.12).

Like DENSE, SENC is a STEAM technique but with magnetization modulation in the through-plane, rather than the in-plane, direction. However, rather than encoding displacement in the phase of the image, SENC requires the acquisition of two datasets with different demodulating gradients and, as discussed previ-

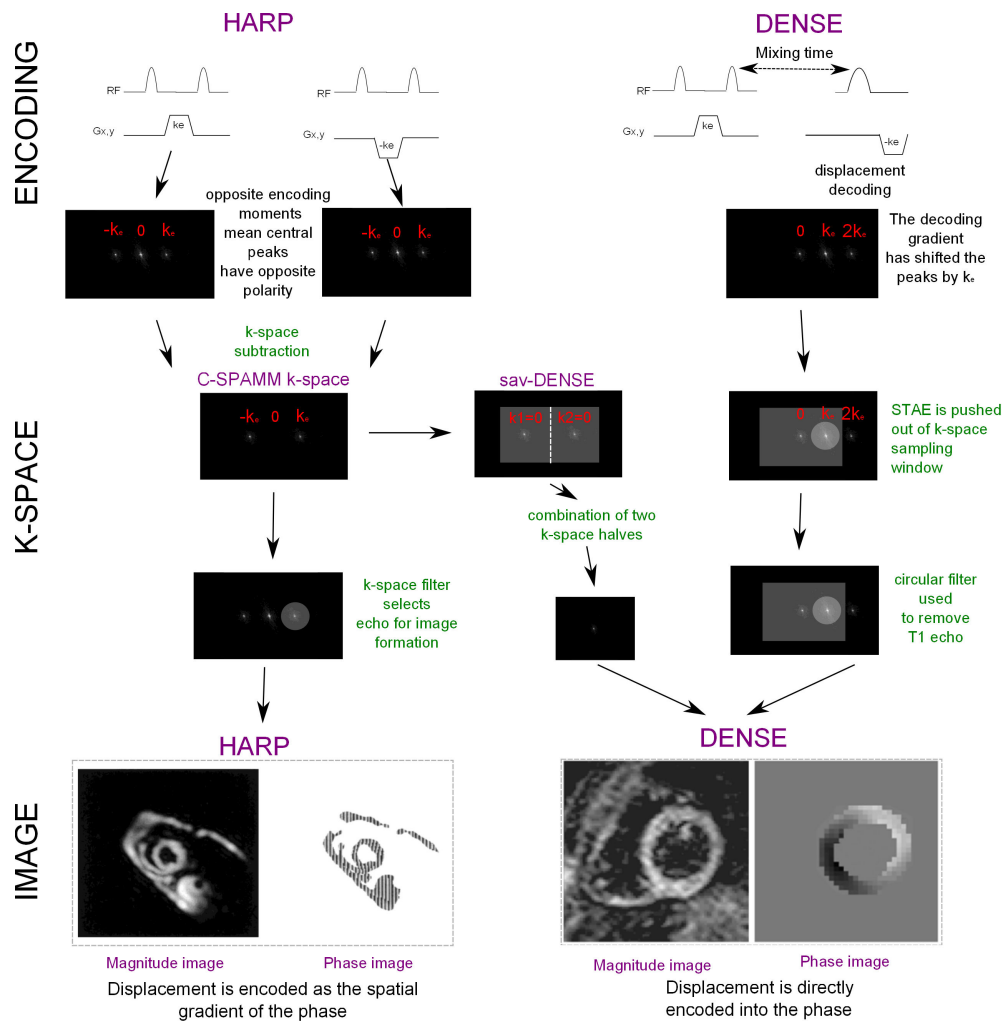


Figure 2.12: The similarities between HARP and DENSE. Although the initial encoding and final images are different, the k-space of the two techniques is very similar. The similarity is highlighted by the sav-DENSE technique which uses a standard HARP sequence but manipulates k-space to result in DENSE images. HARP images reproduced with permission from Osman et al. (1999), DENSE images from Kim et al. (2004a).

ously, the displacement information is obtained directly from the magnitude images.

There are also similarities between the phase velocity mapping and DENSE techniques in that phase velocity mapping may be regarded as the encoding of

displacement over a short period of time (the time between the two lobes of the bipolar pulse). While displacement could be encoded over longer time intervals (by increasing the time between the gradient lobes), $T2^*$ signal loss would make this unfeasible. By using a STEAM acquisition, DENSE enables displacement to be encoded over longer time intervals with signal loss resulting from slower $T1$ decay, rather than $T2^*$ decay. In phase velocity mapping, the bipolar gradients are effectively the same as the encoding and decoding gradients in DENSE. Encoding and decoding is repeated many times throughout the cardiac cycle over times which are short enough to assume a constant velocity between the gradient lobes. In DENSE however, displacement is encoded once then decoded one or more times through the cardiac cycle to measure displacement over intervals where the constant velocity assumption is no longer valid.

	Tagging	HARP	SENC	DENSE	Phase velocity
What does it measure	Displacement by following tags	Displacement encoded in phase pixel by pixel	Strain encoded in intensity pixel by pixel	Displacement encoded in phase pixel by pixel	Velocity encoded in phase pixel by pixel
How to get strain	Lagrangian strain from difference in distance between two points at two time points	Eulerian strain from spatial gradient of phase. Lagrangian strain from following points of invariant phase.	Directly measures Eulerian strain	Eulerian strain calculated from displacement field using finite element analysis. Lagrangian strain from cine DENSE between two time points	Velocity from phase map is related to Eulerian strain-rate. Integrate to get strain.
Spatial resolution	Limited by tag spacing	Limited to pixel size but is much reduced due to required k-space filter	Limited to pixel size	Limited to pixel size but can be reduced due to k-space filter	Limited to pixel size
Advantages	Visually appealing	Quick processing Used clinically	Through plane measurements Very quick processing	Quick processing	Standard on scanners
Disadvantages	Slow processing Tags fade through cycle	Low SNR due to selecting one spectral peak Tags fade through cycle Limited spatial resolution	Not widely tested Low SNR Cannot measure radial strain Tags fade through cycle	Not widely tested Low SNR due to selecting one spectral peak Tags fade through cycle Limited spatial resolution	Quick processing Can analyse entire cycle Prone to motion artefacts Integrating to get strain leads to error propagation High resolution images require lengthy acquisition times

Table 2.2: Comparison of the advantages and disadvantages of the four MR techniques

2.5.1 Need for improvements

The above methods are all capable of measuring certain aspects of myocardial mechanics. However they each have limitations and none of the techniques is yet widely used as a clinical tool. Tissue tagging is visually appealing, however conventional image-based analysis is slow and the spatial resolution of tagging is limited to the tag spacing. While the spatial resolution of HARP is higher than the tag spacing, it is still limited due to the use of k-space filters, a process which also reduces SNR. DENSE and SENC share this issue, while SENC has the additional disadvantage that it can only measure through plane strain. Tagging (with or without HARP), DENSE and SENC all suffer from tag fading which limits them to analysing the first two thirds of the cardiac cycle. The main advantages and disadvantages of each of the techniques can be found in Table 2.2.

PVM stands out from the other techniques as it requires no filtering of k-space (allowing higher spatial resolution to be acquired) and is not inherently limited to fractions of the cardiac cycle by tag fading. Although it does not measure deformation in the same way as the other techniques, myocardial velocities measured by TDI (see Section 1.3.1.1) are already used clinically and so it is clear that there is useful information to be gained from PVM in many clinical contexts. PVM can also measure three directions of motion from a single imaging slice (unlike conventional tagging or SENC). Despite the potential, previous sequences that have been used to acquire myocardial PVM data have not exploited the advantages of the technique fully, limiting its clinical applicability.

The use of prospective cardiac gating in all previous work has meant that despite not suffering from tag fading, PVM has been unable to analyse the entire cardiac cycle. The use of retrospective cardiac gating would allow analysis of atrial systole with PVM (a part of the cardiac cycle which is inaccessible to the other MR techniques due to tag fading), which contributes to 20 or 30 percent of

LV filling in healthy motion and is more important in the presence of diastolic dysfunction (Leong et al., 2010).

The application of PVM in a clinical context is currently limited by the use of Cartesian imaging which is an inefficient way to cover k-space. Imaging within a breath-hold ensures a short scan time, however the resolution that could be acquired clinically within a breath-hold with current sequences is very low and would limit the usefulness of the data. Current breath-hold techniques report resolutions of $2.7 \times 1.3 \text{ mm}$ and 37-87ms (with view sharing) in healthy volunteers depending on breath-hold duration (17-29 heartbeats) (Petersen et al., 2006), however these breath-hold times would be difficult to achieve in many clinical cases. Limiting the sequence to a clinically acceptable breath-hold time could lead to severe underestimation of peak velocities due to unacceptably low temporal resolution.

While the temporal resolution has been greatly improved by using respiratory navigator gating (for example $2.7 \times 1.3 \text{ mm}$ and 13.8ms with view sharing) (Jung et al., 2006a), allowing fine details of motion to be seen in both healthy volunteers (Codreanu et al., 2010; Delfino et al., 2008b; Föll et al., 2010) and patients (Codreanu et al., 2011a; Delfino et al., 2006; Föll et al., 2009), scan times are long, taking typically 5 minutes per slice to acquire. Including these acquisitions within a clinical workflow would extend the scan time by at least 15 minutes (to acquire three slices) which is unfeasible in many cases.

By using a more efficient k-space trajectory, high resolution navigator gated images could be acquired within an acceptable time for incorporation into a routine clinical workflow, while the resolution of breath-hold acquisitions could be improved so that they too could be clinically useful. The aim of this PhD project is to achieve these aims by developing a retrospectively gated PVM sequence using spiral k-space trajectories in order to analyse three directional velocities over the entire cardiac cycle. The following chapter gives technical

background about the various developments that are necessary to achieve this.

Chapter 3

Technique Development

3.1 Introduction

This chapter is split into three sections; Sequence Development, Image Reconstruction and Analysis.

Two versions of a myocardial velocity mapping sequence have been developed for use in healthy subject and clinical studies - a high resolution, navigator gated version and a lower resolution, accelerated, breath-hold version. The sequences have been implemented on a 3T Siemens Skyra scanner (Siemens Medical Solutions, Erlangen, Germany) by heavily adapting an existing phase velocity mapping sequence. All gradients and RF pulses have been redesigned for the project, and the looping structure of the sequence has also been changed.

The image reconstruction has been implemented using the Siemens Image Calculation Environment (ICE) and, for the breath-hold reconstruction, the Gadgetron GPU system (Hansen et al., 2012) was used for non-Cartesian SENSE reconstructions.

Analysis tools were developed from scratch using MATLAB (The Mathworks, Natick, MA, USA).

3.2 Sequence Development

Figure 3.1 shows the sequence diagram for the navigator gated sequence with the looping structure for the acquisitions shown in the two diagrams beneath. The breath-hold version is the same except there is no respiratory navigator and the spiral design is different, as discussed later. The following sections describe the background and implementation of each of the parts of the sequence as highlighted in the sequence diagram. In the following discussion ‘Z’ refers to the through-plane direction while ‘X’ and ‘Y’ refer to the two perpendicular in-plane directions.

3.2.1 Respiratory navigator

3.2.1.1 Background

MR images are generally acquired over a period of time ranging from a few hundred milliseconds (low temporal and spatial resolution single-shot data) to several minutes (higher temporal and spatial resolution segmented data). When imaging the heart, dealing with motion is one of the main obstacles to overcome; not only does the heart contract in a complex manner during the cardiac cycle, but the whole heart moves during the slower respiratory cycle. While real-time imaging is showing great potential, particularly for those patients who struggle to hold their breath or who have arrhythmias (Feng et al., 2012), the resolution that can be acquired is currently too low for many applications. Various methods have been proposed to reduce or remove the problems

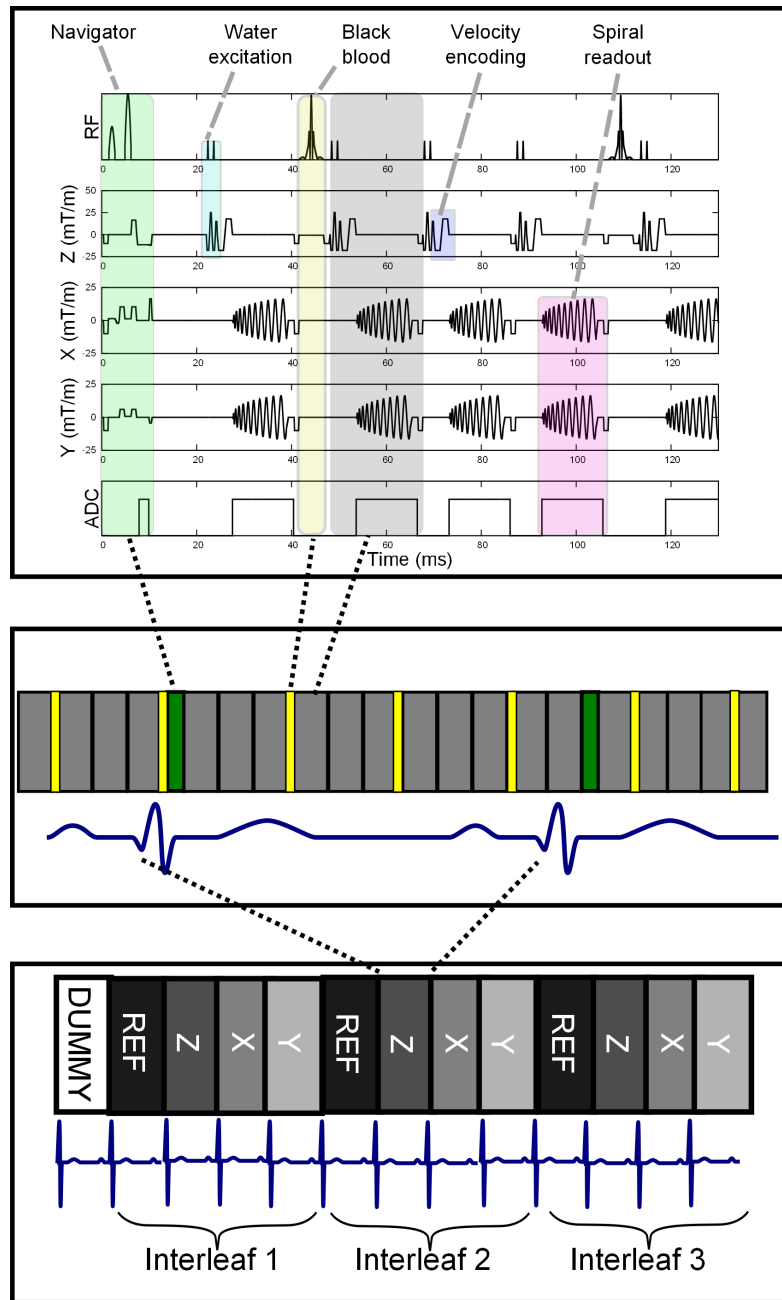


Figure 3.1: Top: Sequence diagram of the navigator gated version. Middle: Acquisition structure over a single heartbeat with black blood pulses every three repeats and a navigator at the beginning of the cycle (not present in breath-hold version). Bottom: Acquisition structure over several heartbeats with reference (REF) and velocity encoded (X, Y and Z) data being acquired on consecutive heartbeats.

of cardiac and respiratory motion in order to be able to image the heart effectively and a comprehensive review of these methods can be found in Scott et al. (2009). The detrimental effects of cardiac motion are usually eliminated by ECG triggering (see Section 3.3.2) and imaging within multiple short periods in the cardiac cycle. The effects of respiratory motion are more difficult to overcome and numerous methods have been proposed and applied, as discussed briefly below.

Early MR studies did not take respiratory motion into account, and averaging was used to reduce the effects of motion (Higgins et al., 1985; Steiner et al., 1983). As improvements in scanner hardware and sequence design reduced acquisition times, scans became short enough to acquire while the subject held their breath, thereby removing any respiratory motion. However this limits the spatial resolution, temporal resolution and SNR to that which can be acquired in a reasonable breathhold duration (Atkinson and Edelman, 1991). Higher resolutions can be obtained by completing a single scan over several breathholds (Feinberg et al., 1985), however this leads to possible issues due to misregistration of different breathhold positions. Another problem is that the breathhold itself may affect the functioning of the heart. Towards the end of a long breathhold, for example, the heart rate is seen to increase which could affect measurements. These issues have been reduced with patient feedback (Wang et al., 1995) although with limited success.

In order to get higher resolution images, the respiratory cycle can be monitored and imaging can be performed only at certain times when the motion is limited - this is known as respiratory gating. End expiration is the most common gating position as it is more stable than end inspiration (Holland et al., 1998). Monitoring of the respiratory cycle can be achieved by measuring the position of the chest using a belt or respiratory bellows (McConnell et al., 1997; Wang et al., 1995), measuring inspired and expired gases (Ehman et al., 1984), or monitoring the position of the diaphragm using MR images known as navigators.

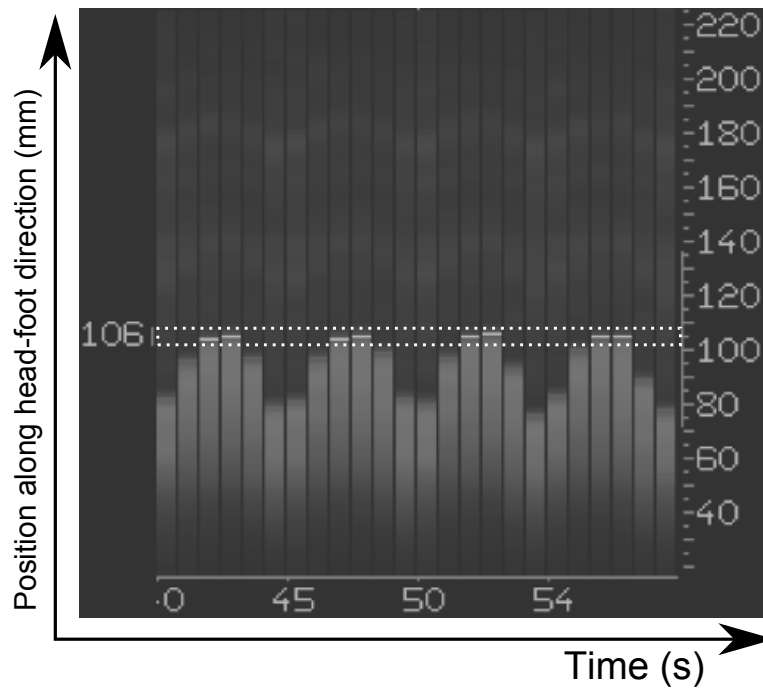


Figure 3.2: Example navigator trace showing a series of 1D images acquired during normal breathing. The motion of the diaphragm can be seen as the height of the bars changes. The heavy white lines show detected edges which lie within the predefined acceptance window (dotted box).

Navigators are typically played out once per cardiac cycle immediately before image data is acquired and generally involve exciting a column of tissue that passes through the dome of the right hemi-diaphragm.

Spiral excitation trajectories can be used to excite a column of tissue (Cline et al., 1991) or a crossed pairs spin echo sequence can be used (Ehman and Felmlee, 1989). When the latter is used the 90° and 180° pulses are played out in two intersecting planes, and a spin echo is generated from only the column of tissue affected by both pulses (Feinberg et al., 1985). The readout gradient is then aligned along the column length and the position of the diaphragm can be measured automatically in the 1D navigator image by edge detection, correlation or least squares fit algorithms (Wang et al., 1996a). The measured position

can be used to trigger or gate acquisitions depending on whether the diaphragm is within the desired range at that time or not. An example navigator trace (one per cardiac cycle), showing a series of 1D navigator images over time, is shown in Figure 3.2.

The gating window is defined by using a separate scout acquisition where the navigator sequence is played out repeatedly (every few hundred milliseconds) for a number of respiratory cycles and the end expiration position is measured. An acceptance window of a set size is then placed around this position. The size of the acceptance window determines how much respiratory motion is accepted and therefore determines the respiratory efficiency - the percentage of acquired data which is used in the final images. The choice of window size is therefore a compromise between respiratory efficiency (and hence scan length) and final image quality. A typical window size of 5mm leads to an efficiency of around 40% (Taylor et al., 1999).

Most navigator gated acquisitions in clinical cardiovascular MR acquire data at a single time point in the cardiac cycle and it is assumed that the navigator position determined immediately before data acquisition reflects the respiratory position at the time of the data acquisition. Typically a single navigator is acquired per R-R interval and its position is used to determine whether data acquired in that heartbeat is used for the final image (known as a prospective acceptance-rejection algorithm (ARA)) (Oshinski et al., 1996; Sachs et al., 1994). For long readout times, or for cine-imaging, respiratory motion within the data acquisition period may still degrade image quality. This has been shown in a coronary artery imaging study comparing images acquired 100ms after the navigator with images acquired just 20ms after the navigator. Image quality (both by visual scoring and by quantitative measures of contrast to noise ratio) significantly improved for the shorter delay period (Spuentrup et al., 2002). To deal with this problem two navigators can be acquired, one at either side of the imaging window, and both can be used to decide whether data is accepted,

ensuring that very little motion can occur during imaging (Wang et al., 1996b). However this reduces the respiratory efficiency as more data is rejected.

A fixed navigator acceptance window can result in a very inefficient scan (or even a scan which fails to complete) if the subject's breathing drifts during imaging. Algorithms which adapt the gating window position or the acquisition order in real time can be used to make sure the acquisition is completed as efficiently as possible, examples are PAWS (phase ordering with automatic window selection) (Jhooti et al., 2000), MAG (motion adapted gating) (Sinkus and Börnert, 1999) and CLAWS (continuously adaptive windowing strategy) (Jhooti et al., 2010).

Another way to improve the efficiency of navigator gated scans is to use biofeedback - the subject can be informed when the diaphragm is in the correct position either by an auditory signal (Wang et al., 1995) or by displaying the navigator trace (Liu et al., 1993). The navigator trace can be represented in a game-like interface to improve patient compliance (Jhooti et al., 2011).

3.2.1.2 Implementation

A crossed-pair spin-echo based respiratory navigator has been used to monitor the position of the diaphragm (see Section 3.2.1). It is only used for the high resolution images since the breath-hold acquisitions have no need for respiratory motion compensation.

When the navigator sequence is being played out, no imaging data can be collected. In order that as much of the cardiac cycle as possible is imaged, the navigator has been adapted to make it as short as possible. This has been achieved by using shorter RF pulses (which have a less sharp slice profile) and by shortening the echo time of the navigator sequence (6.8ms compared with 20.5ms for the original navigator sequence).

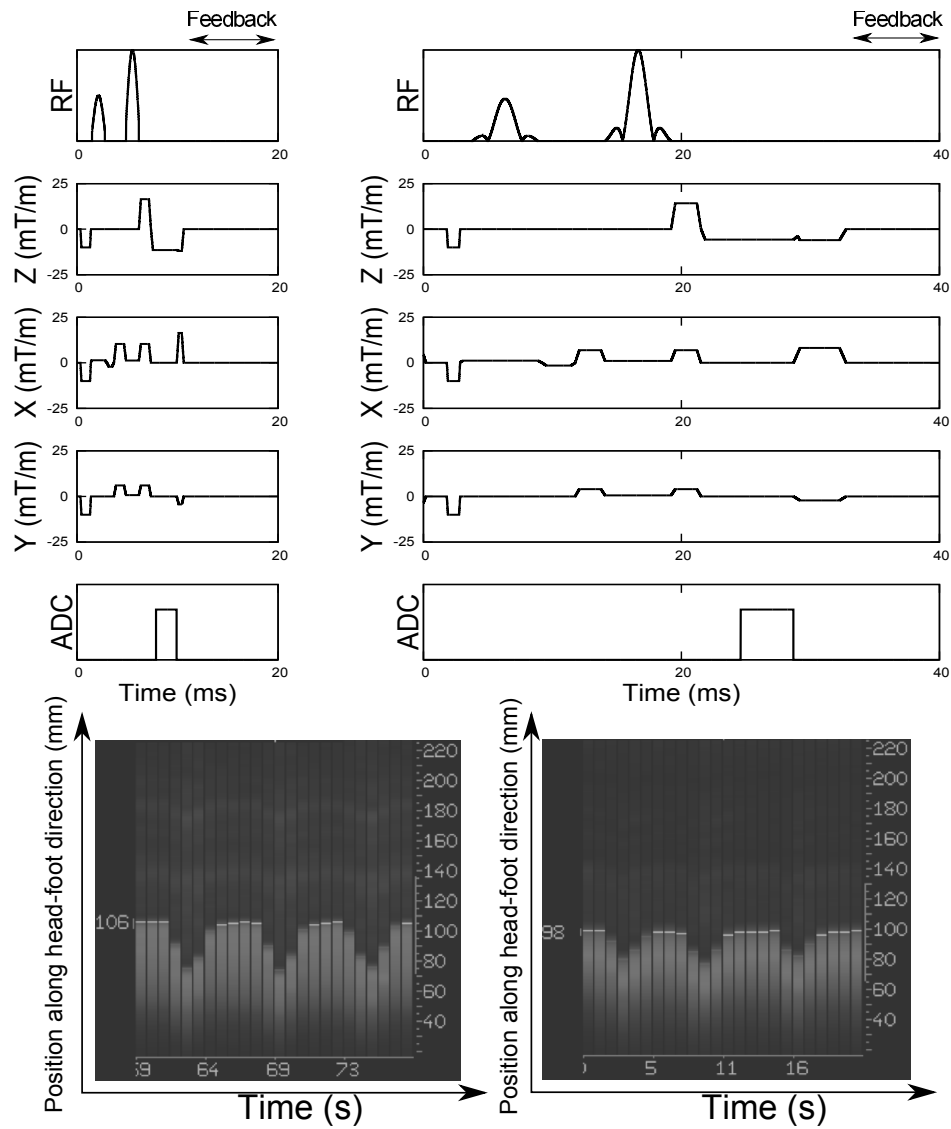


Figure 3.3: Shortened (left) and original (right) navigator sequence diagrams (top) and navigator traces acquired from the same subject (bottom). The shortened sequence takes just 9ms plus 10ms feedback time, whereas the original sequence takes 30ms plus 10ms feedback time.

The shortened sequence can be seen in Figure 3.3 along with the original sequence. The changes implemented have reduced the time taken to play out the navigator sequence from 30ms to just 9ms (in each case 10ms feedback time is needed after the navigator sequence is played out). The figure also shows example navigator traces taken with the original and shortened navigator sequences in the same subject. Despite the less precise excitation profile and the lowered SNR (average SNR for the original sequence is 5.64 and for the shortened sequence is 3.55), the shortened navigator sequence is clearly capable of consistently tracking respiratory motion.

3.2.1.2.1 Modified navigator algorithm During preliminary testing it was seen that a single navigator per cardiac cycle was not sufficient to repress respiratory motion over the entire cardiac cycle as significant respiratory motion can occur during a heartbeat. This can be seen in the top images of Figure 3.4 which show that a conventional prospective accept-reject algorithm allows motion to corrupt the later images, blurring the images towards the end of the cardiac cycle (shown by white arrows). This is particularly apparent in subjects with long RR durations. A modified, stricter, criterion was therefore used in order to remove this residual respiratory motion.

The modified algorithm requires the navigator for the current *and following* heartbeat to be within the acceptance window in order for data acquired in that heartbeat to be used for the final images (this differs from conventional before and after gating which acquires two navigators in each cardiac cycle and would therefore further reduce the time available for imaging). Implementing this required significant alterations to the navigator reconstruction code. In a conventional single-navigator accept-reject algorithm the navigator information acquired in one heartbeat is used to decide what data to acquire in the *following* heartbeat, whereas for this modified algorithm the information is needed for the *current* heartbeat.

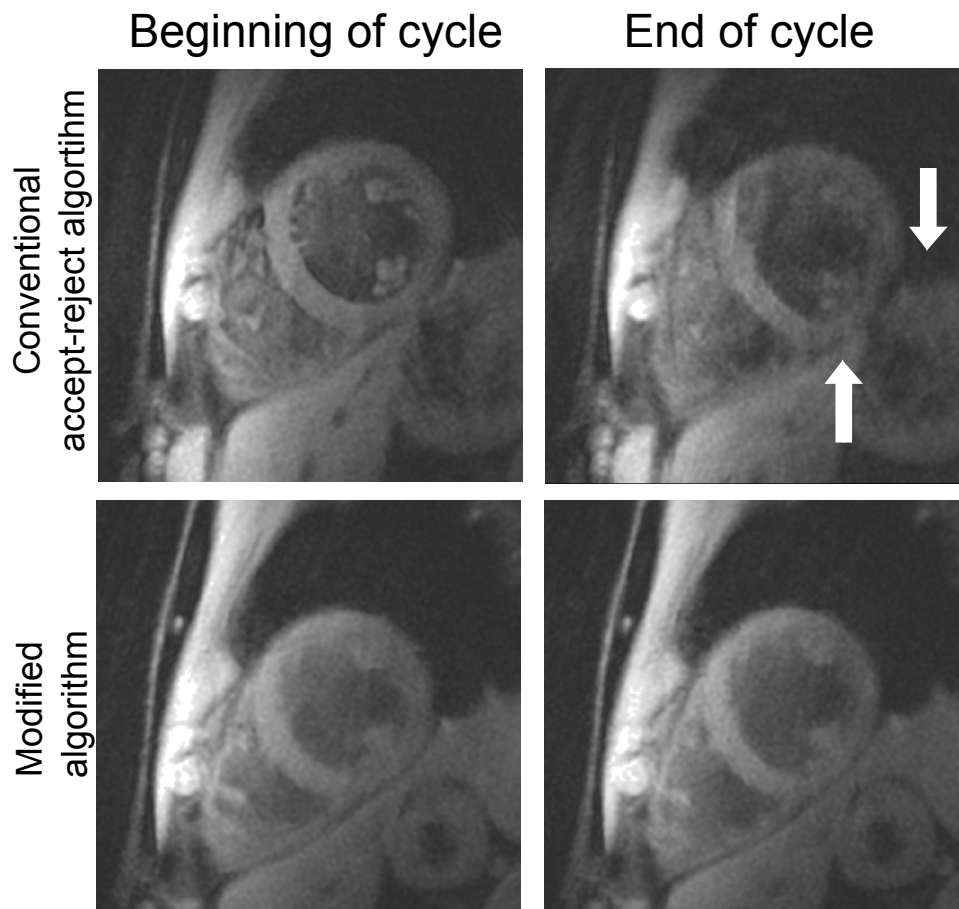


Figure 3.4: Early (left) and late (right) frames from navigator gated cine acquisitions with a single navigator per cardiac cycle. The top images were acquired with the conventional accept-reject algorithm while the bottom images were acquired with a modified, stricter algorithm. The white arrows indicate areas in the image which are corrupted by unsuppressed respiratory motion when using the conventional accept-reject navigator algorithm.

While use of the modified algorithm improves image quality, respiratory efficiency is reduced as can be seen in Figure 3.5. In this Figure an example diaphragm motion trace is shown in the middle along with an acceptance window (green box). At the top, the progression of the sequence according to the conventional algorithm is shown (green arrows show heartbeats from which data is accepted into the final images). At the bottom, the progression using the modi-

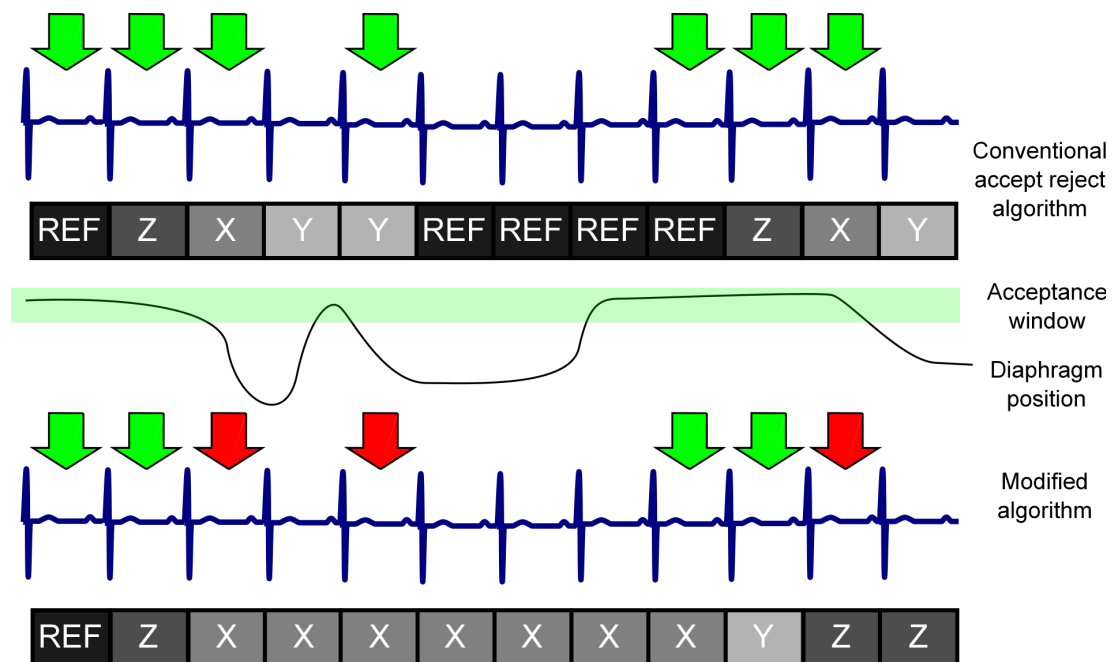


Figure 3.5: The effect of the modified navigator algorithm on the efficiency of the technique. The progression of the scan for the same respiratory motion is shown for the conventional accept reject algorithm (top) and the modified algorithm (bottom). Green arrows show accepted data, red arrows indicate data that is accepted by the conventional algorithm but not by the modified algorithm.

fied algorithm is shown (red arrows show heartbeats which were accepted with the conventional algorithm but are rejected with the modified algorithm). After the twelve heartbeats shown the conventional algorithm has progressed much further through the acquisition and hence the respiratory efficiency is much higher than the modified algorithm. However data from three heartbeats with significant respiratory motion have been accepted and this data will corrupt the final image. The decrease in efficiency depends on the breathing pattern of the subject and on the time between navigators (RR duration). If the end expiratory pause is shorter than the RR duration the scan will never complete, whereas if the pause is much longer than the RR duration the efficiency will not be affected as much.

In order to increase the efficiency of the navigator technique, and therefore keep the scan duration to a reasonable time, a biofeedback mechanism in the form of a screen at the back of the scanner room was used to display the navigator trace to the subject during image acquisition. The volunteers can therefore guide their breathing into the acceptance window and so complete the scan either by slow and steady breathing or by a series of short breath-holds.

3.2.2 Water excitation

3.2.2.1 Background

MRI relies on the fact that hydrogen nuclei within water will all precess at the same frequency when in the same magnetic field. However, hydrogen nuclei which are in different chemical environments will precess at different frequencies, a phenomenon known as chemical shift. While the majority of hydrogen nuclei within the body are contained within water, a significant number are also found in fat. They precess at a different frequency to the hydrogen in water and can therefore cause problems for imaging due to off resonance effects, particularly for imaging techniques with long readout times like EPI or spiral trajectories. In Cartesian imaging off resonance effects lead to a simple translation of the signal in the readout direction while for other trajectories the effect is more complicated. Therefore there is a need for imaging in a way which reduces the signal from fat and hence reduces the artefacts caused by off resonance. Several techniques have been developed to accomplish this (Bley et al., 2010).

For imaging at a single time point in the cardiac cycle, inversion recovery can be used to suppress fat signal. An example is Short T_1 /Tau Inversion Recovery (STIR) (Bydder et al., 1985) which exploits the short T_1 of fat (around 260ms at 1.5T) compared with other tissues (for example myocardial T_1 is closer to 1000ms). In STIR imaging all of the longitudinal magnetisation is inverted and

then imaging takes place at the point when the longitudinal magnetisation of fat is passing through the null point. This effectively eliminates the signal from fat, however some of the water signal is also lost (around 40-50% (Bley et al., 2010)). The technique is reliable and insensitive to B_0 inhomogeneity, although it can be sensitive to B_1 inhomogeneities if an adiabatic inversion pulse is not used. In addition image contrast is affected by this method of fat suppression as the resulting images will be inherently T_1 weighted.

Spectrally selective RF pulses can also be used to excite fat before using crusher gradients to spoil the resulting transverse magnetisation. Conventional imaging then follows before the fat magnetisation has time to recover with the result that no fat signal is acquired (Haase et al., 1985). However these techniques are sensitive to B_0 and B_1 inhomogeneity which can lead to incomplete suppression of fat signal or even accidental suppression of water signal.

Dixon's two point method involves acquiring two images with different echo times, one with fat and water in phase, and one with fat and water 180° out of phase. These images can then be combined to produce images with only fat or with only water signal (Dixon, 1984). Extensions to the original two-point technique (Glover, 1991; Glover and Schneider, 1991) deal with B_0 sensitivity. However they are not suitable for cine imaging, and they require complicated reconstruction.

Rather than suppressing fat signal, water excitation uses a binomial series of RF pulses to excite only a selected spectral band of frequencies centred on the frequency of water (Levitt, 1986; Meyer et al., 1990; Schick, 1998), and in this way avoid exciting fat. A water excitation consists of a series of RF pulses separated by a time τ . The ratio of flip angles follows a binomial sequence while the sum of the flip angles is the desired flip angle ϕ . If τ is chosen so that the off resonance frequency of fat is $\frac{1}{2\tau}$ then while the magnetisation of water will not nutate at all (in the rotating frame of reference) between pulses (because it

is at the resonance frequency), fat will nutate by π radians between each pulse. This effectively means that at the end of the excitation water has been flipped by ϕ where as fat has been flipped by

$$\alpha \sum_{j=0}^n (-1)^j \binom{n}{j}. \quad (3.1)$$

α is a normalisation factor which ensures that the sum of the flip angle magnitudes is ϕ . The nutation between each pulse of π radians effectively reverses the direction of the next flip angle (hence the $(-1)^j$ factor), and $\binom{n}{j}$ is the binomial coefficient. This sum is equal to zero (which can be proved by induction, see Appendix A), so fat is not excited at all, which is the desired result.

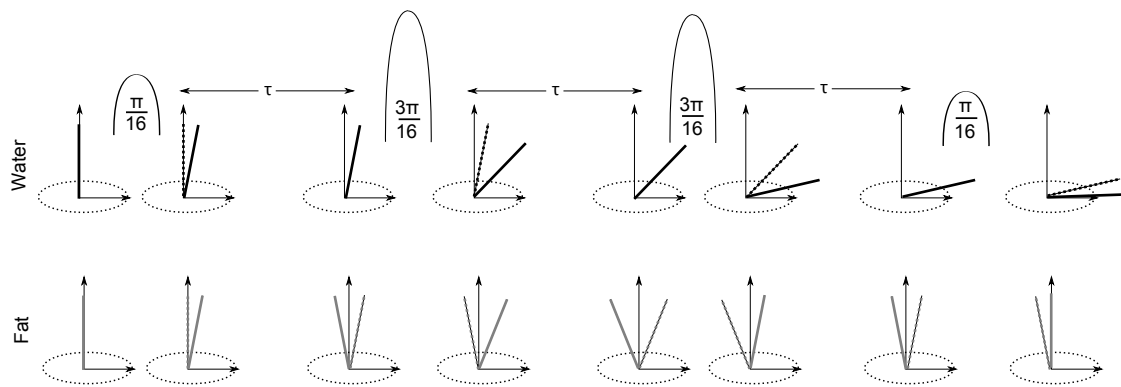


Figure 3.6: The effect of a 1-3-3-1 water excitation (RF pulses separated by time τ with respective flip angles shown at the top) on water (black lines) and fat (grey lines). In each case the solid line represents the current magnetisation and the dotted line represents the previous magnetisation.

This process is shown diagrammatically for a 1-3-3-1 water excitation with a total flip angle of $\frac{\pi}{2}$ in Figure 3.6. Before the first pulse both water and fat magnetisation point along the longitudinal direction. After the first pulse both have been flipped by $\frac{\pi}{16}$. Before the next pulse the fat has nutated by $\frac{\pi}{2}$, while water has not changed. The process continues in this way with fat nutating $\frac{\pi}{2}$ between each pulse. By the end of the excitation water is flipped by $\frac{\pi}{2}$ but fat

has returned to the longitudinal direction and hence contributes no signal.

While any series of appropriately separated binomial pulses will have this effect, the longer the train is, the more precise the frequency response will be and hence the more specific the excitation (Bernstein, 2004). However this will obviously extend the repeat time of the sequence so long trains are not acceptable for cine imaging. Water excitation is most commonly used with long readout imaging techniques such as spiral or EPI (Schick et al., 1998).

3.2.2.2 Implementation

As shown in the previous section, any series of binomial RF pulses with appropriate time separation can be used to excite only water and not fat. The shortest of these is a simple 1-1 pulse which uses two RF pulses of equal magnitude. This adequately removes fat signal and has been used in both sequences so that the repeat time of the sequence is kept as short as possible. The water excitation RF pulses and gradients can be seen in Figure 3.7.

The two RF pulses are the same, each with a flip angle of half the total user-defined flip angle and a bandwidth time product of 1.996. The time separation of the RF pulses is 1.2ms. This time is calculated such that the fat accrues a phase of π radians between the pulses:

$$\text{Water-fat separation} \approx 420\text{Hz} \quad (3.2)$$

$$\text{time to accrue } \pi \text{ phase} = \frac{\pi}{420\text{Hz} \times 2\pi} = 1.2\text{ms}. \quad (3.3)$$

G1 and G3 are the slice select gradients and their amplitude is calculated based on the user-defined slice thickness. G2 and G4 are then calculated automat-

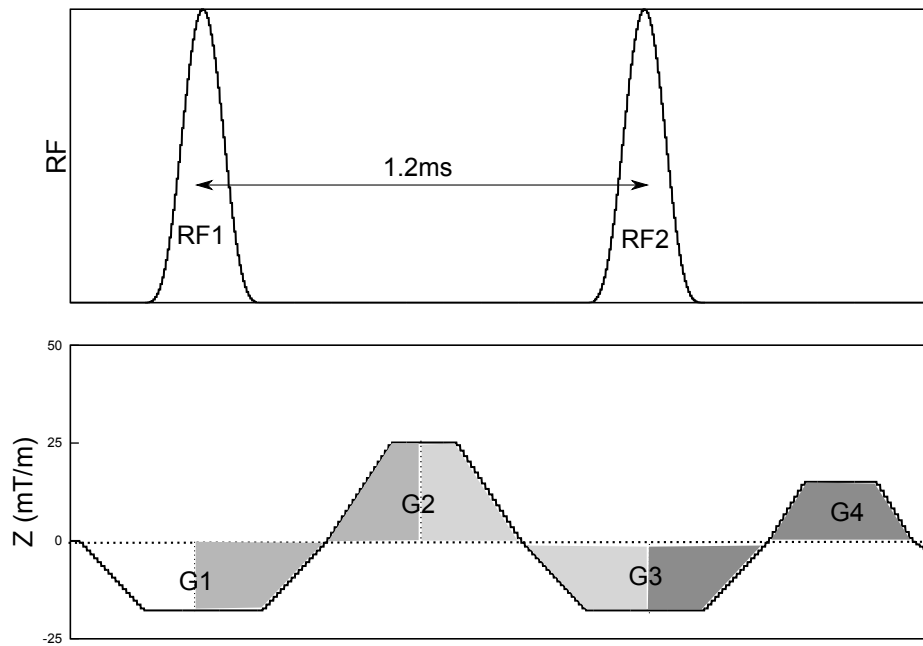


Figure 3.7: 1-1 binomial water excitation. The RF separation is such that the difference in phase between water and fat is π radians (1.2ms at 3T). The gradients are calculated so that the areas shaded in the same greyscale are equal.

ically such that the areas shaded in equal greyscale are equal. They are constrained in such a way that the slew-rate never exceeds the maximum possible slew rate.

3.2.3 Black blood pulse

3.2.3.1 Background

Phase velocity mapping is typically used to measure blood flow and hence good blood signal is required. However, when measuring myocardial velocities, high blood signal can be detrimental, making the myocardium-blood boundary hard to segment, causing aliasing of the much higher velocities in blood than in myocardium, and causing artefacts due to beat-to-beat variations in blood flow.

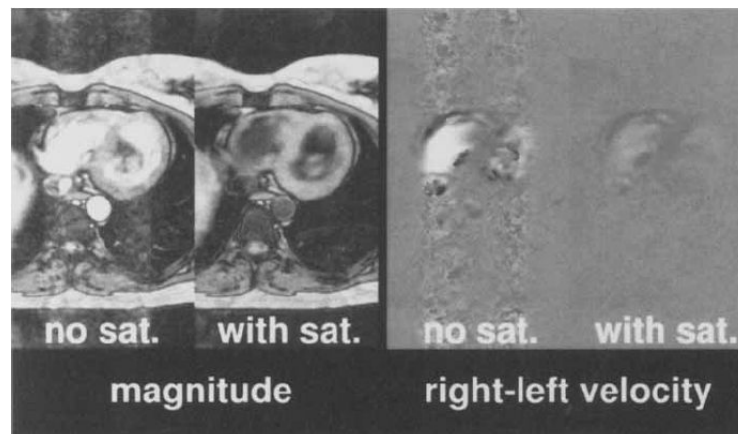


Figure 3.8: The effect of a black blood pulse in Cartesian phase velocity mapping (the phase encoding direction is anterior to posterior). The artefact caused by beat to beat variations in blood flow can be seen in the 'no sat' magnitude images and velocity maps but is removed by the black blood pulse as can be seen on the 'with sat' images and velocity maps. From Drangova et al. (1997).

For Cartesian imaging this causes ghosting in the phase encoding direction (see Figure 3.8). Removing this artefact using a black blood pulse has been shown to improve the reproducibility ($P < 0.001$) of myocardial motion measurements in the areas affected by the ghosting (Drangova et al., 1997). For non Cartesian imaging strategies the artefacts may be less coherent (for example the 'swirl' artefact in spiral imaging) but may still affect measurements in the myocardium.

Black blood images are usually obtained by using single (Mayo et al., 1989) or double (Edelman et al., 1991) inversion recovery methods, which rely on the fact that blood flows out of the imaging slice between magnetisation preparation and imaging. Imaging occurs at a set time known as the inversion time (TI) after magnetisation preparation at which point the signal from blood flowing into the slice is nulled. While this can produce good blood suppression for techniques which image at a single point in the cardiac cycle, it is not appropriate for cine imaging where constant suppression of blood signal is required.

Instead, a black blood saturation pulse can be used.

The black blood pulse works by exciting slabs of material on either side of the slice to be imaged and then dephasing the magnetisation with a large spoiler gradient. The result is that the imaging slice is untouched while the blood on either side is saturated. If the black blood pulse is repeated at short enough intervals the result is that saturated blood flows into the imaging slice and no signal is received from blood during data acquisition (Felmlee and Ehman, 1987).

3.2.3.2 Implementation

The blackblood pulse used can be seen in Figure 3.9 and was developed by the Freiburg group (Hennig et al., 1998). It is designed by adding together a 90° pulse acting on a 4cm thick slab centred on the imaging slice and a -90° pulse acting on an 18cm thick slab, also centred on the imaging slice, with the result that a central 4cm slab is unaffected while 7cm slabs on either side receive a -90° excitation, the signal from which is then dephased (see Figure 3.9). The total time taken to play out the black blood module is 6.5ms.

The benefits of using the blackblood pulse for spiral imaging can be seen in Figure 3.10. The top images have no blackblood pulse whereas the bottom images have blackblood pulses played out on every other phase. The images are taken from early diastole when there is a lot of blood flow into the left ventricle. Beat to beat variations in this flow cause artefacts that can be seen in both the magnitude images (left) and velocity maps (right) when black-blood pulses are not used. Instead of the ghosting seen with Cartesian trajectories (see Figure 3.8), these artefacts are seen as ‘swirling’ throughout the image. Removing the blood signal removes these artefacts and also makes defining the bloodpool-myocardium boundary easier.

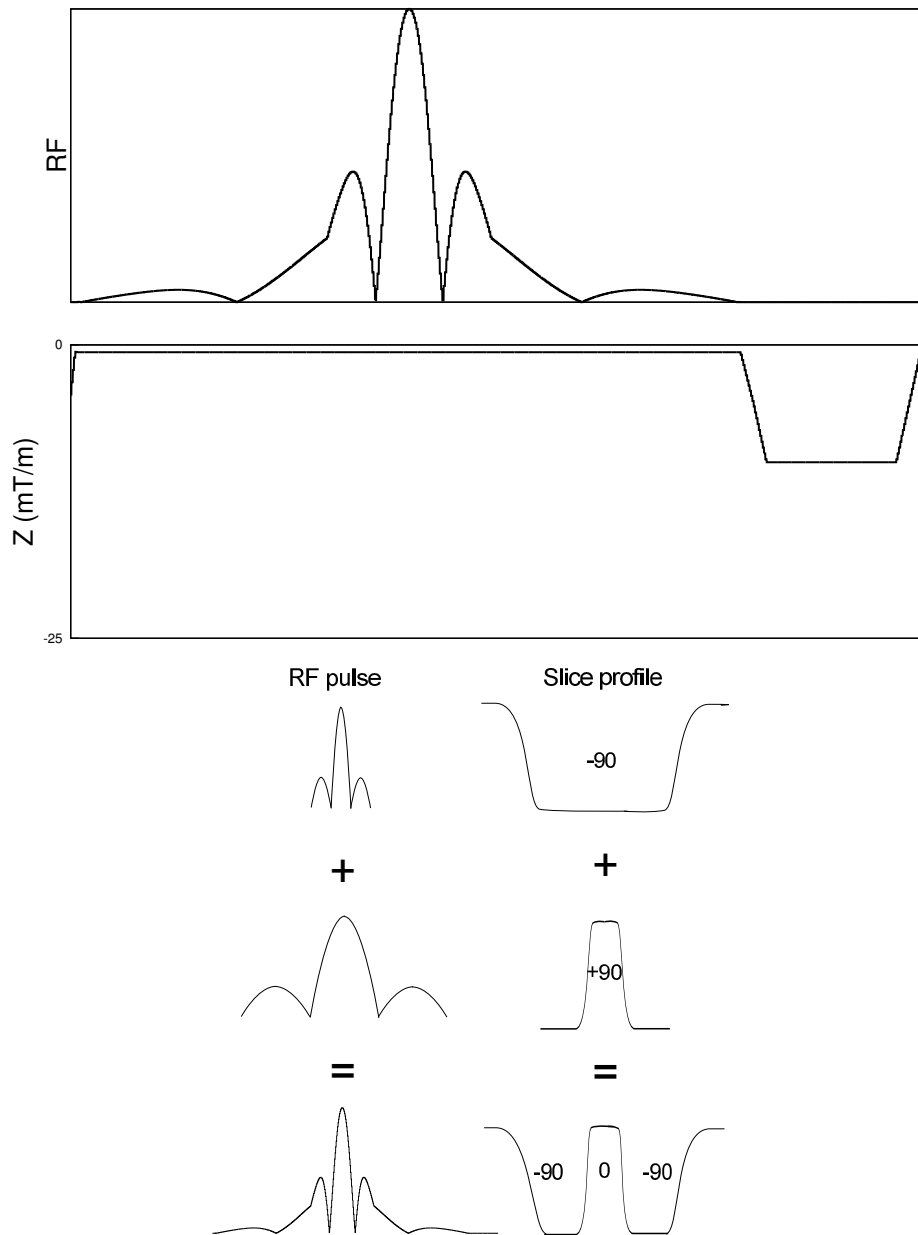


Figure 3.9: Top: Black blood pulse with associated gradients. Bottom: Explanation of the black blood pulse slice profile. The combination of two pulses with different slice profiles and opposite excitation direction results in slabs on either side of the imaging slice being excited while the imaging slice itself is not excited.

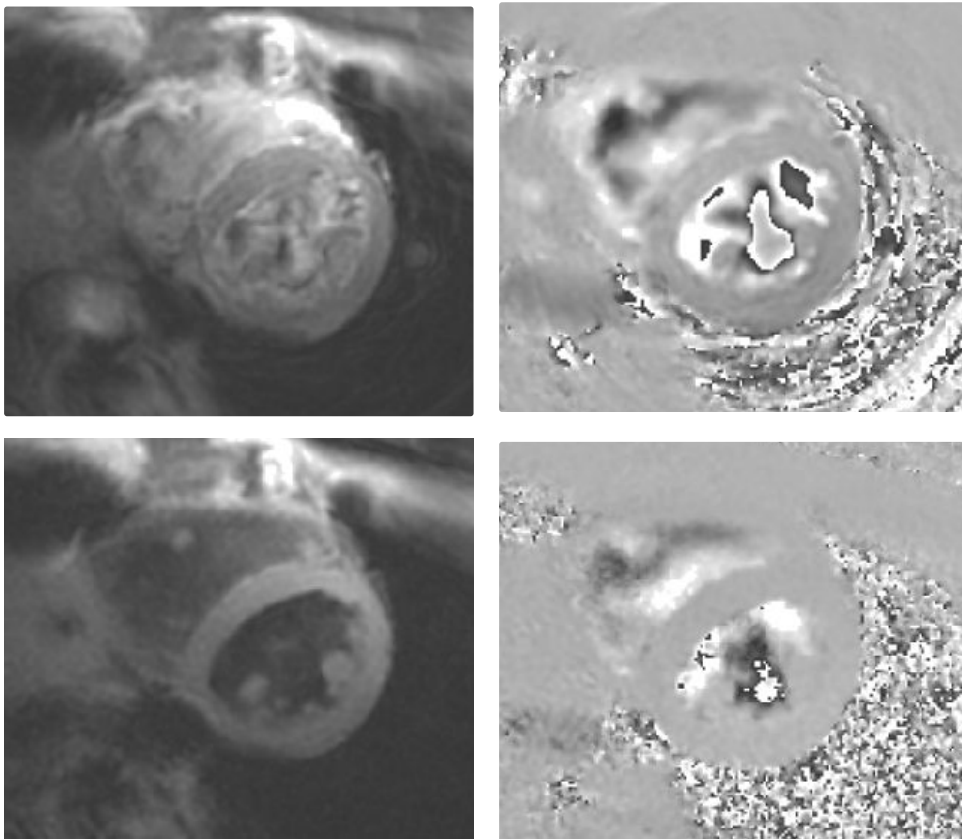


Figure 3.10: Top: Magnitude image and velocity map taken from early diastole without black blood pulses. Artefacts due to beat-to-beat variations of blood flow can be seen as ‘swirling’ throughout the images, while aliasing due to high blood velocities is seen in the velocity maps. Bottom: By using black blood pulses the artefacts are removed.

3.2.3.3 Frequency of black blood pulses

The black blood pulse increases the repeat time of the sequence so it is advantageous to play it out as little as possible. The effect of the blackblood pulse lasts until either blood outside of the saturated bands starts to reach the imaging slice, or the blood signal recovers due to T_1 recovery. The design of the black blood pulse is such that the saturated region is about 7 cm thick on either side of the unsaturated region. At a maximum healthy filling blood velocity of around

85cm/s (Appleton et al., 1988), unsaturated blood would take approximately 80ms to reach the imaging slice. The T_1 of blood at 3T is around 1500ms (Lu et al., 2004) so in this time the blood would only have recovered to around 5% of its unsaturated value. Theoretically therefore the black blood pulses should be played out at least every 80ms in order to ensure no unsaturated blood reaches the imaging slice at any point in the cardiac cycle.

In order to decide how often the blackblood pulse should be played out in practice, mid ventricular short axis slices were acquired five times with different blackblood frequencies in three healthy volunteers with a preliminary sequence version. The blackblood pulse was played out on every phase (BB1), every other phase (BB2), every third phase (BB3), every fourth phase (BB4) and without any black blood pulses (BB0). K-space was covered using 11 spiral interleaves each of 17ms duration, leading to an acquired temporal resolution of 35ms and acquired spatial resolution of 1.95x1.95mm. This version of the sequence used prospective cardiac gating and only acquired through plane velocities (with a VENC of 30cm/s), allowing acquisition within a 23 second breathhold. The TR was kept constant whether or not a black blood pulse was being used on that repeat - when black blood pulses were not used, a delay of the same duration was inserted. Slice thickness was 10mm and a 1-1 water excitation was used with flip angle of 15 degrees.

The images were analysed quantitatively and qualitatively to decide how often the black blood pulse should be played out.

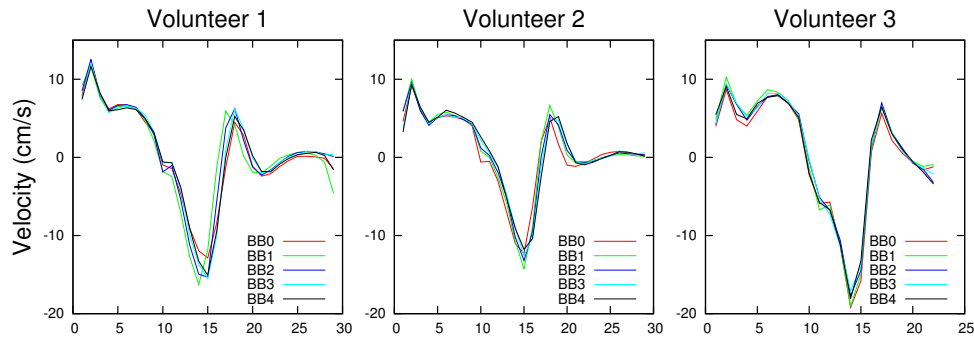


Figure 3.11: Global longitudinal velocities from all three volunteers acquired with different blackblood frequencies

3.2.3.3.1 Results The global myocardial velocities measured from the acquisitions with BB0 to BB4 from all three volunteers are shown in Figure 3.11. The features of the curves are similar in all cases but some differences in peak velocities are seen between the different acquisitions. However peak velocities are not affected consistently by reducing the blackblood frequency.

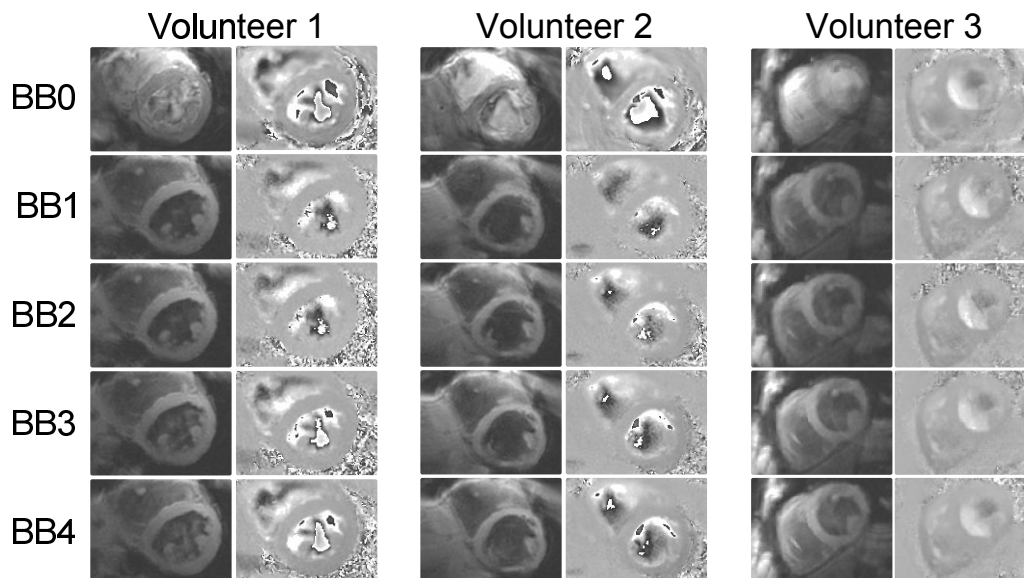


Figure 3.12: Images from different blackblood frequencies

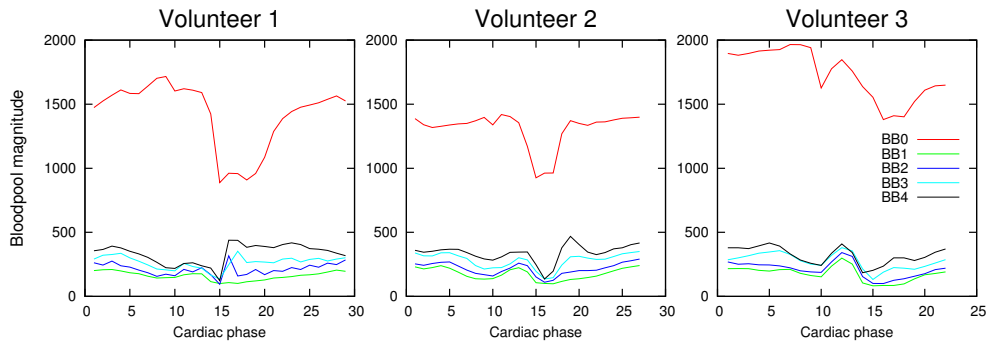


Figure 3.13: Bloodpool signal magnitude over the cardiac cycle for different blackblood frequencies

	BB1	BB2	BB3	BB4
Volunteer 1	0.12	0.18	0.21	0.25
Volunteer 2	0.15	0.17	0.19	0.21
Volunteer 3	0.18	0.22	0.26	0.33

Table 3.1: Ratio of maximum bloodpool signal with different blackblood frequencies to the maximum signal with no blood suppression.

Early diastolic images from all three volunteers with the different frequencies of black blood pulses can be seen in Figure 3.12. Artefacts can clearly be seen in all of the BB0 images, and the vast majority of those artefacts is removed for BB1-BB4. However an increasing amount of blood pool signal as the black blood pulse frequency is reduced can be seen, particularly in Volunteer 1. The magnitude of blood signal in the bloodpool of each acquisition was measured over time and is plotted in Figure 3.13. The blood signal is clearly reduced for BB1-BB4 throughout the cardiac cycle when compared with BB0 (the dip in magnitude in early diastole in the BB0 curves of Volunteers 1 and 2 is due to signal loss from intravoxel dephasing in the fast moving blood). The ratio of the maximum blood signal in the black blood acquisitions with the maximum blood

signal in BB0 acquisitions was then calculated. Values are shown in Table 3.1 and in all cases show an increasing level of blood signal in the bloodpool as black blood pulses are played out less frequently.

3.2.3.3.2 Conclusions The measured global velocity time curves are very similar for different frequencies of black blood pulse and peak velocities do not vary consistently as the blackblood frequency is reduced. However, the images in Figure 3.12 show that black blood pulses remove the artefacts caused by beat to beat variations in blood flow and also improve the blood-myocardium contrast, making segmentation easier. As black blood pulses are played out less often, the level of blood signal in the blood pool increases. This is likely to be because more blood is getting into the LV during diastolic filling without being fully saturated.

From this investigation the level of blood signal does not appear to significantly affect the measured velocities in spiral imaging. However it is still desirable to reduce the blood signal to make segmentation easier and to ensure there are no artefacts due to fast flowing blood which could reduce overall image quality. A compromise between temporal resolution and blood suppression is needed. It was decided that blood pool signal should be kept below 25% of its unsaturated value which, for this sequence means using BB2. With a TR of 35ms this means one blackblood pulse approximately every 70ms, which agrees well with the approximate theoretical value of 80ms found above.

In the two final sequences used for this thesis the TRs are 21ms and 24ms. To ensure good blood suppression, BB3 has been used, corresponding to a black-blood pulse every 63ms and 72ms respectively.

3.2.4 Velocity encoding

3.2.4.1 Background

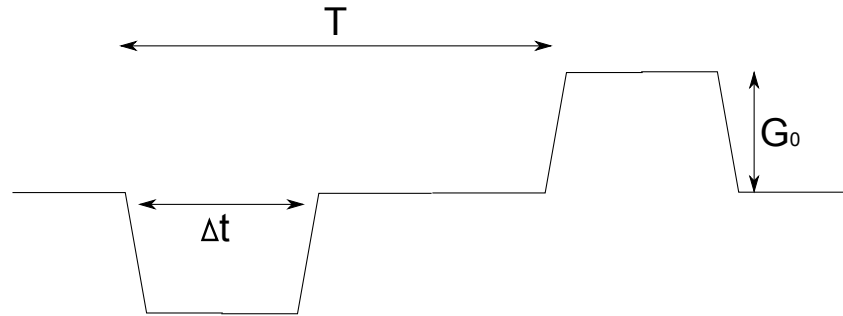


Figure 3.14: A bipolar gradient which can be used to introduce velocity sensitivity into the phase of a spin

The theory behind velocity encoding was briefly introduced in Section 2.2. Velocity is encoded into the phase of an MR signal by using a bipolar gradient (see Figure 3.14). At time τ the phase of a spin at position $x(\tau)$ and experiencing gradient strength $G(\tau)$ is

$$\phi(t) = \gamma \int_0^t G(\tau)x(\tau)d\tau. \quad (3.4)$$

Expanding $x(\tau)$ in a Maclaurin series gives:

$$\begin{aligned} x(\tau) &= \sum_{m=0}^{\infty} \frac{1}{m!} \frac{d^m x}{d\tau^m}(0) \tau^m \\ &= x(0) + x'(0)\tau + \frac{1}{2}x''(0)\tau^2 + \dots \end{aligned} \quad (3.5)$$

where a prime indicates differentiation with respect to τ . Substituting this into Equation 3.4 we can see that the phase caused by velocity x' (ϕ_v) is

$$\phi_v(t) = \gamma \int_0^t G(\tau) x'(0) \tau d\tau \quad (3.6)$$

Bringing constants outside of the integral and using the bipolar waveform in Figure 3.14 for $G(\tau)$, we can write the phase caused by velocity as

$$\phi_v(t) = \gamma x'(0) G_0 \left(\int_0^{\Delta t} -\tau d\tau + \int_T^{T+\Delta t} \tau d\tau \right). \quad (3.7)$$

Carrying out the integral and rearranging:

$$\begin{aligned} \phi_v(t) &= \frac{1}{2} \gamma x'(0) G_0 (-\Delta t^2 + (T + \Delta t)^2 - T^2) \\ &= \gamma x'(0) G_0 \Delta t T \\ &= \gamma A T x'(0) \end{aligned} \quad (3.8)$$

Where A is the area of one lobe of the bipolar gradient. This equation shows how the phase accrued by spins can be manipulated by the design of the bipolar gradient - increasing the area of the lobe or the time between the bipolar lobes increases the phase for a given spin velocity. This introduces the concept of VENC - the maximum range of velocities that can be measured before phase wrapping occurs is $\pm$ VENC. Velocities which cause phases separated by 2π will be indistinguishable. The VENC for a given bipolar pulse can easily be calculated by setting ϕ_v to π :

$$\pi = \gamma A T \cdot VENC \quad (3.9)$$

$$VENC = \frac{\pi}{\gamma A T} \quad (3.10)$$

Setting the VENC too low will cause aliasing which could lead to inaccurate

velocity measurements, while setting it too high reduces the velocity-to-noise ratio. Hence it is necessary to know the range of velocities that are expected in an acquisition before it is acquired, and to design the bipolar gradients accordingly. Myocardial velocities are typically much lower than blood velocities and consequently tissue phase velocity mapping sequences require larger amplitude gradients than a standard sequence for measuring blood flow (alternatively the bipolar gradient could be made longer, however this would increase the TR). Large gradients cause increased eddy currents which need to be considered. Typical through-plane VENC values for imaging in the short-axis are 25-30cm/s and in-plane values are 15-30cm/s (Jung et al., 2006a; Petersen et al., 2006; Steeden et al., 2013).

The above equations assume that phase shift measured is only caused by velocity and not by any other orders of derivatives of motion. By using a bipolar gradient the 0th order is nulled since the total area of the bipolar gradient is zero. However higher order terms are not nulled. An order of magnitude calculation can be carried out to check whether higher order terms are likely to be significant when compared with the velocity induced phase (a fuller treatment of this kind of analysis can be found in Kouwenhoven et al. (1995)). We want to show that the ratio of the phase induced by the mth derivative of motion and the phase induced by velocity (the 1st derivative) is small. Using Equations 3.4 and 3.5 we can write this ratio as

$$\begin{aligned}
 \frac{\phi_m}{\phi_1} &= \frac{\frac{d^m x}{d\tau^m}(0) \int G(\tau) \tau^m d\tau}{v(0) \int G(\tau) \tau d\tau} \\
 &\propto \frac{\frac{d^m x}{d\tau^m}(0) \mathcal{O}(\Delta t^{m+1})}{v(0) \mathcal{O}(\Delta t^2)} \\
 &\propto \frac{\frac{d^m x}{d\tau^m}(0)}{v(0)} \mathcal{O}(\Delta t^{m-1}).
 \end{aligned} \tag{3.11}$$

In the above equations, T is assumed to be approximately equal to Δt , and $\mathcal{O}(\Delta t^n)$ indicates an expression that is dominated by the size of Δt^n . With Δt of the order of 10^{-3} seconds, for $m > 2$ the $\mathcal{O}(\Delta t^{m-1})$ will dominate the expres-

sion. The ratio will therefore be small and higher order terms can be ignored.

3.2.4.1.1 Encoding strategies As described in Section 3.2.4.1.3 a phase map subtraction is required in order to remove some of the errors which arise when using PVM. The obvious acquisition strategy would be to acquire one reference scan (with no velocity encoding) and one encoded scan with the full required VENC, known as asymmetric encoding.

For symmetric encoding, equal but opposite encoding values are used for the two acquisitions to be subtracted (practically this means that the lobes of the bipolar gradient are swapped from one acquisition to the other). An advantage of using this technique is that the gradient amplitude needed can be halved for the same VENC compared with what would be possible from an asymmetrically encoded acquisition (see Equation 3.10), reducing the eddy currents which arise. However this is only simple for acquisitions measuring velocity in a single direction.

The two velocity encodings can be acquired consecutively in the same cardiac cycle, therefore not extending the scan duration when compared to a single acquisition and ensuring that heart rate variation does not introduce increased registration errors caused by subtracting maps acquired in different stages of the cardiac cycle. However, the temporal resolution is reduced by a factor of the number of encodings required and if TR is long significant motion could occur between the two acquisitions. Alternatively, each direction of encoding can be acquired in consecutive heartbeats. This means that the temporal resolution is not affected, but the scan duration is multiplied by the number of acquired encodings. With this technique, while large variations in heart rate between encodings could cause misregistration, with no heart rate variation the two datasets will be acquired at exactly the same point in the cardiac cycle.

3.2.4.1.2 Velocity compensation Any gradients between RF excitation and readout will cause sensitivity to motion (see Equation 3.6) and in order to acquire a true reference (or velocity compensated) image the effect of the slice select gradient must be accounted for. If measuring through plane velocities the size of the velocity encoding gradient is altered to ensure the correct VENC is applied, whereas if measuring in-plane velocities a small bipolar gradient is played out on the slice select axis at the same time as the in-plane velocity encoding gradients to remove through plane velocity sensitivity.

3.2.4.1.3 Errors Phase velocity mapping suffers from various sources of error caused both by imperfections in the MR system (field inhomogeneities or gradient errors) and by fundamental physical phenomena (concomitant fields and eddy currents, see below). The errors fall into two main categories; those which are the same for both reference and velocity encoded acquisitions, and those which are not. The former can be removed by phase map subtraction (see Section 3.3.5), while the remaining errors must also be corrected by modelling the residual offsets or by phantom subtraction (see Section 3.2.4.1.4).

3.2.4.1.3.1 Concomitant fields Concomitant fields are gradients which arise perpendicular to any applied gradient due to fundamental physical effects (Bernstein et al., 1998; Norris and Hutchison, 1990). They are predicted by the Maxwell equations and hence are also known as Maxwell gradients. The additional fields cause additional phase which is dependent on time and on spatial position. The size of the concomitant field produced is related to the gradient amplitude (Bernstein et al., 1998) in such a way that reducing the size of gradients used for imaging will reduce the errors, as will avoiding playing out gradients on two axes concurrently (as this increases the magnitude of the effective gradient being played out). However, these two strategies may not be possible for applications where temporal resolution needs to be maximised.

Concomitant fields are a fundamental physical effect, and can therefore be calculated accurately. This allows the error to be calculated and corrected automatically by the reconstruction software prior to the phase subtraction process (Bernstein et al., 1998).

3.2.4.1.3.2 Eddy currents As magnetic field gradients are switched on and off, unwanted electrical currents are caused to flow in the scanner hardware which, in turn, produce their own unwanted magnetic fields. Unlike concomitant fields, these cannot be predicted accurately since they depend on the exact geometry and hardware being used. Active shielding of the gradients can be used to reduce the induced currents and gradient pre-emphasis can be used to compensate for (although not remove) the currents by altering the input gradient waveform. Phase map subtraction of reference and velocity encoded acquisitions will not correct for eddy current effects since the velocity encoding gradients in the latter cause the two acquisitions to have different phase errors due to eddy currents. To remove errors caused by eddy currents a background offset correction must be performed.

3.2.4.1.4 Background offsets Eddy current effects, as well as any other residual phase errors after phase map subtraction, cause errors in velocity measurements of 1-2cm/s, varying gradually over an image. The errors also vary depending on the sequence and sequence parameters being used for imaging and the slice position (Gatehouse et al., 2010, 2012). Although this is a small effect for measuring blood velocities in the great arteries, for blood flow measurements the error accumulates when velocity curves are integrated over time. For myocardial velocities the error can be large relative to the velocities measured.

One way to deal with the background offset is to segment tissue within each image which is known to be stationary (Lingamneni et al., 1995; Walker et al., 1993). In order to accurately model the spatially varying offset it is desirable

that stationary tissue is available on all sides of the region of interest. The measured values are then used to fit a linear or polynomial function. While this may be possible in some areas (such as venous flow in the leg), for measuring blood flow in the great arteries or for measuring myocardial velocities there may not be enough surrounding stationary tissue to model the offset accurately. Despite this limitation, modelling of the background offset has been used in several studies measuring myocardial velocities (Delfino et al., 2006), while in other studies it is unclear whether any background correction has been performed (Jung et al., 2006a; Petersen et al., 2006; Steeden et al., 2013).

Alternatively, a separate scan can be performed in a large homogeneous stationary phantom in order to directly measure the background offsets (Caprihan et al., 1990; Chernobelsky et al., 2007; Lankhaar et al., 2005). By imaging the phantom with the same parameters, in the same slice position and with the same approximate RR-interval, the same background offsets will arise in the phantom as were present in the initial scan (neglecting the effects caused by the different shapes and materials). While this provides a more accurate way of correcting the offsets for those regions where not enough stationary tissue is available for an accurate model to be produced (Chernobelsky et al., 2007; Holland et al., 2010), it is time consuming and consequently difficult to achieve in a clinical workflow.

3.2.4.2 Implementation

For this thesis, a four point velocity encoding strategy has been used to measure three directions of velocity plus a true reference (velocity compensated) acquisition, with each direction acquired in a separate heartbeat to maximise temporal resolution. This means that for each spiral interleaf four heartbeats are required, one to collect reference (velocity compensated) data, and then one for each of the three orthogonal directions of velocity encoding (through-plane

plus two in-plane directions).

Figure 3.1 shows the sequence diagram for data collected with sensitivity to through-plane velocities. The in-plane equivalents are the same except with a small bipolar pulse on the through-plane axis (for velocity compensation as discussed in Section 3.2.4.1.2) and with the large bipolar velocity encoding gradient moved to one of the in-plane axes. A VENC of 30cm/s for through-plane and 20cm/s for in-plane velocities has been used in volunteer studies, in order to cover the range of velocities expected. This can however be changed by the user prior to scanning.

The velocity encoding gradients have a set duration of 1.6ms for each lobe. Concomitant gradients are corrected for automatically in the Siemens software (Bernstein et al., 1998) and background offsets are corrected for by subtraction of a separate phantom acquisition.

3.2.5 Spiral trajectories

3.2.5.1 Background

3.2.5.1.1 Advantages of non-Cartesian trajectories The time dependent signal, $S(t)$, in an MR experiment can be written

$$S(t) \propto \int_V \rho(\mathbf{r}) e^{-i2\pi\mathbf{k}(t)\cdot\mathbf{r}} d\mathbf{r} \quad (3.12)$$

where $\mathbf{r}$ is the spatial position, V is the volume from which signal is measured, $\rho(\mathbf{r})$ is the spin density at position $\mathbf{r}$ and

$$\mathbf{k}(t) = \frac{\gamma}{2\pi} \int_0^t \mathbf{G}(\tau) d\tau \quad (3.13)$$

where $\mathbf{G}(\tau)$ is the applied magnetic field gradient at time τ (the $\tau = 0$ point is at the mid point of the RF excitation pulse). The constant of proportionality is determined by the imaging parameters. By changing the magnetic field gradient over time, the signal is measured for different values of $\mathbf{k}$. Instead of moving through image space and measuring the spin density at each position, the MR experiment moves through k-space, measuring the response at each value of $\mathbf{k}$.

Once enough samples have been collected, an approximation to the object's spin density can be obtained by moving back into image space from k-space using the inverse FT:

$$\rho(\mathbf{r}) = \int_V S(\mathbf{k}) e^{i2\pi\mathbf{k}(t) \cdot \mathbf{r}} d\mathbf{k} \quad (3.14)$$

where the accuracy of the approximation increases as the number of samples increases. The centre of k-space contains low spatial frequency information (and hence most of the image energy), while the outer edges of k-space contain high spatial frequency information (small details and edges). Theoretically, sampling further and further out into k-space increases the resolution of the resulting image, however at large k-space values (ie far from the centre) the signal is small so practically the resolution is limited by the level at which these values become indistinguishable from noise.

So far there is no restriction on the exact path through k-space that should be used. However for the sake of efficiency the trajectory should travel on a smooth path through k-space, allowing incremental changes in the gradient strength which can be carried out quickly. Another issue which needs to be considered is how Equation 3.14 is to be achieved. In order to carry out a FT as in Equation 3.14, $S(\mathbf{k})$ would need to be known for all values of $\mathbf{k}$. After an MR experiment, $S(\mathbf{k})$ is known only at a series of N discrete points in k-space $S(\mathbf{k}_i)$, so rather than a full FT, a discrete Fourier Transform is needed:

$$\rho(\mathbf{r}) = \sum_{k_i=k_1}^{k_N} S(\mathbf{k}_i) e^{i2\pi\mathbf{k}_i(t)\cdot\mathbf{r}} \quad (3.15)$$

If the points $S(\mathbf{k}_i)$ lie on a Cartesian grid a Fast Fourier Transform algorithm can be used which is why Cartesian trajectories are most common in modern MR pulse sequences. Collecting single lines of k-space at a time also keeps the read-out time short (depending on the number of samples collected and the bandwidth used) so Cartesian imaging is robust to artefacts caused by off-resonance effects. However, covering k-space in this manner is not very efficient or flexible.

Cartesian trajectories have uniform sampling density over all of k-space, however since most of the energy of an image is found in the centre, this may not be necessary. Also the centre of k-space is covered only by a few of the acquired lines. If these lines are corrupted by, for example, motion, the entire image will be strongly affected.

Several developments have been made to speed up the acquisition of data while still using a Cartesian grid. For gated acquisitions, several k-space lines can be acquired in each heartbeat, lowering the temporal resolution but greatly decreasing the length of the scan (Edelman et al., 1990; Pauly et al., 1993). EPI acquires several lines of k-space for each excitation in a back-and-forth trajectory, again reducing acquisition time but by increasing the readout time the sensitivity of the trajectory to off-resonance effects is also increased.

Artefacts in Cartesian imaging can be strongly directional - for example the blood-flow artefact discussed in Section 3.2.3 is seen as ghosting in the phase encoding direction for Cartesian imaging (Drangova et al., 1997). This is due to the fact that the readout and phase encoding directions are always the same throughout data collection. This is often not the case for non-Cartesian imaging (for example the readout direction in spiral imaging is constantly changing)

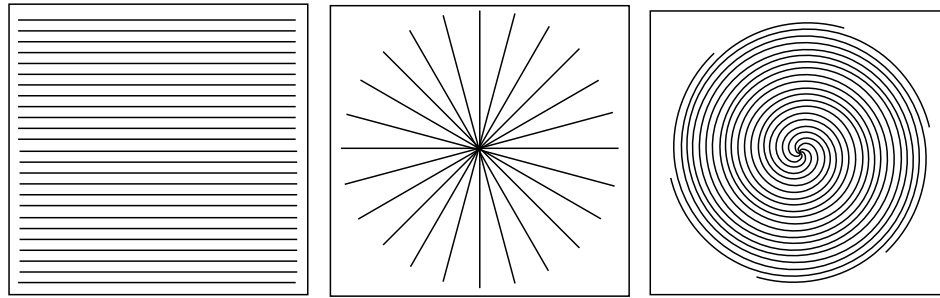


Figure 3.15: Example Cartesian, radial and spiral trajectories

which leads to artefacts which are less directionally dependent which could be an advantage in some situations.

One of the main problems with non-Cartesian trajectories is that data acquired cannot be directly Fourier Transformed. This means that image processing will be more complicated than for Cartesian imaging and will take longer. Many different non-Cartesian trajectories have been proposed, however two are more widely researched than the others - radial and spiral (see Figure 3.15).

3.2.5.1.1.1 Radial Radial trajectories use many spoke-like lines to cover k-space and were actually the first trajectories used for MRI (Lauterbur, 1989). As with standard Cartesian imaging, the readout time is short and so the technique is robust to off resonance effects. An advantage over Cartesian imaging is that each of the readouts passes through the centre of k-space rather than it being covered by a small fraction of the acquired lines, making the trajectory more robust to motion (Glover and Pauly, 1992). This also means that the centre of k-space has a higher sampling density than the edges.

In order to reconstruct an image from radially acquired data, the data must first be gridded which increases the reconstruction time (see Section 3.3.3). However recent developments in real-time imaging have shown that radial trajectories with golden angles allow extremely flexible real time imaging with retrospec-

tive reconstruction (Hansen et al., 2012; Winkelmann et al., 2007). In a golden angle acquisition, each radial spoke is rotated by the golden angle (111.246 degrees) in relation to the previously acquired spoke, ensuring that the sampling density is always as uniform as possible and allowing reconstruction at different temporal resolutions. This is successful in part due to the fact that artefacts in images formed from undersampled radial data are much more benign than in Cartesian imaging (Scheffler and Hennig, 1998).

3.2.5.1.1.2 Spiral Spiral trajectories, as the name suggests, cover k-space with one spiral (single shot) or a series of spirals rotated with respect to one another (interleaved). As with radial trajectories, each spiral covers the centre of k-space, however an advantage over radial trajectories is that the centre of k-space is acquired at the beginning of each spiral readout rather than in the middle of each radial readout. K-space can be covered in fewer spirals than radial spokes, speeding up acquisition. However the readouts tend to be longer making them sensitive to off-resonance artefacts (Delattre et al., 2010).

The next section describes in detail the theory and application of spiral trajectories in MRI.

3.2.5.1.2 Spiral imaging Much research has been carried out into imaging with spiral k-space trajectories. The different spiral designs which have been proposed, along with their advantages and disadvantages are described below, as well as the available methods for reconstructing images acquired with a spiral trajectory. An excellent resource for information about all aspects of spiral imaging is the review paper Delattre et al. (2010).

3.2.5.1.3 Spiral design There are many ways to design a spiral to cover k-space and different designs will be more suited for different applications. How-

ever any spiral can be written:

$$k = \lambda \tau^\alpha e^{i\omega t} \quad (3.16)$$

where k is the position in k -space, $\lambda = N/2 \times$ field of view (FOV) where N is the matrix size, τ is a function of time, t , running from 0 to 1, α controls the sampling variability and $\omega = 2\pi n$ where n is the number of turns in the spiral (Delattre et al., 2010).

The first considerations when designing a spiral trajectory are spatial resolution, temporal resolution and scan duration and the final design usually involves a compromise for all three parameters. To increase spatial resolution the extent of k -space covered by the spirals is increased, however this either means that the spiral duration has to be increased (decreasing temporal resolution and increasing the sensitivity to off-resonance), or the number of spiral interleaves has to be increased (increasing scan time). The image FOV is determined by the distance between adjacent windings of the spirals.

The most practical (and hence most common) spiral design is Archimedian - the separation between adjacent windings of the spiral is kept constant, as is the speed at which k -space is traversed and hence the sampling density is constant throughout k -space. However certain advantages can be gained by varying the sampling density throughout k -space. An example of this is a trajectory which follows an Archimedian spiral but which varies the k -space velocity such that all acquired samples lie on radial spokes - the constant angle trajectory (Ahn et al., 1986). This trajectory has benign undersampled artefacts and also has advantages for accelerated imaging (Heidemann et al., 2006).

Non-Archimedian spiral designs do not have equal spacing between spiral windings. Advantages offered by these designs include the ability to oversample the centre of k -space and thereby reduce the sensitivity to motion (Liao et al., 1997),

reduce artefacts in undersampled data (Tsai and Nishimura, 2000) or to more effectively use the gradients available.

3.2.5.1.4 Artefacts Field inhomogeneities cause unwanted phase accrual during data acquisition, in effect adding an additional term to the exponential in Equation 3.12. The long readout time of spirals means they are very sensitive to field inhomogeneities. In Cartesian imaging gradients are only played out in the readout direction during data acquisition so that off resonance effects cause a simple position shift of the final image. However the effect of off resonance in spiral imaging is less benign: both x and y gradients are used during readout which means the image is shifted in different directions at different points in the readout. This leads to blurring in the final reconstructed image. In order to reduce the level of artefact as much as possible the field should therefore be made as uniform as possible by careful shimming. However it is never possible to remove all field inhomogeneities due to effects such as susceptibility changes between air and tissue (which cause sharp changes in the field), the position and severity of which can vary from patient to patient. If the scan duration or resolution allows, the artefacts can be limited by reducing the length of the spirals, however this may not be possible or desirable.

Another possibility is to carry out an off resonance correction in post processing. Often a low resolution field map is obtained by subtracting the phase of two images acquired at different echo times. This normally requires a separate acquisition and hence extends the scan duration, however some techniques incorporate the acquisition of the field map into the imaging acquisition, for example by using variable density spirals to oversample the centre of k-space (Nayak et al., 2001). Other work has focussed on estimating the field map from the image data itself (Man et al., 1997). The pixel values of the map can then be used to calculate the off resonance frequency at each spatial location. These values can then be used to predict the additional phase that would be accrued

during the readout and hence a correction can be performed. The correction is carried out by convolving the image with the inverse point spread function (PSF) corresponding to the off resonance frequency at each pixel (Ahunbay and Pipe, 2000). While these techniques can significantly improve the image quality of spirals, they all result in increased processing time which may be undesirable.

3.2.5.2 Implementation

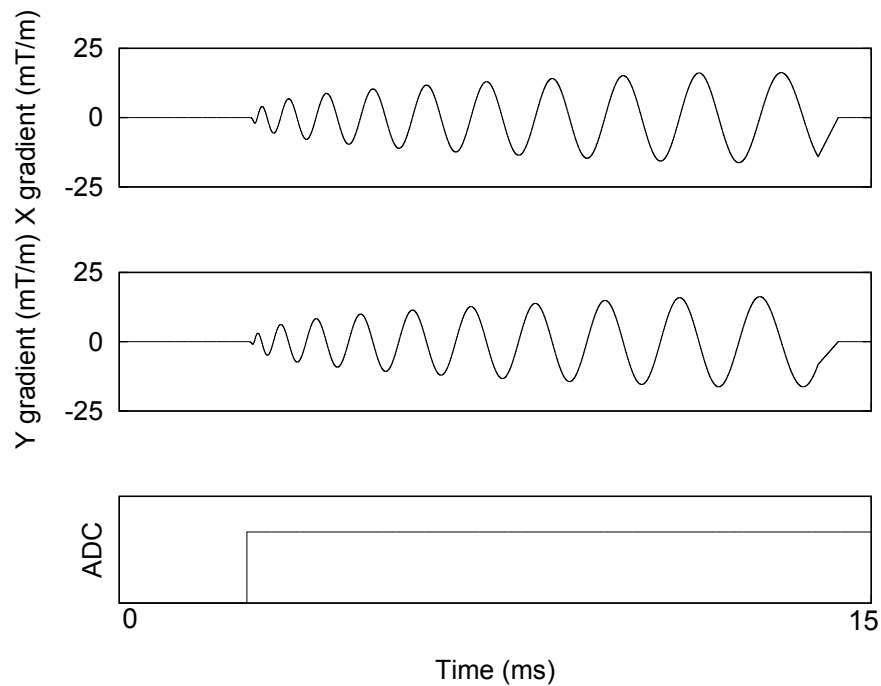


Figure 3.16: A single spiral interleaf, formed by gradients oscillating out of phase on the X and Y axes. The duration and magnitude of the spirals depends on the spiral design, as does the number of spirals needed to fully sample k-space.

Figure 3.16 shows an example spiral interleaf which involves oscillating gradients which are played out simultaneously on the x and y axes, thereby traversing k-space in a centre-out spiral trajectory. The spirals were designed using

code written at the Royal Brompton Hospital by Dr Peter Gatehouse. Archimedian spirals with constant sampling density are used. They are designed such that they use the maximum slew-rate (S_m) in the centre of k-space, until the maximum gradient (G_m) is reached and thereafter they continue at the maximum gradient amplitude.

Equation 3.16 shows the formula for a constant density Archimedian spiral. For the slew rate limited regime τ can be written

$$\tau = \left[\frac{3 S_m \gamma}{2 \lambda \omega^2} t \right]^{\frac{2}{3}} \quad (3.17)$$

and for the gradient limited regime

$$\tau = \left[2 \frac{G_m \gamma}{\lambda \omega} t \right]^{\frac{1}{2}}. \quad (3.18)$$

A constant sampling rate of $2.5\mu\text{s}$ is used which leads to a fixed bandwidth of 400kHz. The other parameters for the navigator and breath-hold sequences can be seen in Table 3.2.

Parameter	Navigator	Breath-hold
Number of spirals	13	8
FOV (mm)	350	360
Pixel size (mm)	1.4	1.7
Peak slew-rate (mT/m/ms)	120	120
Peak gradient (mT/m)	30	30
Duration (ms)	11.8	14.0
Scan length (heartbeats)	53 (100 % efficiency)	33 (fully sampled) 17 (SENSE factor 2) 13 (SENSE factor 2.7)

Table 3.2: Parameters for spiral design

It should be noted that the peak slew-rate (120mT/m/ms) and gradient (30mT/m) are not the maximum possible on the scanner (180mT/m/ms and 43mT/m respectively). This is to avoid hitting patient stimulation limits.

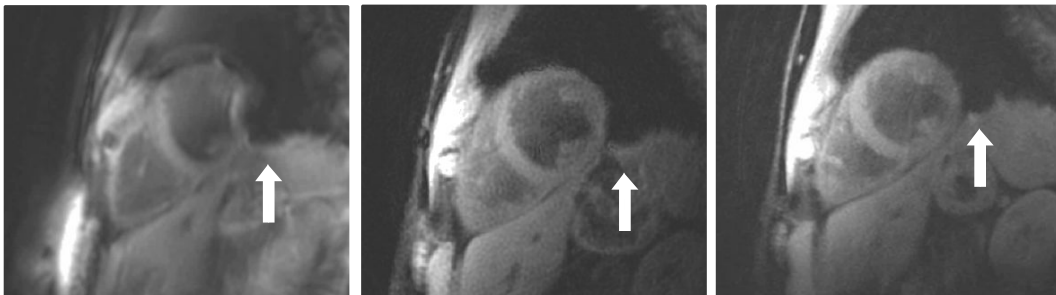


Figure 3.17: The effect of spiral duration on off resonance artefacts. Spiral duration is decreasing from left to right (23ms, 14ms and 12ms respectively) which improves the susceptibility artefact indicated by the white arrows. The shim settings and centre frequency are the same for all acquisitions.

The spiral duration is an important consideration when designing spiral trajectories, not only because it determines the possible temporal resolution but also because the longer the spirals are, the more susceptible they are to off-

resonance effects. This can be seen in Figure 3.17 where data from the same patient have been acquired using spirals with duration of 23ms, 14ms and 12ms (left to right). The off resonance artefact shown by white arrows gets progressively smaller as the spiral duration decreases, as does the amount of blurring in the image. This artefact is caused by the sudden change in field at the interface between air in the lungs and tissue in the heart and liver. The artefact is present in many subjects although its severity is variable. Even the small reduction in spiral duration between 14 and 12ms improves the artefact level.

3.2.6 Coil sensitivity maps

For undersampled breath-hold data acquisitions, fully sampled coil sensitivity maps are required for the non-Cartesian SENSE reconstruction (see Section 3.3.4). These are acquired with low temporal resolution during the first heartbeat of the breath-hold acquisitions. In this heartbeat the spiral interleaves are played out consecutively and the first full set of interleaves are used to create the coil sensitivity maps. This data is marked so that it is ignored by the Siemens image reconstruction and passed straight to the Gadgetron reconstruction system (see below).

3.3 Image Reconstruction

In order to obtain velocity maps from the data acquired with the sequences described in the previous section, the main reconstruction steps are:

- initial processing of the data - labelling, channel scaling, noise decorrelation
- re-ordering the data

- performing the interpolation necessary for retrospective ECG gating
- regridding the data and Fourier Transforming
- carrying out a phase map subtraction to obtain velocity maps
- final scaling and image display

In the two reconstruction platforms used in this project (ICE and the Gadgetron), each of these tasks is split into a separate module (called a functor or a Gadget respectively) allowing a customised pipeline of modules to be constructed for each type of reconstruction. This makes modification of the reconstruction easier and additional modules can be designed and inserted into the pipeline for specific applications.

The Gadgetron allows much easier prototyping than is possible on the ICE system and also has graphics processing unit (GPU) algorithms which are not yet implemented in ICE. It can be used in such a way that the operator may not realise the data is being reconstructed outside of ICE, as the resulting images are displayed on the Siemens system just as if they had been reconstructed entirely in ICE. This is achieved via two special ICE functors; the ‘Gadgetron emitter functor’ and the ‘Gadgetron injector functor’. As the names suggest, these functors are used to pass the data from ICE to the Gadgetron and back again. These can be placed anywhere in the ICE pipeline allowing the strengths of each system to be exploited.

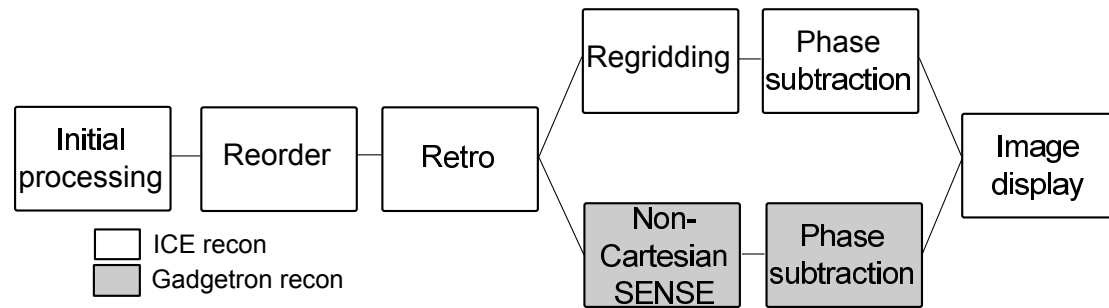


Figure 3.18: The reconstruction pipelines

Simplified pipelines for the navigator and breath-hold reconstructions can be seen in Figure 3.18. The navigator version is carried out entirely in ICE while for the breath-hold version the Gadgetron emitter functor is placed after the retrospective reconstruction to take advantage of a GPU implementation of non-Cartesian SENSE (Sørensen et al., 2009) which has been implemented on the Gadgetron by Michael Hansen at NIH (Hansen and Sørensen, 2013). The purpose of each functor and gadget is explained in the following sections, and the modifications that have been made are also outlined.

3.3.1 Re-order functor

The reorder functor has been written and inserted into the pipeline specifically for this application (it was heavily adapted from a functor written by Dr Permi Jhooti at the Royal Brompton Hospital for respiratory ordered acquisitions) and is necessary because the retro functor expects the data in a particular order. Standard flow sequences (on which the sequences above are based) acquire the reference and velocity encoded acquisitions consecutively *within the same heartbeat* whereas, in order to maximise temporal resolution, we have acquired reference and velocity encoded acquisitions in *consecutive heartbeats* (see Section 3.2.4.1.1). The retrospective reconstruction expects the data to arrive

in the usual order and, rather than alter the retrospective reconstruction, the re-order functor was designed and implemented.

The functor works by storing all of the data until the scan is finished. Each line of data is then sent down the pipeline in the order expected by the rest of the reconstruction. The retrospective reconstruction can then work as normal.

3.3.2 Retrospective cardiac gating functor

3.3.2.1 Background

Although recent developments have lead to an increased interest in real time or self gated imaging (Feng et al., 2012; Hansen et al., 2012), cardiac motion is generally removed from images by using ECG gating. The main QRS complex (see Section 1.1.3.1) occurs at the beginning of each heart cycle and can be detected automatically using a vector ECG measurement (Chia et al., 2000). It is therefore suitable to be used to trigger an acquisition, although at high field strengths ($>3T$) the ECG signal can become distorted and unreliable. If acquiring an image at single time point, a constant delay can be used between detection of the R-wave and imaging so that the correct phase of the cycle is imaged each time. However if a series of images is to be acquired through time, there are two main options, prospective or retrospective cardiac gating. A short description of the two options is given below, however more information can be found in Chapter 6.

3.3.2.1.1 Prospective gating When prospective cardiac gating is used on a Siemens platform, imaging starts at the ECG trigger and continues for a set length of time known as the acquisition window. Each image in the cardiac cycle is reconstructed from data which is acquired at exactly the same time after the ECG trigger. If there is significant heart rate variation during the acquisi-

tion image quality will be affected, particularly towards the second half of the cardiac cycle. The acquisition window length is set prior to the beginning of the scan and is typically around 90% of the RR-interval, so that natural heart rate variations do not lead to ECG triggers being missed. Another disadvantage of prospective gating therefore is that the entire cardiac cycle cannot be imaged.

3.3.2.1.2 Retrospective gating Retrospective cardiac gating on a Siemens platform acquires data continuously while simultaneously recording ECG information (Lenz et al., 1989). Each line of acquired data is given a timestamp according to how long after the last R-wave it was acquired. Once acquisition is completed, each heartbeat is normalised to the same nominal duration. The acquired data is then binned according to where in the normalised heartbeat it was acquired and the number of phases to be reconstructed. The number of phases to be reconstructed is chosen by the user, however it should not be set significantly higher than the acquired number of phases. In this way the entire cardiac cycle is covered.

3.3.2.2 Implementation

The only changes made to the Siemens implementation of retrospective cardiac gating were to accommodate the fact that each velocity encoding direction could have a different number of acquired phases (since they are acquired in different heartbeats which could be different lengths).

A schematic representation of the retrospective reconstruction can be seen in Figure 3.19 where the acquisition of two interleaves is shown. The aim is to produce a series of images which are equally spaced throughout the cardiac cycle, which is achieved by continuously repeating the sequence, changing the interleaf when an R-wave signal is received. Unfortunately due to natural variations in heart-rate, each of the spirals will in general be acquired a different

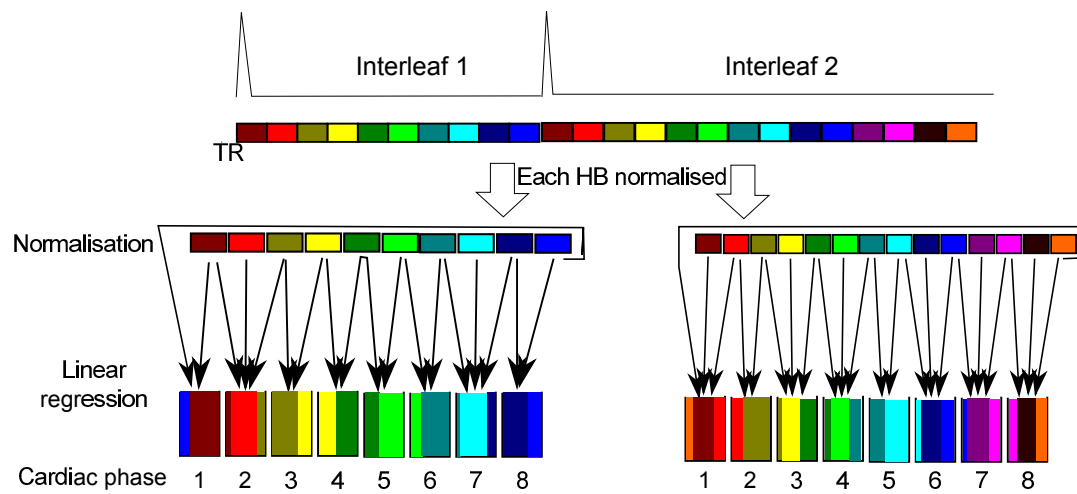


Figure 3.19: The retrospective reconstruction algorithm. Data is acquired constantly (top), normalised (middle) and binned (bottom) to produce equally spaced phases throughout the cardiac cycle.

number of times, making reconstruction more complicated (in the Figure more time points are acquired for interleaf 2 (14) than for interleaf 1 (10)).

Each heartbeat is normalised to a fixed length and then split equally into N sections where N is the number of cardiac phases to be reconstructed. Acquired time points lying within each of the N sections of the cardiac cycles are then combined via a linear regression to calculate the value at the centre of each section. If only one point lies within the window, the nearest neighbours are considered. The last acquired points in each heartbeat can be used in the first section.

Once there are N time points for each interleaf they can be passed along the pipeline to be regridded.

3.3.3 Regridding functor

3.3.3.1 Background

Image reconstruction is more complicated for spiral imaging than for Cartesian imaging because the fast Fourier transform (FFT) can only be used on data points which are on a regular grid. A FT can be carried out on spiral data, however it is extremely time consuming. The most common technique is to regrid the spiral data by interpolating the acquired data points onto the Cartesian grid and then carry out the FFT as before. The extra reconstruction step prior to the FFT increases the reconstruction time for spiral images when compared with Cartesian, however it has been shown that a well designed regridding algorithm should only approximately double the reconstruction time (Beatty et al., 2005).

The spiral gridding and reconstruction process consists of five steps which are outlined below:

1. Density compensation - Spiral data points are not acquired uniformly over k-space as they are in traditional Cartesian trajectories. This means that if the uneven sampling is not taken into account, the low spatial frequencies would have a higher weighting than the high spatial frequencies, resulting in image artefacts. For most spirals this can be corrected for by using the spiral trajectories to create a weighting function.
2. Blurring - The acquired data points must then be interpolated so that estimated values at any point in k-space can be obtained. This is done by convolving the acquired data points with a convolution kernel (also referred to as a window function) to effectively smear out the acquired data points, resulting in a continuous function that covers all of k-space. The shape and size of the kernel will affect the quality of the final reconstruc-

tion and the time taken to carry out this step.

3. Resampling - Having blurred the acquired data set, it can now be resampled onto a Cartesian grid by evaluating the continuous function at regular k-space positions.
4. FFT - The FFT can now be performed as in a conventional Cartesian reconstruction to produce an image.
5. De-apodisation - The convolution carried out during regridding causes apodisation of the final image - the edges of the image appear darker than the centre. This can be corrected by dividing the image by the FT of the convolution kernel.

3.3.3.2 Implementation

A spiral regridding algorithm developed by Prof Guang-Zhong Yang at the Royal Brompton Hospital and transferred into ICE by Dr Matthew Robson was used to perform the data regridding for the navigator sequence. Modifications were made to allow reconstruction of the spirals designed for this project. The algorithm uses the following kernel to perform blurring of the data (see Section 3.3.3.1):

$$c(r, u, v) = \exp \left(-\frac{20\alpha r^2(0.1 + \beta D(u, v))}{w^2} \right) \quad (3.19)$$

where r is the distance from the acquired data point to a Cartesian grid point (u, v) , $D(u, v)$ is the sampling density at (u, v) , w is the window size, α determines the kernel drop-off and β is used to control the effect of $D(u, v)$. The $D(u, v)$ term is used to perform the sampling density compensation along with an additional correction after convolution where the values of $c(r, u, v)$ are summed for each u, v for all relevant raw data points.

Previous work by Dr Andrew Scott performed during a PhD project carried out at the Royal Brompton Hospital compared reconstructions with this kernel to those using a more conventional Kaiser-Bessel kernel and found that they were extremely similar. Values of α , β and w were chosen by visual comparisons of images with different combinations of values and represent a compromise between image quality and reconstruction time. The values used were $\alpha = 2$, $\beta = 4$ and $w = 3$.

3.3.4 Non-Cartesian SENSE gadget

3.3.4.1 Background

When imaging using MR, several coil elements are typically used to receive RF signals. Increasing the number of coils increases the SNR of the final image, since the noise for each coil is different, but the object being imaged will be the same. However, instead of increasing SNR, the number of coils can be used to speed up the acquisition by using one of several ‘parallel imaging’ algorithms.

Many early algorithms were proposed but they can be split broadly into image based reconstructions such as Sensitivity encoding (SENSE) (Pruessmann et al., 1999), or k-space reconstructions such as Generalised Autocalibrating Partially Parallel Acquisitions (GRAPPA) (Griswold et al., 2002). In either case a small amount of fully sampled data is acquired, followed by an undersampled imaging acquisition. If more than one coil is used, even though the data is undersampled, a full image can be reconstructed by exploiting the extra information gained from the initial fully sampled data, as long as the number of coils is greater than or equal to the factor by which the data is undersampled. The two methods are explained below.

3.3.4.1.1 GRAPPA GRAPPA is a generalised algorithm which encompasses several earlier techniques (such as SMASH (Sodickson and Manning, 1997)) that perform parallel imaging by reconstructing missing k-space information. GRAPPA works by acquiring several calibrating lines, along with the under-sampled imaging data. The calibrating lines form a subset of the k-space lines which are not acquired during the undersampled imaging acquisition. The relationship between the acquired lines and the calibrating lines can be used to infer the similar relationship between the acquired lines and the unacquired lines.

The reason the algorithm works is that an acquired value in k-space from a single coil is actually the result of the k-space value convolved with the coil's sensitivity profile. This convolution effectively smears out the k-space values, leading to information about k-space values being encoded in data acquired from a different position. By using the calibration lines and by using information from several coils, this information can be recovered. Since the 'smearing' is the same throughout k-space, a few extra calibration lines can be used to calculate weights which can then be used to estimate the unacquired data over all of k-space. The process is shown schematically in Figure 3.20.

By using the calibrating lines the relationship between an acquired line and a line which is one k-space step away (Δk) or the relationship between an acquired line and a line which is two steps away (and so on) can be found. A perfect reconstruction would use relationships that spanned the entire size of the acquired k-space, however this would be computationally expensive. Instead the reconstruction uses only N_b steps of Δk , where N_b is known as the number of blocks. In most cases an N_b of around 5 is needed for a good reconstruction.

The relationships between data at relative k-space positions are known as weights and are collected in a matrix of weights, w . Each value in the weights matrix is the relationship between a line of data from one coil ($S(C_a)$ is the data from coil

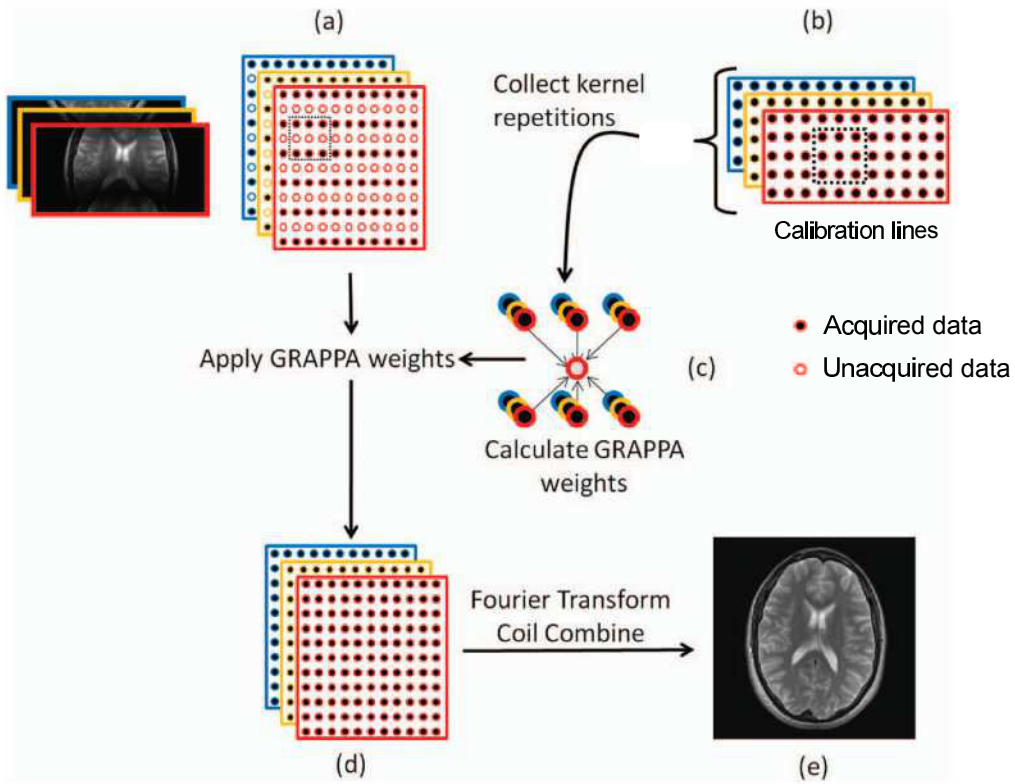


Figure 3.20: The GRAPPA reconstruction acquires undersampled data (a) along with some additional calibration lines (b). Together they are used to calculate the GRAPPA weights (c) which are then used to fill in the unacquired data (d). Full images can then be reconstructed (e). Figure adapted with permission from Deshmene et al. (2012).

a), to a line of data from another coil (or the same coil) and from n k-space steps away, so $w = w(C_a, C_b, n\Delta k)$. Once the values in w have been calculated, any line of data from any coil (C_c) can be calculated using

$$S(C_c) = \sum_{d=1}^{N_C} \sum_{m=0}^{N_b-1} w(C_c, C_d, m\Delta k) S(C_d, m\Delta k) \quad (3.20)$$

where N_C is the number of coils. From this, a full k-space for each coil is recon-

structed, and these can be combined in the normal way.

3.3.4.1.2 SENSE Undersampling data effectively decreases the FOV of the image being acquired. Any material that lies outside of the FOV then wraps into the image and a pixel in the final image ends up as the combination of the signal from several spatial positions. However, if several coils are used for imaging, each coil has a different sensitivity profile. A SENSE reconstruction uses this fact to construct full FOV images from undersampled data.

If an image is undersampled by a factor of 2, then each pixel ($p(x)$) contains the information from two different spatial locations (x_1 and x_2):

$$p(x) = I(x_1) + I(x_2). \quad (3.21)$$

This is a single equation with two unknowns and so cannot be solved. However in reality the information that is measured is not just the amount of signal coming from each spatial location, it is also multiplied by the coil sensitivity at that point ($C(x)$), so $I(x) = C(x) \cdot J(x)$ where $J(x)$ is the pixel value in an unaliased image. Although this is still underdetermined, if two coils are used we can reconstruct two images (p_1 and p_2) from the two coils (C_1 and C_2), giving two equations:

$$\begin{aligned} p_1(x) &= C_1(x_1) \cdot J(x_1) + C_1(x_2) \cdot J(x_2) \\ p_2(x) &= C_2(x_1) \cdot J(x_1) + C_2(x_2) \cdot J(x_2) \end{aligned} \quad (3.22)$$

If the coil sensitivities are known, there are now two equations and two unknowns which is a solvable problem. This means that the coil sensitivities for the imaging slice have to be measured prior to image reconstruction, although as coil sensitivity has a smooth spatial variation the resolution does not have to be as high as the subsequent image. Motion between the acquisition of the

coil sensitivities and the imaging will cause artefacts and areas of low signal (such as the lungs) can be too noisy to accurately measure the coil sensitivity. However SENSE is a robust technique that is regularly used in clinical practice.

3.3.4.1.3 Non-Cartesian acceleration Both of the above techniques were originally developed for application to Cartesian imaging, but they have both been extended to allow acceleration of other trajectories. An extension of GRAPPA to radial trajectories is fairly simple; the lines in k-space are replaced by radial spokes and the reconstruction is carried out as before. Spiral trajectories can also be reconstructed in this way by first interpolating the acquired spiral data such that the points used in reconstruction all lie on radial spokes (Heidemann et al., 2006).

The extension is not so simple for non-Cartesian SENSE. Cartesian undersampling happens only along the k-space axes so that the number of pixels folded onto the undersampled image pixels is just equal to the factor of the undersampling. For non-Cartesian trajectories this is no longer the case and each undersampled image pixel contains information from many different pixels, making the system of equations extremely complicated to solve. Instead, iterative techniques are used to find a solution. Typically the Conjugate Gradient method (Hestenes and Stiefel, 1952) is used although this is just one way of finding the solution (Pruessmann et al., 2001).

An iterative method works by starting with the aliased image then making guesses about the missing information. The resulting images are compared with the initial images and by minimising the difference, a better guess can be made. After several iterations, a reasonable guess at the full image is obtained. Regularisation terms can be added to speed up the reconstruction by providing more information about the resulting images. A schematic diagram of this process can be seen in Figure 3.21.

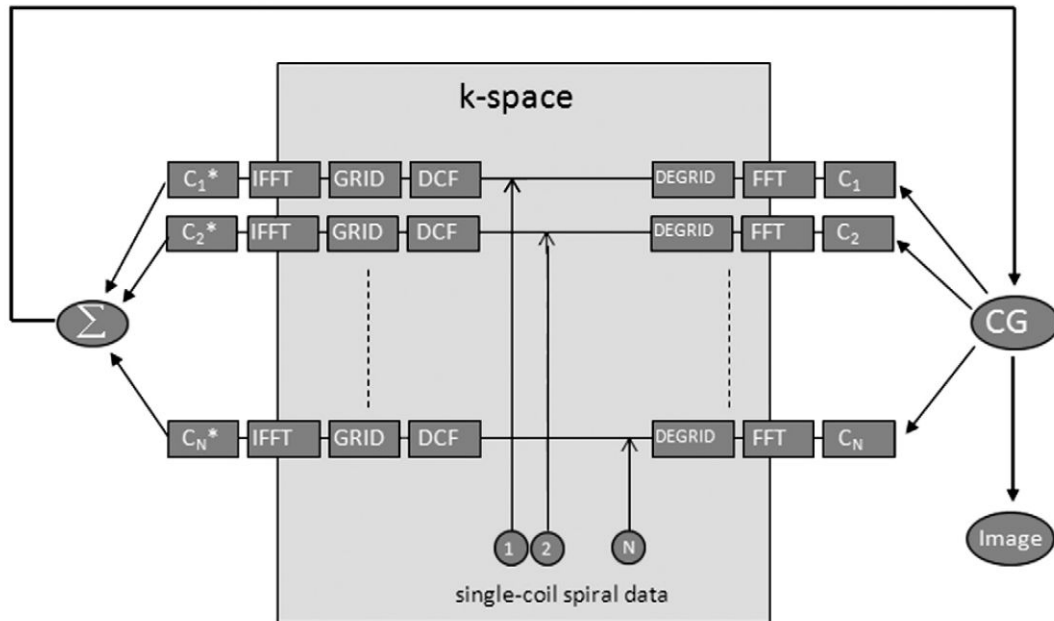


Figure 3.21: A schematic diagram of the CG SENSE reconstruction. C_i is the i th coil sensitivity map. Figure reproduced with permission from Delattre et al. (2010)

3.3.4.2 Implementation

The Gadgetron GPU implementation of non-Cartesian SENSE was used with few modifications, although extensive modifications were made to the Gadgetron CPU code responsible for accepting and storing the data ready to be reconstructed so that the different directions of velocity encoding could be accommodated. A phase subtraction gadget was also written from scratch.

The non-Cartesian SENSE GPU implementation is described in detail in Sørensen et al. (2009). A conjugate-gradient iterative algorithm (see Figure 3.21) is used with a limit of 5 iterations to ensure a reasonable reconstruction time. A Kaiser-Bessel kernel with width 5.5 and oversampling of 1.25 is used for gridding of the data.

3.3.5 Phase map subtraction

3.3.5.1 Background

This discussion can be found in Bernstein and Ikezaki (1991); Bernstein et al. (1994). Having regridded and Fourier Transformed the reference and velocity encoded spiral data, two independent complex images result. The pixels in the two images can be denoted

$$Z_1 = x_1 + iy_1 = \rho_1 \exp^{i\phi_1} \quad (3.23)$$

and

$$Z_2 = x_2 + iy_2 = \rho_2 \exp^{i\phi_2} \quad (3.24)$$

respectively. The velocity of tissue in each pixel is calculated from the difference in phase between the two images

$$\Delta\phi = \arctan\left(\frac{y_1}{x_1}\right) - \arctan\left(\frac{y_2}{x_2}\right) = \phi_1 - \phi_2. \quad (3.25)$$

However, calculating the phase difference in this manner means performing two separate arctan operations for each pixel which is computationally expensive. The same result can be obtained using a single arctan operation by

$$\Delta\phi = \arg\left(\frac{Z_1}{Z_2}\right) = \arg(Z_1 Z_2^*) = \arctan\left(\frac{\text{Im}(Z_1 Z_2^*)}{\text{Re}(Z_1 Z_2^*)}\right) \quad (3.26)$$

thereby saving computation time.

3.3.5.2 Implementation

For the navigator sequence, the standard Siemens phase subtraction functor is used without alteration. For the breath-hold sequence, Equation 3.26 was implemented in a separate phase subtraction gadget.

3.4 Analysis

Analysis of images is carried out using a GUI developed for the purpose from scratch using MATLAB. A screenshot of the GUI during analysis can be seen in Figure 3.22.

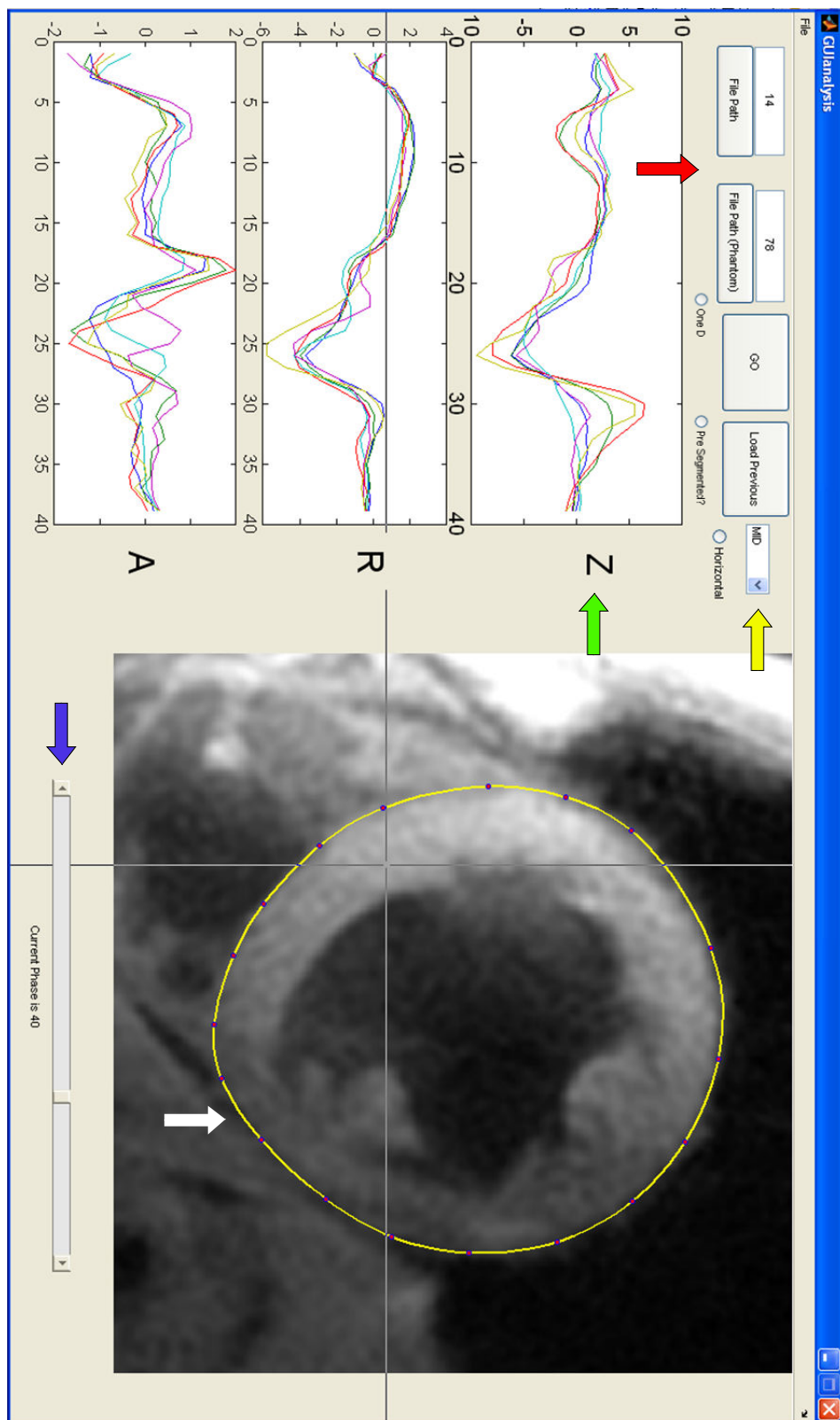


Figure 3.22: Screenshot of the GUI during analysis. The data set is specified using the inputs at top left (red and yellow arrows). The myocardium is segmented manually on the right (white arrow) and regional velocity-time curves are plotted on the left (green arrow).

The analysis process is carried out as follows

- Identify the series to be analysed (red arrow). All images from the scanner are saved onto a secure network drive under the name of the patient or volunteer. Each series of images in a session is given a unique number. The number of the first series in the scans to be processed is written in the box, along with the corresponding series for the phantom scan for the phantom subtraction (see Section 3.2.4.1.4).
- Identify the slice 'base', 'mid' or 'apex' (yellow arrow).
- Press the 'GO' button. This brings up the first image in a series which the user crops to isolate the heart.
- The cropped image appears at the right of the GUI (as in Figure 3.22). The user clicks in the centre of the septum in order to set up the in-plane polar co-ordinate system (the centre of mass of the segmented myocardium is also used).
- The user then segments the myocardium (white arrow). This is done by clicking at several points around the outer edge of the myocardium (purple dots) which are automatically joined together by a spline drawing algorithm (Lee, 1989) (yellow line). Double clicking brings up the velocity map where the segmentation can be adjusted to make sure it is as accurate as possible. The process is then repeated for the inner edge of the myocardium. A mask is then produced from the spline curves.
- The mask is used to segment the myocardium in the velocity maps for each direction of encoding and the phantom background maps are subtracted (having first been smoothed using a median filtering technique to avoid adding noise). The mask is automatically split into 6 circumferential regions and velocities in each direction are averaged with the results

(up to the current phase) plotted on the three axes at the left of the GUI (green arrow). Global velocities averaged over the whole mask are also calculated.

- All velocities and masks are saved after each image is segmented. This allows the user to segment part of a series and return to it later (pressing 'Load' instead of 'GO').
- The image selection bar (blue arrow) is used to move on to the next image. The process is repeated. The previous segmentation is used as a starting point for the next image in order to save time.
- The 'Pre-segmented' button can be used to carry out new analysis (eg splitting the myocardium into more regions) without having to redefine the co-ordinate axes and myocardial borders.

Chapter 4

Navigator Gated Acquisitions

This Chapter will demonstrate that the navigator sequence is capable of reproducibly measuring peak and time-to-peak values in all three directions and throughout the entire cardiac cycle. It will also show that the resolution is high enough to assess regional variations in motion, both for the healthy population as a whole and on an individual basis. Both the left and right ventricles will be analysed.

Navigator-gated phase velocity mapping sequences using respiratory navigators have previously detected fine features of motion, for example a small biphasic pattern of radial velocities in early diastole (Jung et al., 2006a) or complex patterns of ventricular twisting (Codreanu et al., 2010). Subtle changes in regional motion caused by age and gender have been reported, as well as large differences both in peak velocities and the regional variation of time-to-peak (TTP)s in disease (Delfino et al., 2008b; Föll et al., 2010). However, the acquisition durations for these studies is long (nominally 128 cardiac cycles with acquired spatial resolution of 2.6x1.3mm and temporal resolution of 13.8ms with view sharing (Jung et al., 2006a) or 180 cardiac cycles with acquired spatial resolution of 2.6x1.4mm and temporal resolution of 26ms (Delfino et al., 2008b))

and these are further extended by the inherently poor efficiency (typically 40%) of navigator gating techniques. Prospective cardiac gating has been used in all previous PVM studies of the myocardium which limits data acquisition and analysis of velocities to around 90% of the cardiac cycle.

The navigator-gated technique described in Chapter 3 can acquire images with similar or improved resolution to previous studies, but in a much reduced acquisition time because of the efficient spiral k-space trajectories that have been used and because of our bio-feedback mechanism (see Section 3.2.1.2.1). The use of retrospective cardiac gating also allows us to analyse the entire cardiac cycle, including atrial systole, giving our technique the advantages of efficiency and comprehensive temporal coverage.

Parts of this Chapter are adapted from a paper published in the Journal of Cardiovascular Magnetic Resonance entitled ‘Efficient and reproducible high resolution spiral myocardial phase velocity mapping of the entire cardiac cycle’ (Simpson et al., 2013a). Oral presentations of this work were shortlisted for the basic science Early Career Award at the Society for Cardiovascular Magnetic Resonance conference of 2013 (San Francisco) and awarded a *magna cum laude* award at the International Society of Magnetic Resonance in Medicine conference of 2013 (Salt Lake City). Parts of this work have also been presented at UK conferences and events.

4.1 Methods

4.1.1 Sequence

The navigator version of the sequence as described in Section 3.2 was used to scan ten healthy volunteers (mean age 31 years, range 24-56) on two occasions (9.7 days apart on average). A summary of the sequence details can be found in

Parameter	Value
Acquired temporal resolution	21ms
Acquired spatial resolution	1.4 x 1.4mm
Number of reconstructed phases	60
Reconstructed pixel size	0.7 x 0.7mm (zero-filling)
Number of spirals	13
Spiral duration	12ms
Scan length	53 heartbeats (100% efficiency)
Navigator	90/180 crossed pair
Navigator duration	9ms+10ms feedback time
Acceptance window	5mm
Acceptance criterion	Before and after
Biofeedback	Screen in scanner room
Through-plane VENC	30cm/s
In-plane VENC	20cm/s
Black-blood frequency	Every 3 phases
Flip angle	15°
Field of view	360mm

Table 4.1: Navigator sequence details

Table 4.1.

4.1.2 Protocol

The scans were carried out on a Siemens 3T scanner (MAGNETOM Skyra) equipped with an anterior cardiac 18-element matrix coil and a 48 element spine array. 6 elements of the cardiac coil and 6 elements of the spine coil were used for all acquisitions in order to limit the processing time and the subject and cardiac coil were carefully positioned to ensure complete coil coverage of the heart. The scan protocol was:

- Localiser images (3 sagittal, 3 transverse and 3 coronal)
- Long axis cine (2 chamber view)
- Long axis cine (4 chamber view)
- Mid ventricular short axis cine (50% of ventricular length)
- Diaphragm localiser (6 transverse slices) to identify the dome of the right hemi-diaphragm
- Navigator scout to determine the position of the navigator acceptance window
- Shimming and frequency adjustment
- PVM mid ventricular short axis slice
- Frequency adjustment
- PVM basal short axis slice (25% of ventricular length)
- Frequency adjustment
- PVM apical short axis slice (75% of ventricular length)
- Frequency adjustment
- Repeat of PVM mid short axis slice (this was performed in 7 out of 10 of the volunteers to assess short term reproducibility)

Shimming was carried out based on a user defined adjustment box which covered the entire left ventricle. The Siemens cardiac shim was run 3 times consecutively to ensure a good shim, and then the frequency adjustment was performed. Repeating the shim improves the final result since each shim starts

with the values from the previous shim, iteratively improving the result. Frequency adjustment was also performed before each PVM scan to account for any frequency drift.

Once the subject was out of the scanner the entire protocol was repeated in a large homogeneous stationary phantom (33cmx22cmx42cm, gelatine with 5mM concentration of Gadobutrol to shorten T_1). A simulated ECG with the same heart-rate as the subject was used to trigger the phantom acquisitions. The phantom acquisitions enabled the accurate correction of background phase shifts in the corresponding in vivo acquisitions as described in Section 3.2.4.1.4.

4.1.3 Analysis

The images were all analysed in MATLAB using the custom software described in Section 3.4. The data was analysed globally and regionally with the myocardium being split both circumferentially into 6 regions and radially into 3 regions. As well as velocity-time curves, peak and TTP values were measured. For visualisation, each slice was also split into 24 regions circumferentially and velocities were colour coded to produce colour maps.

Statistical testing was performed using SPSS (SPSS 19, SPSS, Chicago, Ill). After checking for normality using the Shapiro-Wilk test, mean $\pm$ SD of global longitudinal, radial and circumferential parameters was determined for each slice (basal, mid and apical). Repeated measures analysis of variance (with Greenhouse-Geisser correction in the case of non-sphericity) and paired t-testing (with Bonferroni correction for multiple testing) were used to compare peak and TTP velocities between slices. Differences between endo, mid and epicardium velocities were also analysed.

Inter-study reproducibility of all parameters (peak velocities as well as TTP values) was calculated using the mean $\pm$ SD of the signed differences between

repeat acquisitions, together with Bland-Altman analysis. The inter-study reproducibility of TTP values was determined both for absolute measured times from the R-wave (in ms) and for values expressed as a percentage of the length of systole or diastole in order to take into account inter-subject heart rate variation.

For the right ventricle, only global longitudinal velocities were analysed. This is because of the asymmetrical nature of the RV free wall which does not easily lend itself to regional analysis. Results are compared with those from the left ventricle.

4.2 Results

4.2.1 LV

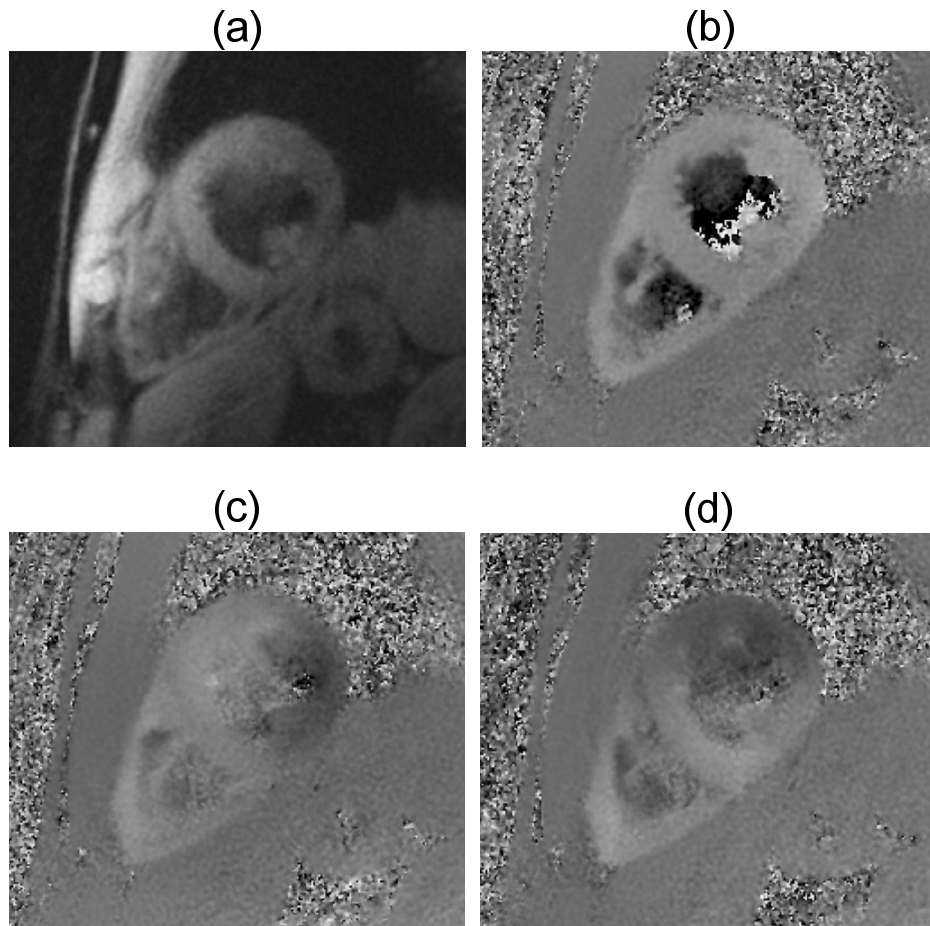


Figure 4.1: Example mid short axis slice image from diastole showing magnitude image (a), through plane velocity map (b) and in plane velocity maps (c) and (d).

Images were successfully acquired from all three slices on two separate occasions for all ten healthy volunteers. Figure 4.1 shows an example diastolic magnitude image of the mid slice of a single volunteer, together with the corresponding velocity maps. The myocardium is clearly depicted, blood and

fat suppression is good and the short spiral duration, combined with careful shimming and frequency adjustment, has minimised off-resonance blurring. The guided breathing (as described in Section 3.2.1.2) was tolerated well by all subjects leading to a mean navigator efficiency of 57% (SD $\pm 9\%$, range = 38% – 82%). The acquisition duration per slice was therefore 95 cardiac cycles (SD ± 16 , range = 65 – 138). The average heartbeat duration was 994ms (SD ± 121 ms, range = 813 – 1226ms). The durations of systole and diastole respectively (as determined from the radial velocity time curves, see the next Section) were 349 ± 38 ms and 645 ± 91 ms.

4.2.1.1 Global velocity curves

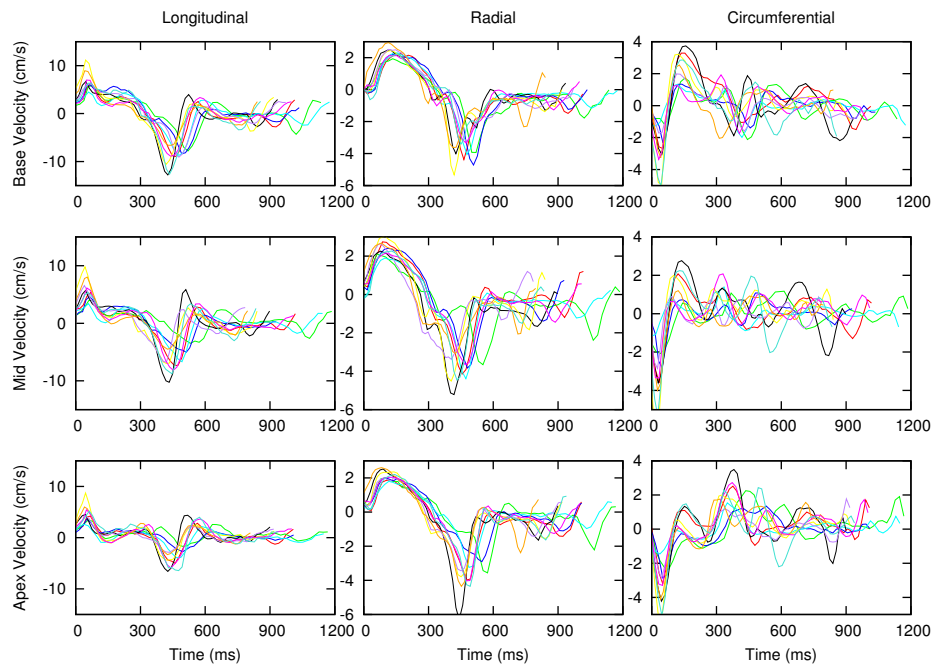


Figure 4.2: Global velocity-time curves for all ten volunteers. Due to variations in heart rate, the position of late diastolic peaks is very variable.

Global (ie averaged over an entire slice) longitudinal, radial and circumferential velocity-time curves in the basal, mid and apical slices can be seen for all ten volunteers in Figure 4.2. The main features of motion are very similar for all volunteers, although differences in heart rate clearly affect the timing of peaks, particularly towards the end of the cardiac cycle.

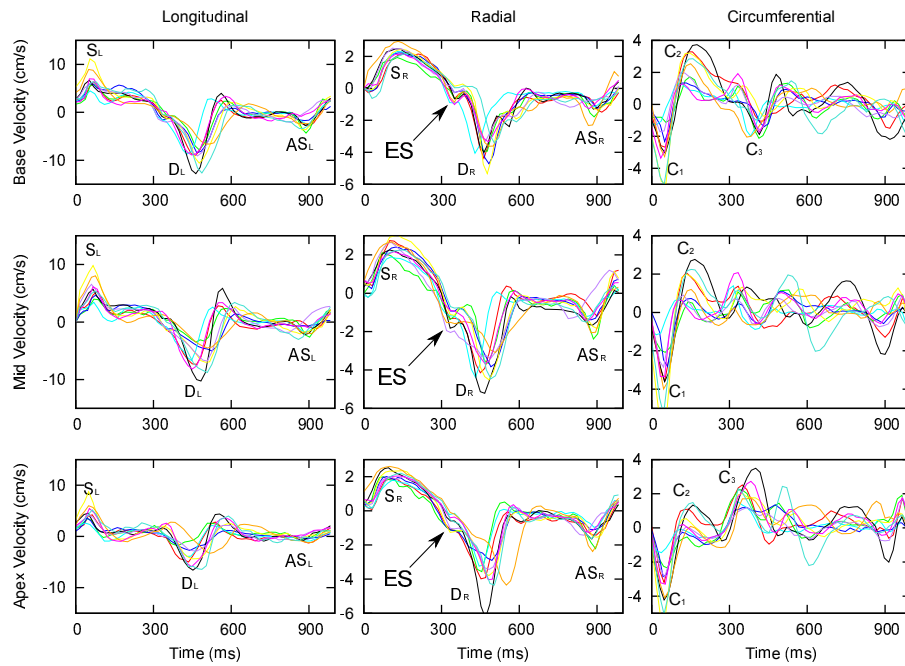


Figure 4.3: Normalised global velocity-time curves for all ten volunteers. Normalising the lengths of systole and diastole makes the position of peaks much more consistent between subjects.

The result of normalising the curves based on the position of end systole can be seen in Figure 4.3 (the position of end systole is marked ES on the radial curves). The normalisation is performed by stretching systole and diastole independently so that systole lasts 350ms and diastole 650ms for each volunteer (350ms and 650ms are approximately the average lengths of systole and diastole over the ten volunteers). This goes some way to removing the variability in timings between volunteers and makes the curves much easier to compare.

The main peaks through the cycle are marked on these curves. In the longitudinal and radial directions there are three main peaks; the systolic peak (referred to as S_L and S_R for longitudinal and radial directions respectively), the early diastolic peak (D_L and D_R) and the atrial systolic peak (AS_L and AS_R). In the circumferential direction, there are two systolic peaks (C_1 and C_2) and one main diastolic peak (C_3). To quantitatively compare curves, the magnitude of these peaks and the times in the cardiac cycle at which they occur can be used as shown in the next section.

4.2.1.2 Global Peak and TTP velocities

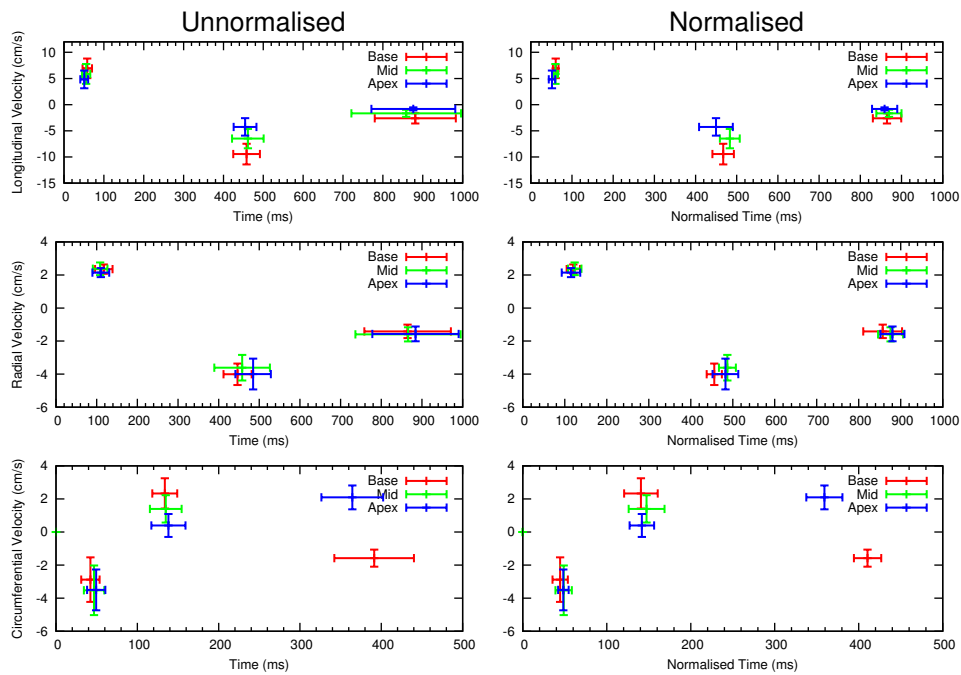


Figure 4.4: Mean $\pm$ SD peak and time-to-peak velocity values as measured (left) and normalised based on the position of end systole (right). Values in each slice (base, mid and apex) are treated separately.

For each of the peaks labelled in Figure 4.3, the peak and time to peak velocity values have been measured in order to characterise the motion. The mean and standard deviation of those peaks and TTPs are shown in Figure 4.4. On the left values are shown as measured, on the right they are shown normalised to end systole as described in the previous section. By normalising to end systole, the standard deviation of TTP values is clearly greatly reduced, particularly for peaks occurring later in the cardiac cycle. The peak and TTP values can be found in Table 4.2.

As expected (see Section 2.2.5) the peak systolic and diastolic velocities in the longitudinal direction are higher at base than apex ($6.94 \pm 1.87\text{cm/s}$ vs $4.83 \pm 1.70\text{cm/s}$, and $-9.45 \pm 1.97\text{cm/s}$ vs $-4.27 \pm 1.67\text{cm/s}$ respectively, $p < 0.001$ for both). In one of the apical velocity-time curves, AS_L was not clearly shown but in the remaining cases, peak AS_L decreased significantly from base to apex ($-2.62 \pm 0.99\text{cm/s}$ vs $-0.81 \pm 0.29\text{cm/s}$, $p < 0.001$).

Peak radial velocities do not decrease from base to apex, with similar peak systolic, diastolic and atrial systolic velocity values at all levels. AS_R is seen clearly in all volunteers and all slices.

Both C_1 and C_2 are higher at base than apex (C_1 $-2.88 \pm 1.35\text{cm/s}$ vs $-3.50 \pm 1.23\text{cm/s}$, $p < 0.01$, C_2 $2.33 \pm 0.91\text{cm/s}$ vs $0.39 \pm 0.69\text{cm/s}$, $p < 0.001$). The opposite polarity of C_3 at base and at apex indicate the characteristic untwisting of the ventricle as it relaxes. In the mid-slice there is no consistent peak in global velocities at early diastole and so no values for C_3 in the mid-slice are reported.

The average velocities over the entire cycle for all velocity-time curves showed small differences from zero (values averaged over slices for global velocity-time curves are $0.24 \pm 0.28\text{cm/s}$ for longitudinal velocities, $-0.25 \pm 0.10\text{cm/s}$ for radial velocities and $0.043 \pm 0.11\text{cm/s}$ for circumferential velocities). This indicates that background phase offsets which are not corrected for in the reconstruction

are being removed by the phantom subtraction. A fuller discussion of background phase offsets and the reasons for the remaining differences from zero can be found in Section 4.2.1.6.

The ratio of the early diastolic peak to the atrial systolic peak in longitudinal and radial directions was also calculated. This is analogous to the parameter E/A (the ratio of peak early (E) filling and late diastolic filling (A)) measured at the level of the mitral valve in echocardiography to assess diastolic function (Nagueh et al., 2009). These values, along with the peak velocity values, can be found in Table 4.2.

	Peak	TTP (ms)	TTP (norm ms)
BASE			
S_L (cm/s)	6.94 ± 1.87	58.3 ± 11.8	60.6 ± 6.7
D_L (cm/s)	-9.45 ± 1.97	458.0 ± 33.3	467 ± 26
AS_L (cm/s)	-2.62 ± 0.99	881.1 ± 101.7	864.8 ± 34.5
E/A_L	4.26 ± 2.39		
S_R (cm/s)	2.35 ± 0.28	117.5 ± 24.5	120.4 ± 15.8
D_R (cm/s)	-4.01 ± 0.65	446.5 ± 34.5	456.0 ± 18.2
AS_R (cm/s)	-1.41 ± 0.41	864.6 ± 106.4	857.0 ± 46.2
E/A_R	3.00 ± 0.76		
C_1 (cm/s)	-2.88 ± 1.35	42.3 ± 11.2	44.5 ± 9.1
C_2 (cm/s)	2.33 ± 0.91	133.8 ± 15.3	140.7 ± 20.0
C_3 (cm/s)	-1.58 ± 0.52	391.2 ± 48.9	410.5 ± 16.3
MID			
S_L (cm/s)	5.87 ± 1.89	55.6 ± 10.3	59.9 ± 6.3
D_L (cm/s)	-6.50 ± 1.85	461.2 ± 39.7	483.3 ± 24.1
AS_L (cm/s)	-1.66 ± 0.67	858.5 ± 137.5	869.4 ± 30.6
E/A_L	4.97 ± 3.29		
S_R (cm/s)	2.38 ± 0.38	108.5 ± 18.0	123.6 ± 16.1
D_R (cm/s)	-3.61 ± 0.77	457.7 ± 68.5	487.2 ± 20.2
AS_R (cm/s)	-1.59 ± 0.43	865.7 ± 129.3	875.9 ± 29.9
E/A_R	2.43 ± 0.87		
C_1 (cm/s)	-3.52 ± 1.50	46.8 ± 12.6	48.7 ± 9.8
C_2 (cm/s)	1.40 ± 0.83	135.0 ± 19.5	147.4 ± 21.4
APEX			
S_L (cm/s)	4.83 ± 1.70	50.7 ± 9.73	51.5 ± 7.7
D_L (cm/s)	-4.27 ± 1.67	454.3 ± 28.6	449.5 ± 41.0
AS_L (cm/s)	$-0.81 \pm 0.29^*$	$876.2 \pm 105.2^*$	859.0 ± 30.6
E/A_L	$5.59 \pm 3.04^*$		
S_R (cm/s)	2.14 ± 0.27	110.2 ± 20.6	114.8 ± 22.1
D_R (cm/s)	-3.99 ± 0.94	484.8 ± 43.6	482.6 ± 30.6
AS_R (cm/s)	-1.57 ± 0.45	884.1 ± 106.1	880.4 ± 28.6
E/A_R	2.67 ± 0.66		
C_1 (cm/s)	-3.50 ± 1.23	49.4 ± 11.2	48.3 ± 6.3
C_2 (cm/s)	0.39 ± 0.69	138.3 ± 21.0	141.8 ± 41.6
C_3 (cm/s)	2.09 ± 0.72	364.3 ± 38.0	359.1 ± 21.5

Table 4.2: Peak and TTP mean $\pm$ SD values in all three slices. TTP values are shown in raw ms values and when normalised to average systolic and diastolic durations. This normalisation reduces the variation in timing for AS peaks in particular.

TTP values are also shown as measured in milliseconds and in normalised milliseconds based on the average lengths of systole (350ms) and diastole (650ms) as described above. The standard deviation of TTP in milliseconds is small for the systolic parameters (S_L , S_R , C_1 and C_2), increases for early diastolic parameters (D_L , D_R and C_3) and increases further for late diastolic parameters (AS_L , AS_R). However, when normalised, the variability of the diastolic TTP values is reduced, particularly for atrial systole. For example the average $\pm$ SD of TTP AS_L is 858.5 ± 137.5 ms from the R-wave but 869.4 ± 30.6 ms when normalised.

4.2.1.3 Regional velocities

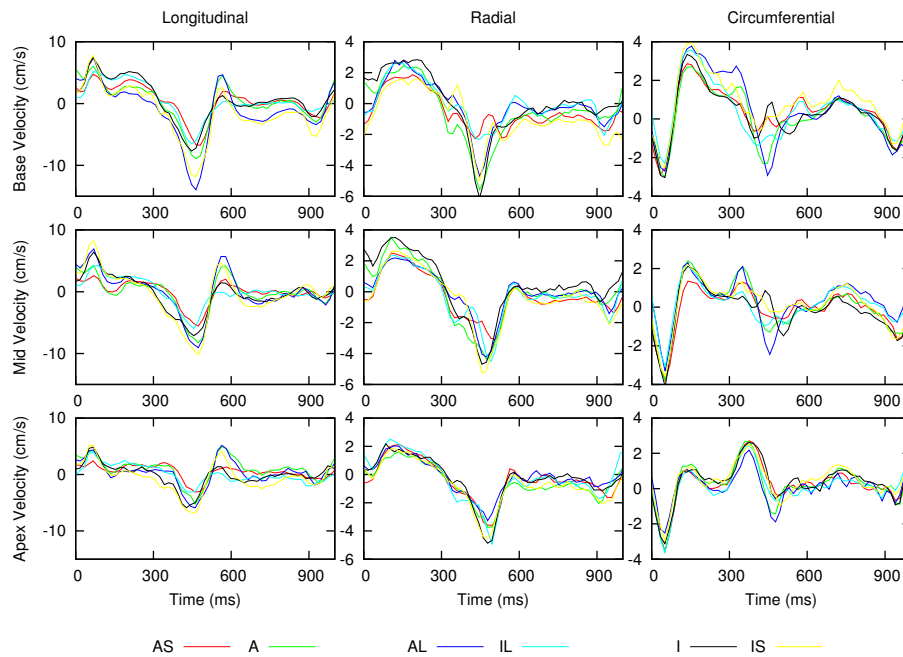


Figure 4.5: Regional velocity-time curves for one volunteer in all directions and slices. See Section 1.4.1 for the definition of circumferential regions

While global velocities are a good way of characterising the myocardial motion, the images acquired have high spatial resolution and so regional analysis

can also be performed. Figure 4.5 shows the longitudinal, radial and circumferential velocities for all three slices in a single volunteer. The different colour coded curves represent different regions in the myocardium as described in Section 1.4.1.

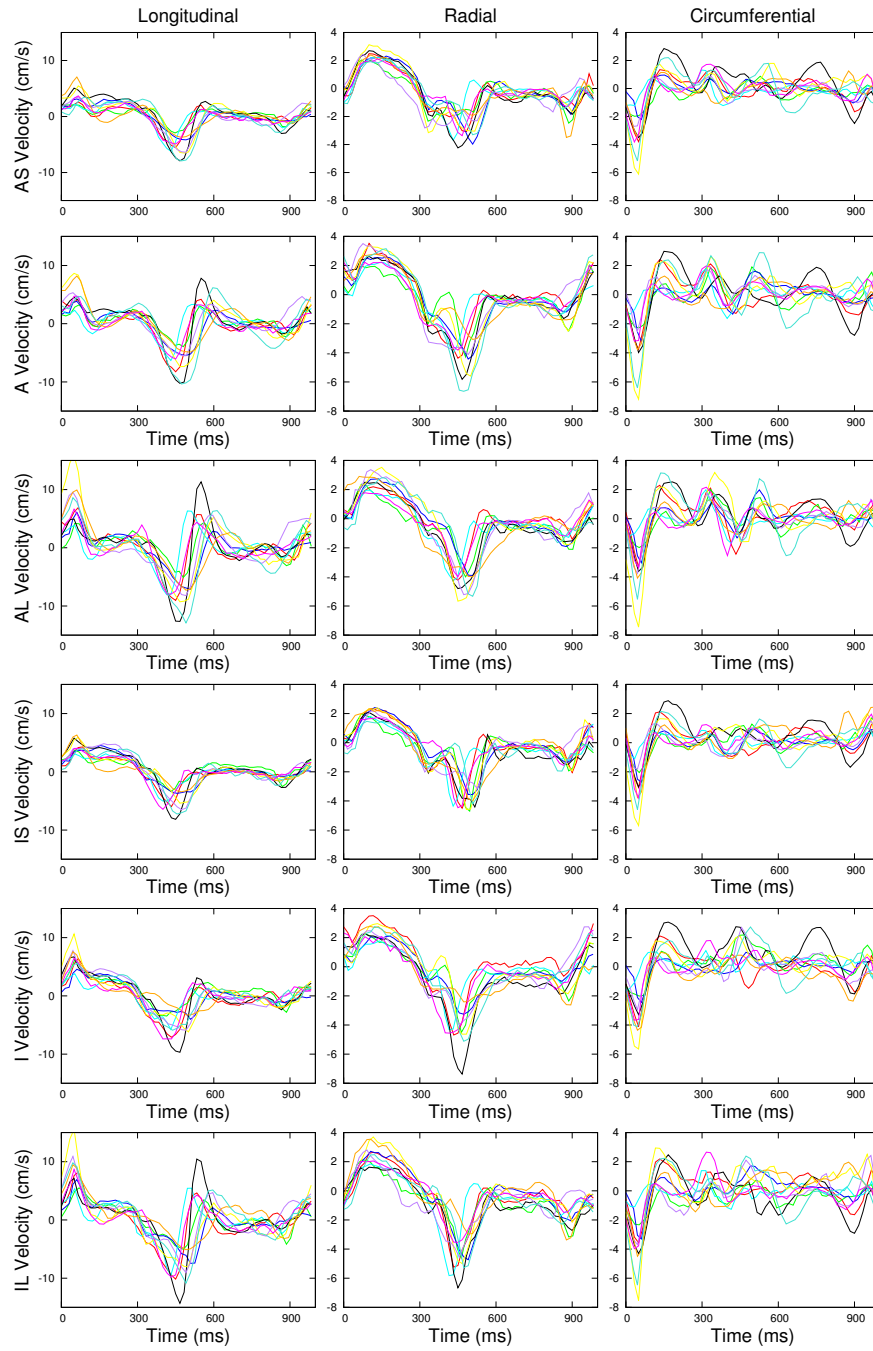


Figure 4.6: Regional longitudinal (left), radial (middle) and circumferential (right) velocity-time curves in each of the six AHA sections of the mid slice for all volunteers.

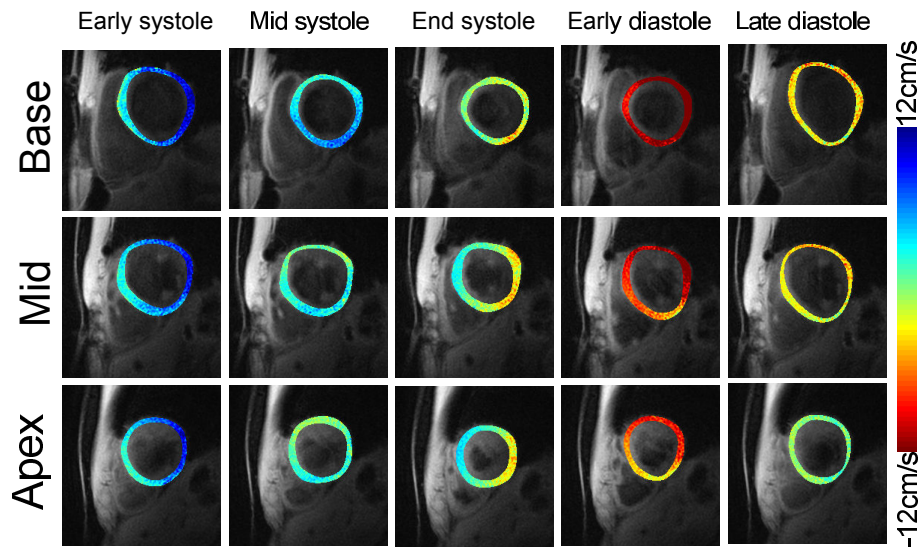


Figure 4.7: Longitudinal colour overlays from a single volunteer in the basal (top), mid (middle) and apical (bottom) slices. Five time points of interest are shown.

Figure 4.6 shows the regional curves from the mid slice of all volunteers in the longitudinal, radial and circumferential directions. From these regional velocity plots we can see certain regional features of motion, for example longitudinal lateral velocities are clearly higher than septal velocities. However the regional segmentation is coarse compared with the image resolution and the plots are overcrowded and not particularly easy to interpret.

Figures 4.7 to 4.9 show magnitude images from a single volunteer with the velocities colour coded and overlaid on top. Each Figure displays a single direction of motion in all three slices and at five time points of interest. The early systolic time point corresponds with the peak systolic longitudinal velocity (S_L) and with the first circumferential peak (C_1), while the mid systolic time point corresponds to S_R and C_1 . The early and late diastolic time points correspond to D_L/D_R and AS_L/AS_R respectively. End systole is also shown. While this shows regional variation of motion at single time points, it is difficult to display the entire cardiac cycle and all three directions of motion in a single figure. A

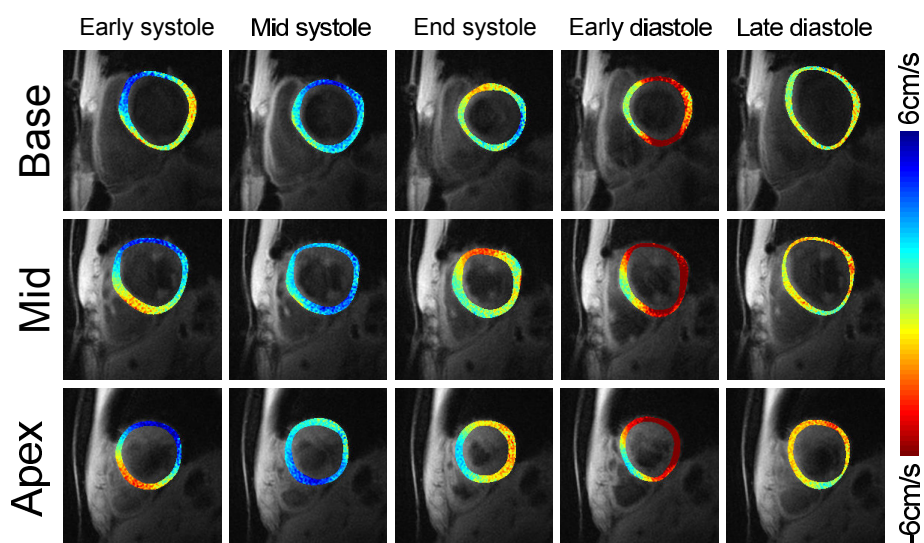


Figure 4.8: Radial colour overlays from a single volunteer in the basal (top), mid (middle) and apical (bottom) slices. Five time points of interest are shown.

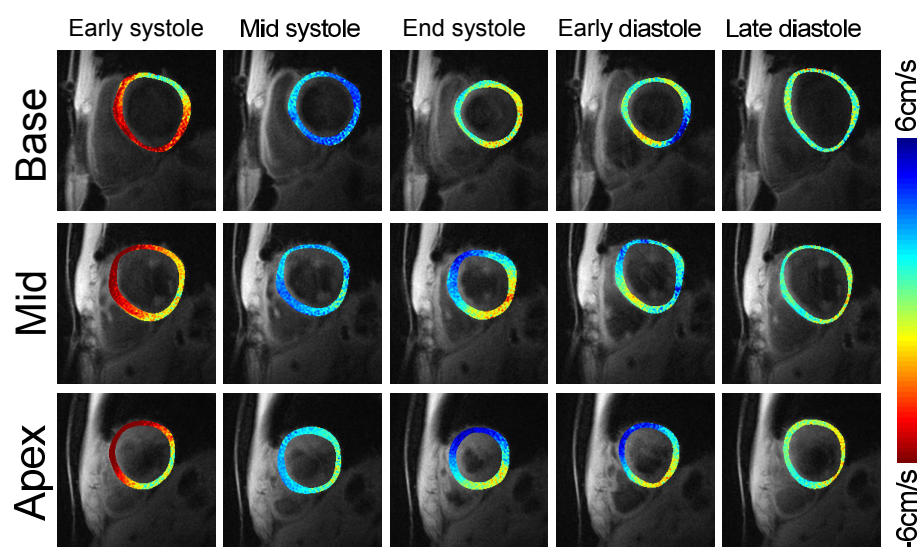


Figure 4.9: Circumferential colour overlays from a single volunteer in the basal (top), mid (middle) and apical (bottom) slices. Five time points of interest are shown.

better visualisation of regional velocities over time has been developed and is described in the following section.

4.2.1.4 Colour plots

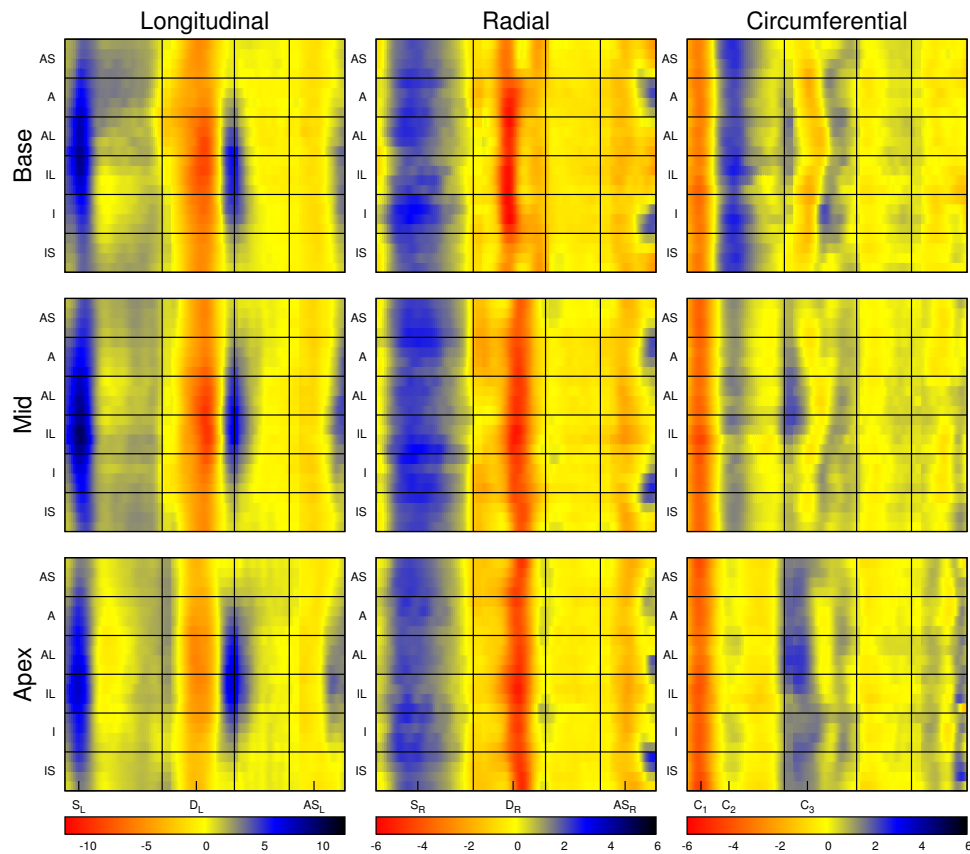


Figure 4.10: Colour plots for average longitudinal (left), radial (middle) and circumferential (right) velocities over the subjects. Colour scale is shown in cm/s. The colour plots clearly show regional variation both between slices and between different regions of the same slice.

Colour plots averaged over all ten volunteers can be seen in Figure 4.10. These are produced by splitting the myocardium circumferentially into 24 regions.

Circumferential position is then plotted on the y-axis against time on the x-axis. In order that averaging over the volunteers does not smear out any fine details of motion, the heartbeat is split into four sections; systole, early diastole, diastasis and atrial systole, and each section is normalised separately. The normalised and averaged velocities are then colour coded to produce the plots for each direction of motion and for each myocardial slice.

The colour plots enable rapid interpretation of a large amount of velocity data. Complicated patterns of motion can be seen in all slices and in all directions. The trend for increasing longitudinal velocities from apex to base, particularly for D_L , can clearly be seen. Regional differences in peak and TTP values are also obvious: for example the systolic peak S_L is strongest in the lateral regions in the basal and mid slices, whereas at apex it is strongest in the inferior segments. The atrial systolic peak is seen clearly at base and mid level and is less clear at apical level.

Radial velocities show greatest regional variation at base. In particular the main diastolic peak D_R is strongest in the anterior and inferior regions at base, with the septum (AS and IS) showing a biphasic pattern as previously described (Jung et al., 2006a). AS_R is strongest in the inferolateral region in all slices.

Circumferential velocities show a strong negative peak (C_1) immediately after the R-wave which is followed by a second in the opposite direction (C_2) in the basal and mid slices. C_2 is also consistently present at apical levels as a point of inflection, at approximately zero velocity (0.39 ± 0.69). During early diastole the motion is highly dependent on position within the ventricle. C_3 is a sharp negative peak at base which shows regional variation in timing, whereas at apex the peak is broader but positive, leading to the characteristic wringing motion of the heart.

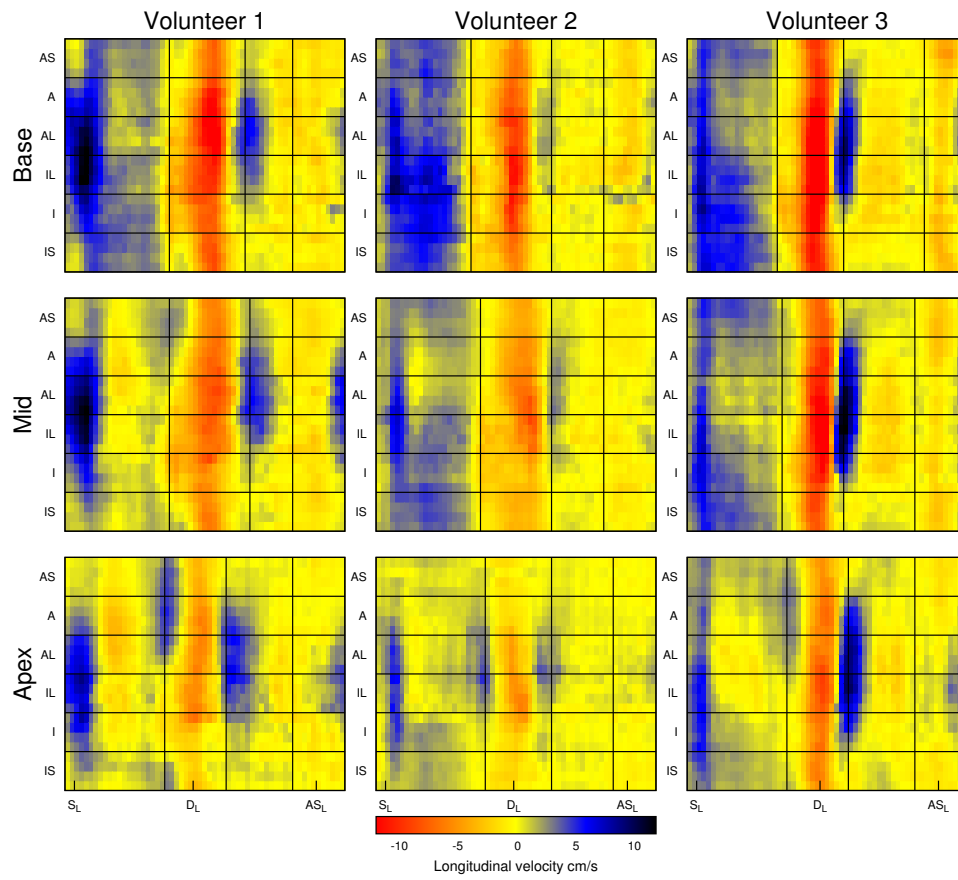


Figure 4.11: Basal (top), mid (middle) and apical (bottom) longitudinal colour plots for three individual volunteers (separate column for each volunteer). Colour scale is shown in cm/s.

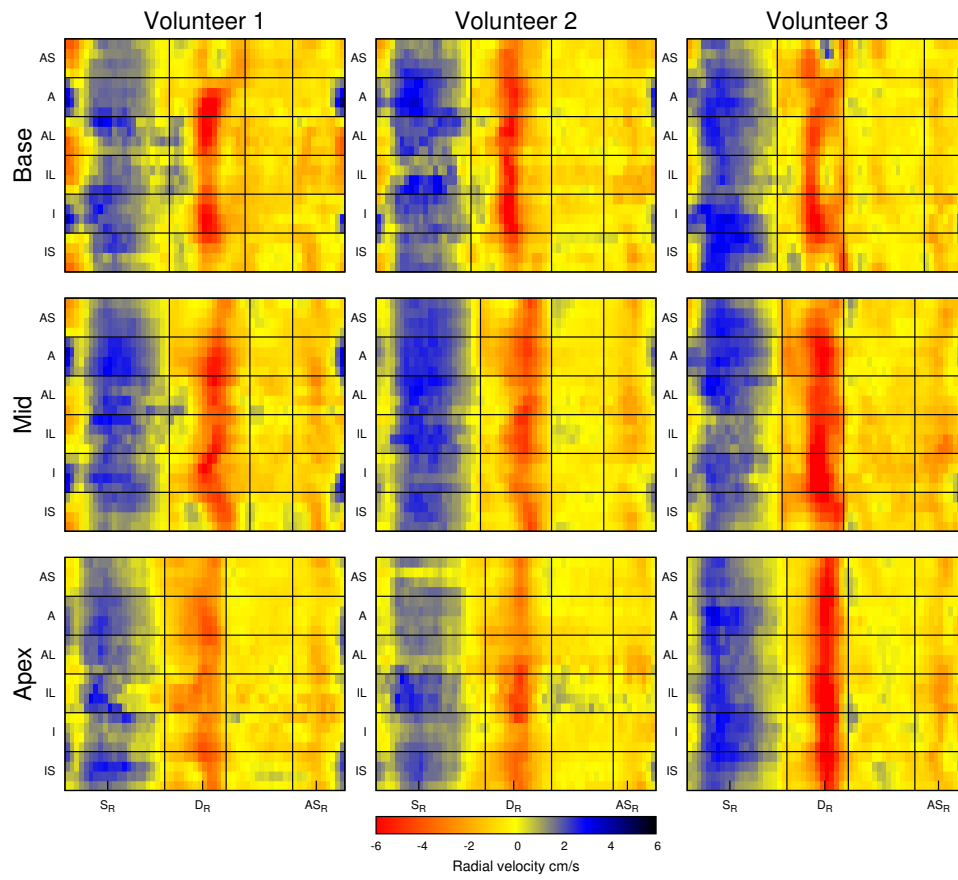


Figure 4.12: Basal (top), mid (middle) and apical (bottom) radial colour plots for three individual volunteers. Colour scale is shown in cm/s.

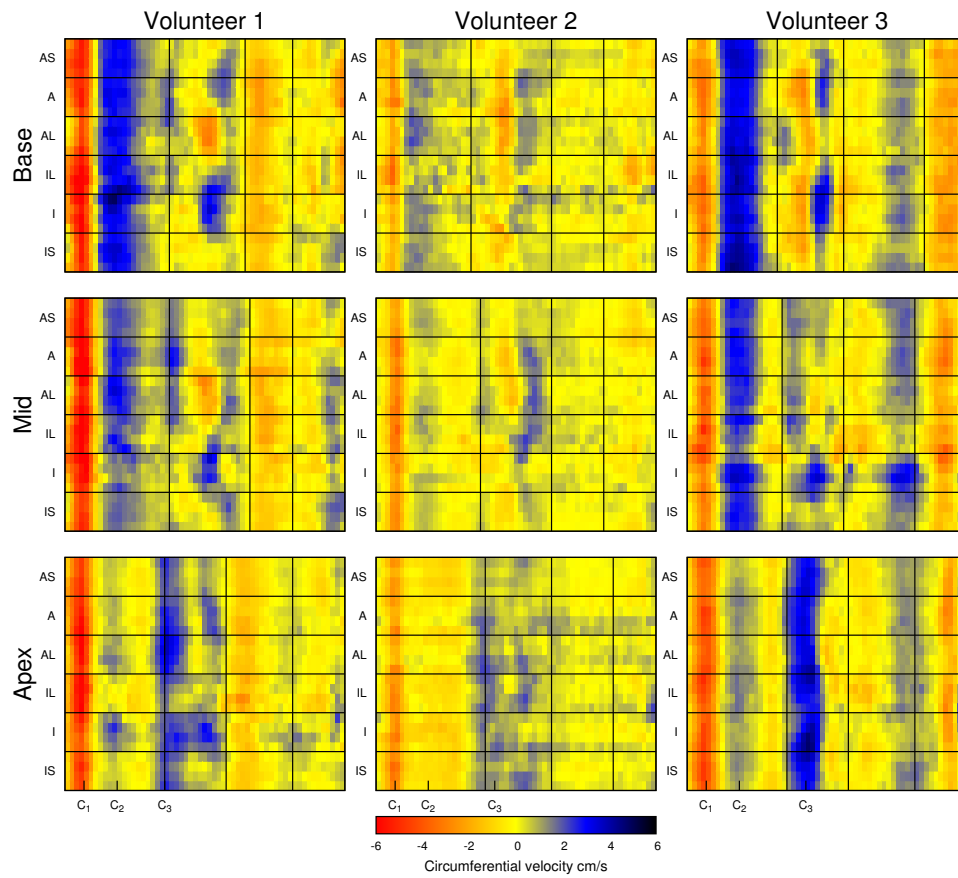


Figure 4.13: Basal (top), mid (middle) and apical (bottom) circumferential colour plots for three individual volunteers. Colour scale is shown in cm/s.

Figures 4.11 to 4.13 show the colour plots for three individual volunteers, chosen to highlight inter-subject variations (Volunteer 1 is the same volunteer shown in Figures 4.7 to 4.9). The three directions of motion are shown in separate figures, allowing comparisons between volunteers. Although the plots are noisier than the averaged version, regional variation of velocities (for example the low longitudinal velocities in the septal regions) is still visible and easily interpretable. The plots are not time normalised which can be seen by the different durations of the various phases of the cycle (as marked by horizontal lines).

In the longitudinal direction differences between the volunteers can be seen,

both in the magnitude of the peaks (D_L is higher in Volunteer 3 than Volunteer 1 in all slices for example), and in the regional variation (S_L is more localised in Volunteer 1 than Volunteers 2 and 3 for example). In the radial direction, the biphasic pattern in the septum is clearly seen in Volunteers 1 and 3 but it not seen in Volunteer 2. Again some differences in magnitude can be seen. The circumferential direction shows the most variation of velocities, particularly in diastole.

The ability to detect inter subject variations suggests that the plots could be useful on a patient-by-patient basis, not just for looking at populations.

4.2.1.5 Transmural velocities

As well as splitting the myocardium circumferentially into regions, the image resolution is high enough that the myocardium can be analysed in different transmural layers. Each slice has been split into three transmural regions (endocardium, mid-myocardium and epicardium) and the average peak velocities in each layer are shown in Table 4.3.

The radial direction shows a consistent velocity gradient across the myocardium throughout the cardiac cycle and in all slices, with endocardial velocities significantly higher than mid-myocardial velocities which in turn are significantly higher than epicardial velocities. The longitudinal direction does not show this pattern, although in a few cases there are significant differences between layers. The circumferential velocities show no differences at base but at mid and apical levels epicardial velocities are generally higher than endocardial velocities - this is a gradient in the opposite direction to that which is seen in radial velocities.

Peak velocity(cm/s)	Endocardium	Mid	Epicardium	P(Endo-Mid)	P(Mid-Epi)
BASE					
S_R	2.55 ± 0.78	2.15 ± 0.64	1.87 ± 0.48	$P < 0.001$	$P < 0.01$
D_R	-4.22 ± 1.02	-3.69 ± 0.80	-3.20 ± 0.58	$P < 0.001$	$P < 0.001$
AS_R	-1.47 ± 0.51	-1.36 ± 0.46	-1.19 ± 0.44	$P = 0.05$	$P < 0.05$
S_Z	7.02 ± 1.89	6.97 ± 1.81	6.79 ± 1.88	NS	NS
D_Z	-9.65 ± 1.95	-9.44 ± 1.96	-9.29 ± 2.05	NS	NS
AS_Z	-2.72 ± 0.82	-2.75 ± 0.87	-2.72 ± 0.87	NS	NS
C_1	-2.33 ± 1.27	-2.75 ± 0.87	-2.72 ± 0.87	NS	NS
C_2	2.01 ± 1.09	1.99 ± 1.15	2.04 ± 1.17	NS	NS
C_3	-1.55 ± 0.45	-1.97 ± 1.16	-1.60 ± 0.49	NS	NS
MID					
S_R	2.75 ± 0.44	2.38 ± 0.41	2.09 ± 0.33	$P < 0.001$	$P < 0.001$
D_R	-4.53 ± 0.74	-4.11 ± 0.61	-3.63 ± 0.51	$P < 0.001$	$P < 0.001$
AS_R	-1.72 ± 0.43	-1.62 ± 0.45	-1.46 ± 0.41	$P < 0.05$	$P < 0.01$
S_L	5.86 ± 1.94	5.92 ± 1.89	5.73 ± 1.89	NS	$P < 0.05$
D_L	-6.67 ± 1.91	-6.72 ± 2.01	-6.60 ± 2.02	NS	$P < 0.05$
AS_L	-1.81 ± 0.68	-1.87 ± 0.71	-1.99 ± 0.64	NS	NS
C_1	-3.45 ± 1.48	-3.60 ± 1.52	-3.56 ± 1.57	$P < 0.05$	NS
C_2	1.26 ± 0.76	1.35 ± 0.81	1.52 ± 0.85	$P < 0.05$	$P < 0.001$
APEX					
S_R	2.45 ± 0.28	2.16 ± 0.27	1.90 ± 0.26	$P < 0.001$	$P < 0.001$
D_R	-4.47 ± 1.05	-4.04 ± 0.93	-3.56 ± 0.85	$P < 0.001$	$P < 0.001$
AS_R	-1.65 ± 0.43	-1.58 ± 0.46	-1.47 ± 0.45	NS	$P < 0.02$
S_Z	4.64 ± 1.73	4.85 ± 1.71	4.89 ± 1.71	$P < 0.02$	NS
D_Z	-4.18 ± 1.71	-4.36 ± 1.70	-4.31 ± 1.67	$P < 0.05$	NS
AS_Z	-0.87 ± 0.31	-0.86 ± 0.34	-0.87 ± 0.35	NS	NS
C_1	-3.28 ± 1.15	-3.52 ± 1.24	-3.65 ± 1.29	$P < 0.001$	$P < 0.01$
C_2	0.21 ± 0.66	0.33 ± 0.74	0.50 ± 0.78	NS	$P < 0.05$
C_3	2.03 ± 0.62	2.15 ± 0.73	2.15 ± 0.75	$P < 0.05$	NS

Table 4.3: Transmural peak velocities in all three slices. Also shown are any significant differences between endocardium and mid myocardium and between mid myocardium and epicardium.

4.2.1.6 Phantom offsets

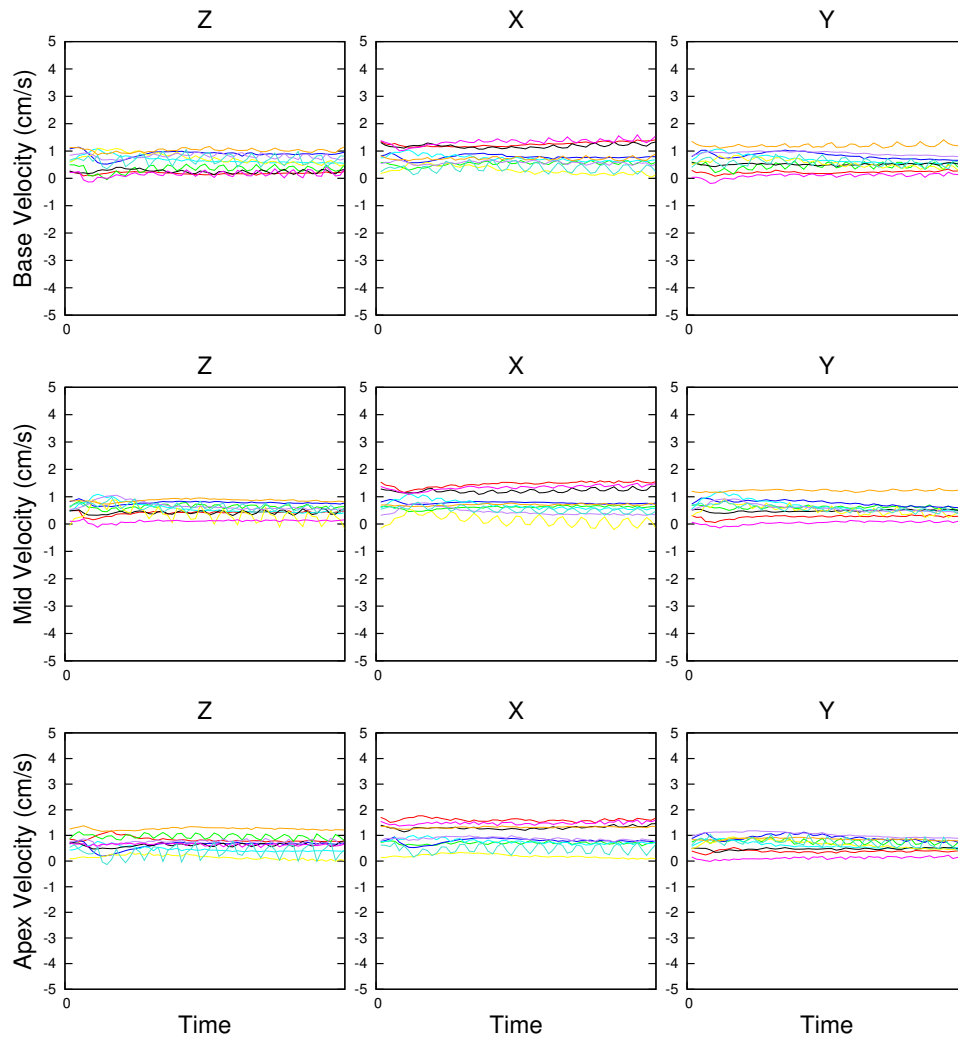


Figure 4.14: Global background offsets through the cardiac cycle for all ten volunteers and in all slices. The directions Z, X and Y are the measured velocity encoding directions rather than the longitudinal, radial and circumferential directions.

In order to show the necessity of the phantom background correction, the average phantom velocities over the area covered by the myocardium in the basal, mid and apical slices for each of the volunteers is shown in Figure 4.14. These

are the errors which would be present in the measured velocities if no correction was performed. In each of the three directions and in all slices the offset is between 0 and 1.5cm/s and is fairly stable over the cardiac cycle, although regular oscillations (possible due to the black blood pulses) are seen. The level of offset is similar for all three slices. A small bump in the trace can be seen towards the beginning of the cardiac cycle, this could potentially be caused by the navigator acquisition disrupting the steady state of the sequence.

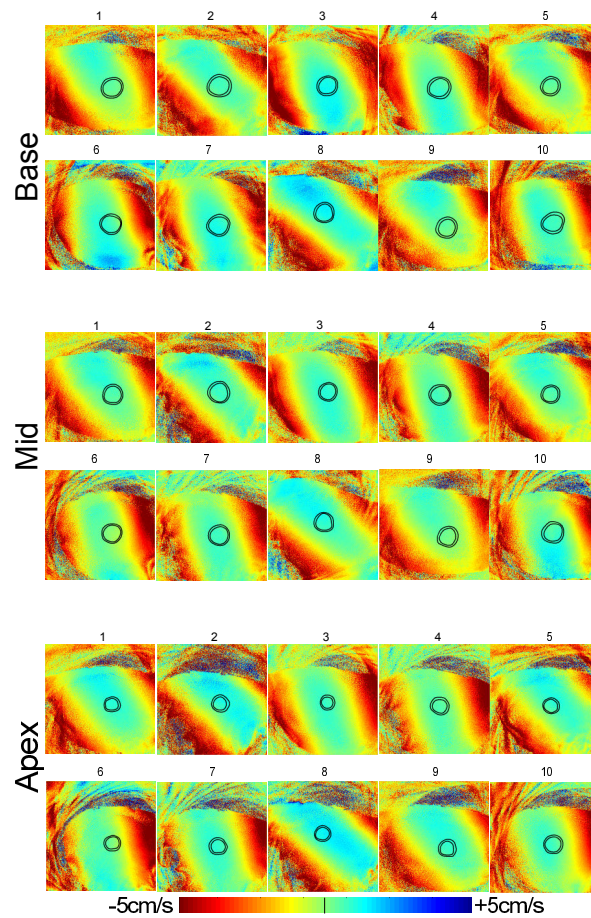


Figure 4.15: Through plane background offsets for all ten volunteers (1-10) in basal, mid and apical slices. The position of the myocardium is marked with a black outline.

To show the regional variation in background offsets, the first phase maps of the

longitudinally encoded phantom acquisitions for all ten volunteers are shown in Figure 4.15 with a colour scale designed to show regional variations. The in plane offsets are shown in Figure 4.16. Towards the edge of the images an offset of around 5cm/s is seen, but in the region of the myocardium (shown by the black outline) little variation is seen in most cases and the offset is close to zero. This is because a cuboid covering the left ventricle is chosen during scanning as the shim region to be optimised, so outside of this region the shim will not be as good. However, in some cases non-zero varying offsets can be seen at the position of the myocardium (for example in the Y direction in the apical slice).

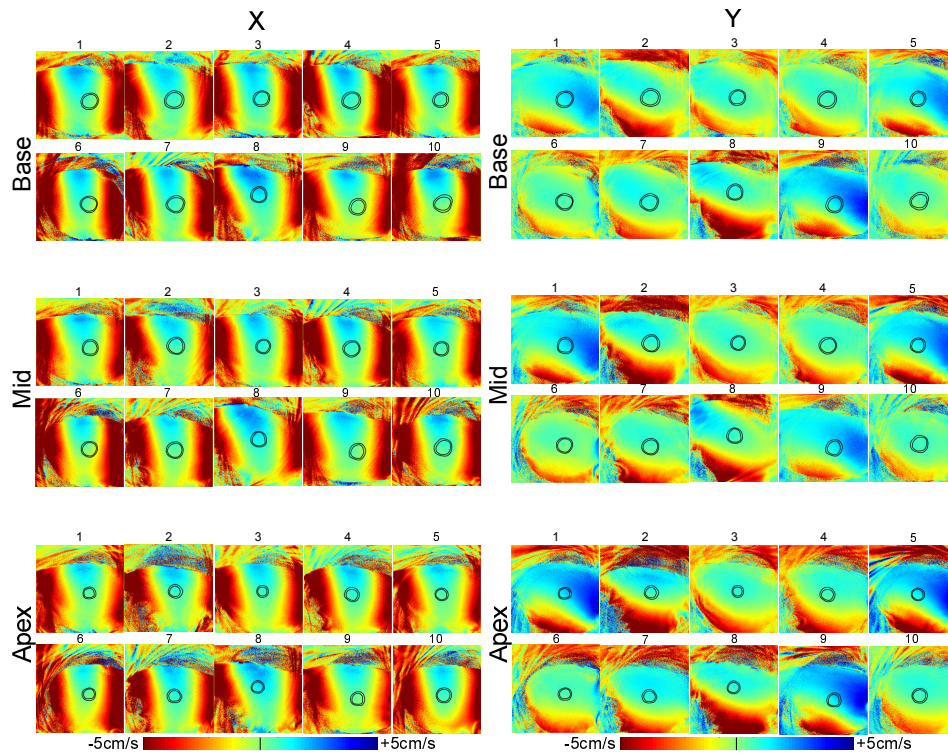


Figure 4.16: In plane background offsets for all ten volunteers (1-10) in basal, mid and apical slices. The position of the myocardium is marked with a black outline.

4.2.1.7 Reproducibility

	Peak	Reproducibility	TTP (ms)	Reproducibility	TTP norm	Reproducibility
BASE						
S_L (cm/s)	6.94±1.87	-0.50±1.07	58.3±11.8	0±8.1	60.6±6.7	-1.8±6.3
D_L (cm/s)	-9.45±1.97	-0.30±1.54	458.0±33.3	18.7±41.1	467±26	4.6±28.0
AS_L (cm/s)	-2.62±0.99	-0.26±1.04	881.1±101.7	57±90.8	864.8±34.5	27.3±52.7
E/A_L	4.26±2.39	-0.20±1.90	-	-	-	-
S_R (cm/s)	2.35±0.28	0.05±0.27	117.5±24.5	4.6±14.4	120.4±15.8	2.5±19.6
D_R (cm/s)	-4.01 ±0.65	-0.20±0.96	446.5±34.5	13.9±30.9	456.0±18.2	1.3±29.3
AS_R (cm/s)	-1.41 ±0.41	-0.15±0.36	864.6±106.4	38.7±91.4	857.0±46.2	9.1±59.2
E/A_R	3.00±0.76	-0.08±0.61	-	-	-	-
C_1 (cm/s)	-2.88±1.35	0.12±0.58	42.3±11.2	0±9.8	44.5±9.1	0.4±12.3
C_2 (cm/s)	2.33±0.91	0.07±0.64	133.8±15.3	-0.2±14.8	140.7±20.0	3.2±18.9
C_3 (cm/s)	-1.58±0.52	-0.37±0.61	391.2±48.9	7.2±35.9	410.5±16.3	3.9±26.7
MID						
S_L (cm/s)	5.87±1.89	-0.56±0.87	55.6±10.3	-1.1±6.6	59.9±6.3	-4.5±7.7
D_L (cm/s)	-6.50±1.85	0.21±1.54	461.2±39.7	20.6±30.4	483.3±24.1	-3.5±22.2
AS_L (cm/s)	-1.66±0.67	0.22±1.08	858.5±137.5	26.6±103.9	869.4±30.6	-1.1±25.6
E/A_Z	4.97±3.29	-1.37±4.95	-	-	-	-
S_R (cm/s)	2.38±0.38	-0.01±0.36	108.5±18.0	-7.1±24.1	123.6±16.1	-13.8±27.4
D_R (cm/s)	-3.61±0.77	0.20±0.56	457.7±68.5	26.3±35.7	487.2±20.2	1.3±21.3
AS_R (cm/s)	-1.59±0.43	0.14±0.42	865.7±129.3	25.4±88.2	875.9±29.9	3.0±10.9
E/A_R	2.43±0.87	-0.01±0.66	-	-	-	-
C_1 (cm/s)	-3.52±1.50	0.10±0.50	46.8±12.6	2.4±10.2	48.7±9.8	0.9±9.5
C_2 (cm/s)	1.40±0.83	-0.20±0.48	135.0±19.5	-2.8±13.6	147.4±21.4	-9.5±7.6
APEX						
S_L (cm/s)	4.83±1.70	-0.11±0.67	50.7±9.73	-1.6±11.5	51.5±7.7	-3.5±8.4
D_L (cm/s)	-4.27±1.67	-0.31±1.35	454.3±28.6	14.6±24.8	449.5±41.0	2.0±24.7
AS_L (cm/s)	-0.81±0.29 *	0.29±0.78 **	876.2±105.2*	37.6±83.7**	859.0±30.6	20.2±33.2
E/A_L	5.59±3.04*	0.30 ± 0.78 **	-	-	-	-
S_R (cm/s)	2.14±0.27	0.02±0.33	110.2±20.6	-1.6±19.8	114.8±22.1	-7.7±18.6
D_R (cm/s)	-3.99±0.94	-0.10±0.95	484.8±43.6	8.0±15.6	482.6±30.6	-3.9±28.6
AS_R (cm/s)	-1.57±0.45	-0.15±0.48	884.1±106.1	14.4±76.6	880.4±28.6	5.2±39.7
E/A_R	2.67±0.66	-0.23±0.64	-	-	-	-
C_1 (cm/s)	-3.50±1.23	-0.04±0.57	49.4±11.2	2.2±10.8	48.3±6.3	-0.4±12.6
C_2 (cm/s)	0.39±0.69	-0.00±0.38	138.3±21.0	-3.2±12.6	141.8±41.6	12.3±22.1
C_3 (cm/s)	2.09±0.72	0.17±0.59	364.3±38.0	10.7±14.6	359.1±21.5	-2.6±36.4

Table 4.4: Reproducibility of Peak and TTP measurements. Asterisks represent parameters which were not seen in all volunteers.

The inter-study reproducibilities for peak and TTP measurements are shown in Table 4.4. For each parameter the mean and standard deviation of the signed differences between the two measurements (made on separate occasions) is quoted. All global peak velocities have high reproducibility with the standard deviation of the signed differences ranging from 0.67 cm/s (apical S_L) to 1.54 cm/s (mid

D_L) in the longitudinal direction, 0.27 cm/s (basal S_R) to 0.96 cm/s (basal D_R) in the radial direction and 0.38 cm/s (apical C_2) to 0.64 cm/s (basal C_3) in the circumferential direction. Atrial systolic measurements are more reproducible in the radial than the longitudinal direction, which also leads to better reproducibility for E/A values in the radial direction.

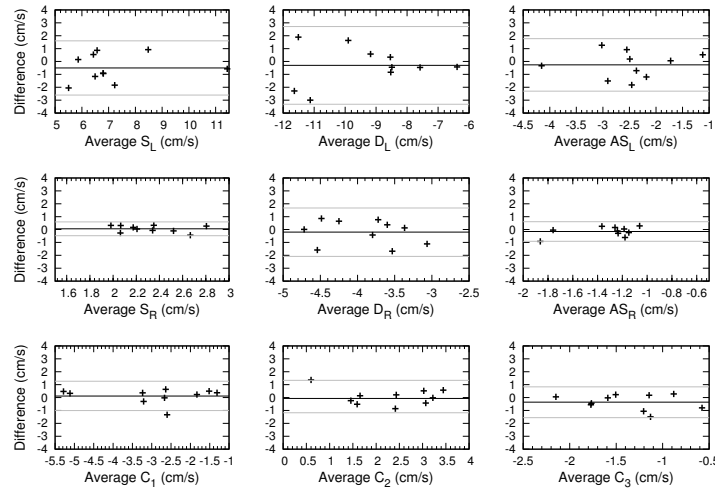


Figure 4.17: Bland-Altman plots for peak velocity values in the basal slice. The average of the two measurements in each of the ten volunteers is plotted on the x-axis against the difference between the measurements on the y-axis.

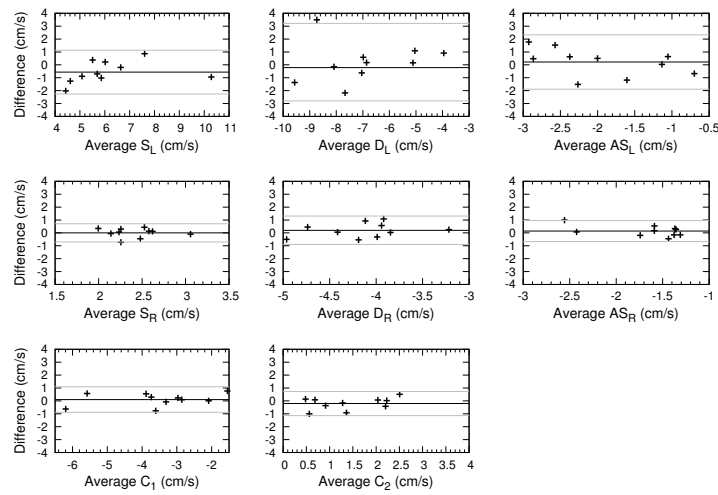


Figure 4.18: Bland-Altman plots for peak velocity values in the mid slice. The average of the two measurements in each of the ten volunteers is plotted on the x-axis against the difference between the measurements on the y-axis.

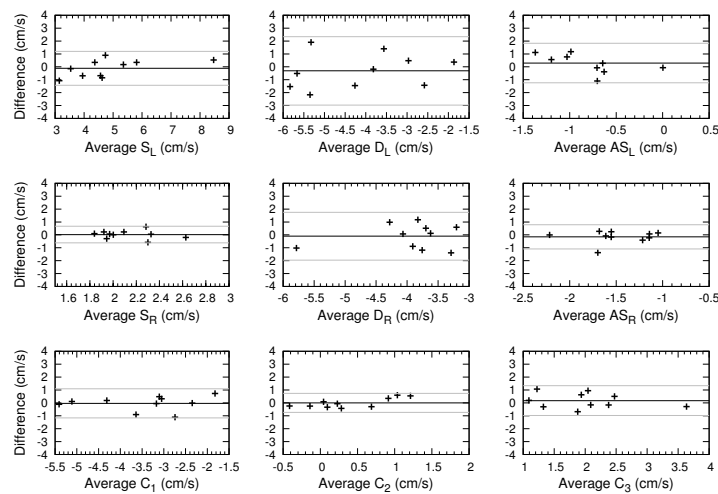


Figure 4.19: Bland-Altman plots for peak velocity values in the apical slice. The average of the two measurements in each of the ten volunteers is plotted on the x-axis against the difference between the measurements on the y-axis.

Figures 4.17 to 4.19 show Bland-Altman plots for peak velocities in the basal,

mid and apical slices respectively. The black horizontal lines show the mean difference and the grey lines show mean $\pm 1.96SD$ of the differences. The y-axis has the same scale for all plots. None of the measurements show systematic differences from zero in any slices. While in most cases the limits of agreement are small compared with the measured peak values, AS_L shows variation that is similar to its value.

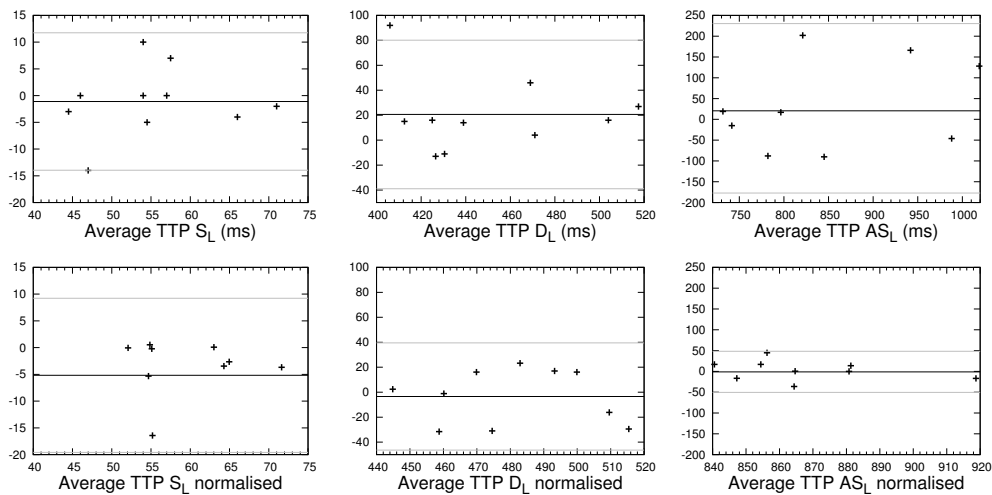


Figure 4.20: Bland-Altman plots for raw (top) and normalised (bottom) TTP S_L (left), D_L (middle) and AS_L (right) for the two measurements in the mid slice in all volunteers. Normalising clearly reduces the variation for AS_L .

The reproducibility of TTP (ms) of the systolic parameters (S_L , S_R , C_1 and C_2) is high at all slice levels (eg at mid level $S_L = -1.1 \pm 6.6$ ms, $S_R = -7.1 \pm 24.1$ ms, $C_1 = 2.4 \pm 10.2$ ms and $C_2 = -2.8 \pm 13.6$ ms), while that of later peaks (diastole and atrial systole) is reduced. When normalised to fixed systolic and diastolic lengths, this degradation of reproducibility through the cycle is removed. The improvement can also be seen in the Bland-Altman plots in Figure 4.20 which show the reproducibility of TTP parameters in the mid slice when unnormalised (top) and normalised (bottom). The improvement in reproducibility for TTP increases through the cardiac cycle. While S_L is not much affected, the improvement in

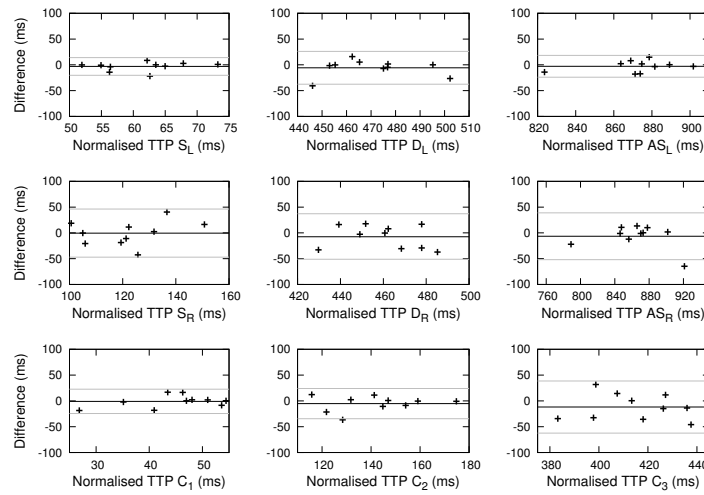


Figure 4.21: Bland-Altman plots for TTP velocity values in the basal slice. The average of the two measurements in each of the ten volunteers is plotted on the x-axis against the difference between the measurements on the y-axis.

reproducibility of TTP atrial systole is clear from comparing the rightmost plots in the first and second rows of this Figure.

The reproducibility for normalised TTPs for all parameters is shown for basal, mid and apical slices in Figures 4.21, 4.22 and 4.23 respectively. Limits of agreement are small for all measured parameters and all slices due to the normalisation.

The intra-study reproducibility from the mid slice parameters is shown in Table 4.5. The values are very similar to those found in the mid slice for inter-study reproducibilities. Normalising the TTP values has again improved the reproducibility of the measured values, particularly for later peaks.

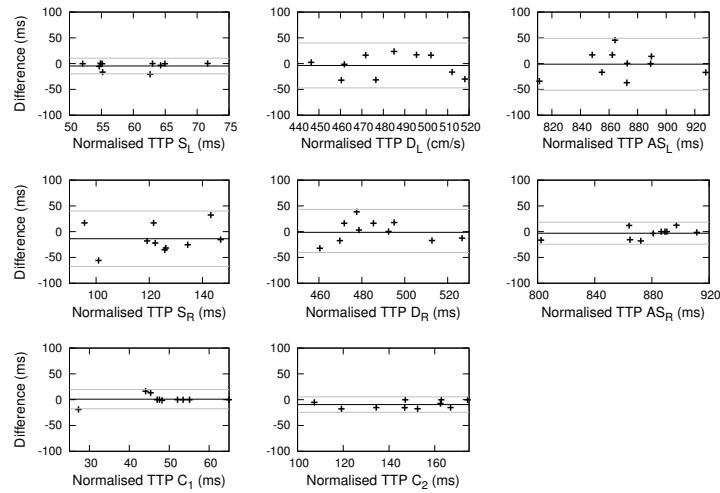


Figure 4.22: Bland-Altman plots for TTP velocity values in the mid slice. The average of the two measurements in each of the ten volunteers is plotted on the x-axis against the difference between the measurements on the y-axis.

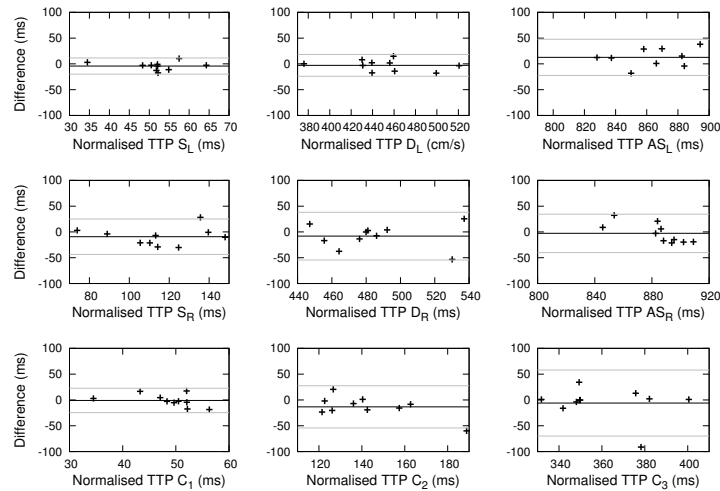


Figure 4.23: Bland-Altman plots for TTP velocity values in the apical slice. The average of the two measurements in each of the ten volunteers is plotted on the x-axis against the difference between the measurements on the y-axis.

	Peak (cm/s)	TTP (ms)	Normalised (normalised ms)
S_L	0.43 ± 0.76	-5.9 ± 10.5	-4.2 ± 7.3
D_L	-0.86 ± 1.55	-12.7 ± 28.7	7.2 ± 12.9
AS_L	-0.90 ± 1.20	-48.9 ± 112.7	-2.7 ± 54.3
S_R	0.18 ± 0.37	12.9 ± 23.0	15.2 ± 21.6
D_R	-0.30 ± 0.50	-15.0 ± 27.5	5.3 ± 11.9
AS_R	-0.28 ± 0.20	-54.0 ± 86.6	-7.5 ± 19.5
C_1	-0.17 ± 0.50	-2.6 ± 4.3	-1.4 ± 3.6
C_2	0.01 ± 0.37	-1.4 ± 12.3	2.7 ± 14.5

Table 4.5: Intra-study reproducibilities for the mid slice. TTP values are shown both as measured values and after normalisation to end systole.

4.2.2 RV

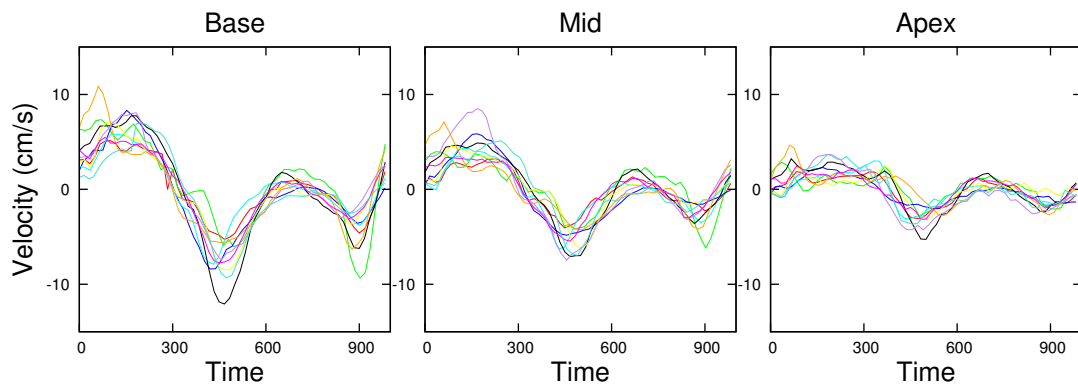


Figure 4.24: Longitudinal RV velocity-time curves for all volunteers in basal (left), mid (middle) and apical (right) slices.

	Peak	TTP (ms)	TTP (norm ms)
BASE			
S_L (cm/s)	7.29±1.65	142.3±50.5	146.6±50.3
D_L (cm/s)	-7.83±2.00	487.2±39.6	495.6±22.4
AS_L (cm/s)	-4.61±2.10	906.8±109.6	903.1±19.5
E/A	2.01±0.91	-	-
MID			
S_L (cm/s)	5.08±1.67	151.4±72.5	152.7±72.2
D_L (cm/s)	-5.67±1.29	479.8±50.5	487.4±24.3
AS_L (cm/s)	-2.42±2.52	867.1±144.1	884.6±24.7
E/A	1.74±1.62	-	-
APEX			
S_L (cm/s)	2.98±0.82	189.4±113.5	188.7±115.0
D_L (cm/s)	-3.34±0.89	511.8±39.0	508.6±35.9
AS_L (cm/s)	-1.87±0.64	901.4±108.8	900.1±28.3
E/A	2.01±0.97	-	-

Table 4.6: Peak and TTP mean $\pm$ SD values in the RV

	Peak Reproducibility	TTP Reproducibility	TTP norm Reproducibility
S_L (cm/s)	0.21±1.31	20.2±72.4	11.6±78.2
D_L (cm/s)	0.15±1.13	12.6±45.3	13.1±30.6
AS_L (cm/s)	0.69±2.39	27.1±99.2	6.7±20.0
E/A	0.33±1.60	-	-

Table 4.7: Reproducibility of peak and TTP mean $\pm$ SD values in the mid slice of the RV

Due to the asymmetrical geometry of the RV only longitudinal velocities have been analysed for this project. Global longitudinal velocity curves for all volunteers and in all three slices can be seen in Figure 4.24. As with LV velocities there are three main peaks in the cardiac cycle, S_L , D_L and AS_L . Peak and TTP (measured and normalised) values for these peaks can be seen in Table 4.6. Reproducibility (mean $\pm$ SD of signed differences) for peak and TTP values is also shown for the measured peaks in the mid slice in Table 4.7.

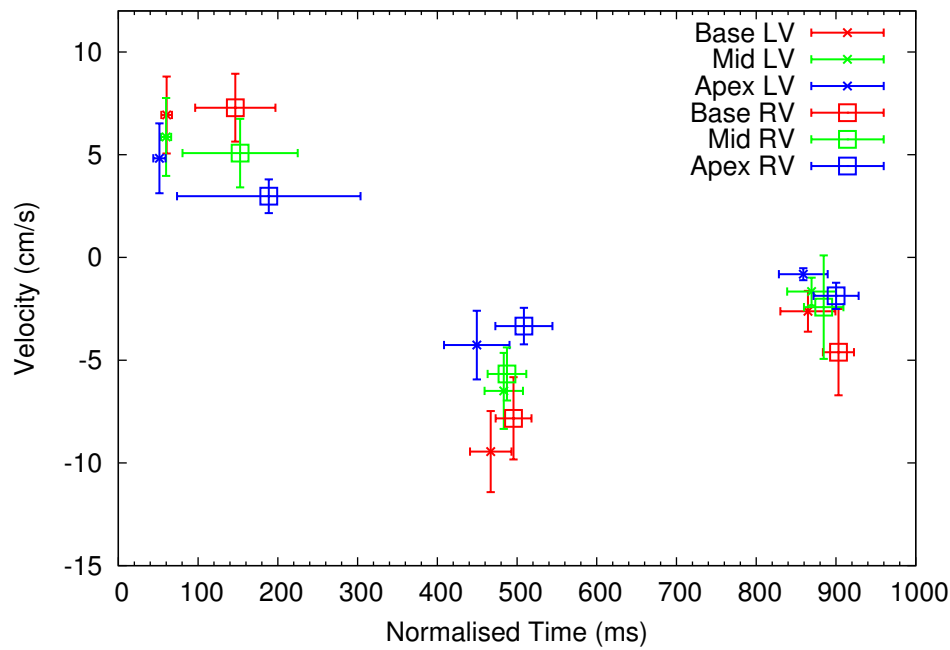


Figure 4.25: Average Peak and TTP values for LV and RV. Mean $\pm$ SD values are shown for all parameters.

Figure 4.25 shows the peak and TTP values for the right ventricle, with the corresponding LV values also shown for comparison. Some differences are immediately obvious; S_L occurs later in the RV than in the LV ($P < 0.005$ for all levels) and has a greater standard deviation. While diastolic velocities are generally slightly higher in the LV ($P < 0.05$ for basal and apical levels), the trend is reversed in atrial systole, with RV velocities slightly higher than the paired LV values ($P < 0.01$ for basal and apical levels). These differences are only very small when compared with the respective standard deviation of peak values (see Tables 4.2 and 4.6).

4.3 Discussion

4.3.1 Data acquisition

The navigator gated method as described in Chapter 3 is capable of acquiring high resolution PVM images in a shorter time than has previously been possible. Retrospective cardiac gating has enabled analysis of myocardial velocities throughout the cardiac cycle, including atrial systole.

The use of spirals has allowed the acquisition of images with high spatial (1.4mm x 1.4mm) and temporal (21ms) resolution in a short time (53 cardiac cycles) which compares favourably with previous Cartesian schemes (eg 2.6 x 1.3mm, 13.8ms (with view-sharing) in 128 cardiac cycles (Jung et al., 2006a) or 2.6 x 1.4mm, 26ms in 180 cardiac cycles (Delfino et al., 2008b)). Spiral imaging can suffer from an increased level of artefact when compared with Cartesian imaging. However, because of the careful attention to shimming, image quality has been very good, despite the high field strength (3T). While off resonance artefact may sometimes be seen in regions of high susceptibility change, such artefacts are well localised and do not appear to interfere with the resulting velocity maps. An example of this type of artefact can be seen in the liver in Figure 4.1 close to the inferior regions of the LV.

By including the restriction that navigators both before and after the data is acquired had to be within the acceptance window, respiratory motion was properly suppressed. Despite the necessity to have these strict navigator acceptance criteria the technique was efficient (average 57%) since the volunteers were able to guide their own breathing and most chose to complete the scan in a series of short breath-holds rather than by regular slow breathing. However difficulties are expected when using this technique to image patients due to the level of compliance needed to use the respiratory trace to guide their own breathing.

More sophisticated biofeedback mechanisms could be implemented in future patient studies (Jhooti et al., 2011).

During navigator output and feedback, no image data may be acquired. For prospective cardiac gating this means that no velocity information is available during this time, whereas for retrospective gating it results in decreased accuracy in the retrospective data interpolation close to the navigator. In this study, the navigator duration (9ms) and feedback time (10ms) were reduced as much as possible to minimise this problem. The retrospective cardiac gating allows us to calculate average velocities for the entire cardiac cycle, and, because they are close to zero (see Section 4.2.1.2), we can be confident that the accuracy of the technique overall is very good (we would not expect the velocities to be exactly zero for several reasons; no slice following was performed, heart rate variations could affect the final velocities measured (see Chapter 6), etc).

4.3.2 Results

Global longitudinal peak systolic and early diastolic velocities show the expected reductions from base to apex (eg Jung et al. (2006a)) and this pattern is also seen in the atrial systolic peak velocities. The atrial systolic peak in longitudinal velocity measures the passive motion of the ventricle as the atria contract, pulling the base of the ventricle towards them. The peak velocity is therefore larger at base (-2.62 ± 0.99 cm/s) than at apex (-0.81 ± 0.29 cm/s) and was not seen in 3 (out of the 20) apical acquisitions, perhaps because atrial systole is not sufficiently strong in some patients to allow passive longitudinal motion to be consistently detected at the apical level (see bottom left graph of Figure 4.3). Atrial systole also causes passive radial motion in the left ventricle at all levels, caused by blood being forced into the LV by the contraction of the atria: reduced radial peak velocity in atrial systole could therefore indicate reduced LV compliance. As expected, in the radial direction, there were

no changes in the magnitude of any of the peak velocities from base to apex while in the circumferential direction, the characteristic wringing of the heart was clearly apparent through the opposite polarity of the C3 peaks at the basal and apical levels.

In addition to the quantification of peak velocities, the retrospective cardiac gating has enabled us to determine the ratio of peak diastolic velocity and peak atrial systolic velocity (here called E/A) in healthy subjects. In echocardiography blood flow velocities at the mitral valve are measured at early diastolic filling (the E-wave) and during atrial systole (the A-wave). The blood velocity is well established to reflect the LA-LV pressure gradient and hence these measurements can give important information about preload, alterations in LV relaxation, LV compliance and LA contractile function: mitral annular velocities are also used to give similar information (Nagueh et al., 2009). The ratio of E/A myocardial velocities could give similar information, helping our understanding of age-related changes of motion as well as pathological motion. In the radial direction this measurement is consistent and has good reproducibility, however in the longitudinal direction it is less reliable.

Time to peak velocities have also been investigated, both as measured from the R-wave and when normalised to a fixed systolic or diastolic length, as appropriate. The latter method greatly reduces the variability of the TTP values between subjects, particularly in early and late diastole, and we suggest that TTP values should always be quoted in this way.

The high spatial resolution of our technique also allows detailed analysis of regional variations of myocardial motion. Regional myocardial velocity information has been displayed on colour plots. These are analogous to bulls eye plots which show all of the velocity information for the complete myocardium at a single time point in the cardiac cycle (Föll et al., 2009), but instead show the regional velocities for a given myocardial slice at all times in the cardiac cy-

cle. This is an effective method of visualising regional variations in all velocity peaks and their timings. Average normal subject plots have been presented and could act as a reference for comparison with the diseased state. Prior to averaging, individual velocity-time curves were normalised to a fixed RR interval. While initial attempts at normalising to a fixed systolic and a fixed diastolic length reduced the blurring of peaks that would be apparent due to heart rate variations between subjects, peak preservation was further improved by normalising each time curve to fixed lengths of systole, early diastole, diastasis and atrial systole. In addition to regional difference in velocities around the myocardium, transmural velocity gradients have also been shown.

4.3.3 Reproducibility

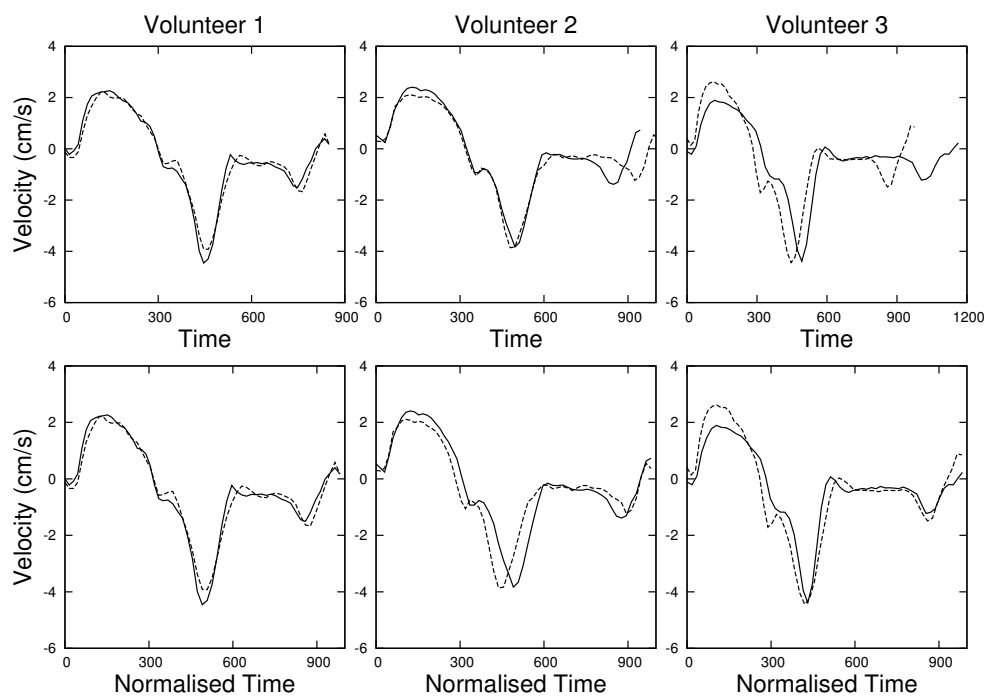


Figure 4.26: Examples of heart rate variation in three volunteers both unnormalised (top) and normalised (bottom).

The inter-study reproducibilities of peak velocity data are high and are better than those obtained with lower temporal resolution sequences, both using breath-holding techniques (eg S_R in the mid slice was -0.01 ± 0.36 cm/s compared with -0.12 ± 0.84 cm/s with 37-87ms temporal resolution (Petersen et al., 2006)) and navigator techniques (eg -0.56 ± 0.87 cm/s for mid D_L compared with -0.51 ± 2.1 cm/s in a navigator study with 35ms resolution (Delfino et al., 2006)). The inter-study reproducibility of TTP (as measured from the R wave) is strongly dependent on heart rate, particularly for the diastolic peaks. This is clear from the example radial velocity plots in the mid slice of three volunteers from acquisitions performed in two separate days which are shown in Figure 4.26. In Volunteer 1, the heart rate was the same on both occasions and the velocity-time curves agree well. In Volunteer 2, the RR interval changed by approximately 50ms between the two acquisitions and, while the systolic and early diastolic portions of the curves agree well, the length of diastasis is different and the atrial peaks therefore do not coincide. In the Volunteer 3, the RR intervals changed by approximately 200ms affecting the timing of all major peaks. By normalising to the length of systole or diastole (Petersen et al., 2006), the reproducibility of TTP measurements is greatly improved (bottom graphs in Figure 4.26). Expressing TTP values relative to systolic or diastolic length is therefore clearly preferable to absolute measurements from the R wave.

4.3.4 RV

Measurements in the RV are difficult to achieve because of the high resolution that is necessary and because of the asymmetrical shape of the RV free wall. The technique has sufficient resolution to analyse right ventricular velocities as is shown by the good reproducibility of the peak and TTP measurements made. The differences which can be seen between the two ventricles are of interest, particularly in atrial systole where RV velocities are significantly higher than in

the LV (-4.61 ± 2.10 cm/s vs -2.62 ± 0.99 cm/s in the base, $p < 0.01$). This could be because the thin right ventricle provides less resistance to the additional blood which is pumped into the ventricles during atrial systole than the left ventricle.

4.3.5 Limitations

While the biofeedback mechanism was well tolerated by the healthy volunteers, and even increased the efficiency of the technique when compared to standard navigator gating, initial experience with patients has shown that significant time is needed to explain the navigator trace and how to guide breathing appropriately. It is therefore not ideal for use in a clinical workflow.

Image reconstruction on the Siemens ICE system is slow and the high temporal resolution of the images means that reconstructing all of the images online greatly increases the time taken to acquire all of the images (reconstructing all 60 phases takes approximately 8 minutes despite the acquisitions being performed with a limited number of coil elements). For this reason the reconstruction was stopped after the first few images had been reconstructed and continued once the volunteer had left the scanner. This too would be difficult in a clinical workflow although the reconstruction can be performed on a standalone computer so access to the scanner is not a necessity.

The collection of phantom data for background phase error correction would also be difficult to achieve in a clinical environment. Previous studies have modelled the background offset based on stationary tissue within the image. While this is likely to achieve a less accurate correction, it makes the technique much more convenient and does not extend analysis time significantly. However this relies on the availability of enough stationary tissue in the image plane to accurately model the offset which may not always be possible.

The time consuming manual delineation of the myocardium is a limitation of this technique but automatic or semi-automatic segmentation algorithms could improve this in the future. So far only global longitudinal velocities have been analysed in the right ventricle. A full investigation into the regional analysis of the three direction velocity vector in the right ventricle is beyond the scope of this project but will be considered for future work.

4.3.6 Conclusion

We have presented an efficient method of collecting high resolution phase velocity mapping data and have comprehensively assessed its reproducibility in healthy volunteers. Coverage of the entire cardiac cycle has allowed the full analysis of atrial systole (a consistent feature of motion in both longitudinal and radial directions). The limitations caused by the use of navigator gating with guided breathing and by the long processing times can be addressed by using the breath-hold version of the sequence. Results from the breath-hold sequence in the same healthy volunteers as presented in this Chapter are shown in the next Chapter.

Chapter 5

Breath-hold acquisitions

This Chapter aims to show that the breath-hold version of the sequence as described in Chapter 3 overcomes some of the limitations of the navigator technique described in the previous Chapter. In particular the need for the complicated biofeedback technique is removed and the scan time is greatly reduced, making this version of the sequence much easier to use clinically.

Breath-hold sequences generally have lower resolution than navigator gated sequences as they have to be completed within an acceptable breath-hold time. This is normally 20-30 seconds for healthy volunteers (Scott et al., 2009) but can be much lower in patients. Previous Cartesian breath-hold PVM sequences have been used to measure regional myocardial velocities in healthy volunteers but with low temporal resolution (eg 2.7x1.3mm and 37-87ms using view sharing acquired in a 17-29 heartbeat breath-hold (Petersen et al., 2006)). They have also used prospective cardiac gating, restricting analysis to 90% of the cardiac cycle.

Several acceleration schemes such as optimised GRAPPA (Peng et al., 2010) and k-t BLAST (Lutz et al., 2011) have been applied to Cartesian PVM to speed up acquisitions, however the resulting accelerated scan times were still too long

for a breath-hold acquisition. Parallel imaging acceleration techniques such as SENSE (Pruessmann et al., 1999) or GRAPPA (Griswold et al., 2002), while originally designed to speed up Cartesian imaging, have been extended to allow use in combination with other, more efficient k-space trajectories such as spirals (Heidemann et al., 2006; Pruessmann et al., 2001).

The implementation of a non-Cartesian SENSE algorithm on the Gadgetron GPU system (see Chapter 3) has allowed the acquisition of data with acceleration of 2 and 2.67 (referred to as R2 and R3). Although the acquired resolution is lower than with the sequence used in the previous Chapter (referred to in this Chapter as HighRes), regional analysis is still possible and the two sequences give results which are in general not significantly different. Where differences are seen they are small and are unlikely to be clinically important.

Parts of this Chapter have been adapted from a paper entitled ‘Spiral tissue phase velocity mapping in a breath-hold with non-Cartesian SENSE’ which has been accepted for publication in the journal *Magnetic Resonance in Medicine*. Abstracts based on this work have also been submitted to international conferences and workshops.

5.1 Methods

5.1.1 Sequence

The breath-hold sequence as described in Section 3.2 was used to scan the same ten healthy volunteers (mean age 32 years, range 25-57) who had previously been scanned with HighRes (see the previous Chapter) to allow full qualitative and quantitative comparison of results. A summary of the sequence details can be found in Table 5.1.

Parameter	Value
Acquired temporal resolution	24ms
Acquired spatial resolution	1.7 x 1.7mm
Number of reconstructed phases	50
Reconstructed pixel size	0.85 x 0.85mm (zero-filling)
Number of spirals	8
Spiral duration	14ms
Scan length	33 heartbeats (fully sampled)
SENSE factors	2 and 2.67
Breath-hold durations	17 and 13 heartbeats
Through-plane VENC	30cm/s
In-plane VENC	20cm/s
Black-blood frequency	Every 3 phases
Flip angle	15°
Field of view	360mm

Table 5.1: Breath-hold sequence details

As described in Section 3.2.6, the dummy heartbeat at the beginning of the acquisition is used to collect the coil sensitivity data by acquiring all eight spiral interleaves consecutively. The image data is then collected as in Figure 3.1 but with only a subset of the eight interleaves being acquired. In the case of R2, interleaves 1, 3, 5 and 7 are acquired and for R3 interleaves 1, 4 and 7 are acquired, leading to scan durations of 17 and 13 heartbeats for R2 and R3 respectively. The undersampled data is passed to the Gadgetron along with the fully sampled coil sensitivity data to be reconstructed using a non-Cartesian SENSE algorithm.

5.1.2 Protocol

All scans were performed on a clinical scanner (3T, MAGNETOM Skyra, Siemens AG Healthcare Sector). The study was approved by an institutional review committee (East London REC 3). All subjects gave written informed consent. 6 elements of an anterior cardiac coil (carefully positioned to give full heart coverage) were used for all acquisitions to limit image reconstruction times. The scan protocol was:

- Localiser images (3 sagittal, 3 transverse and 3 coronal)
- Long axis cine (2 chamber view)
- Long axis cine (4 chamber view)
- Mid ventricular short axis cine (50% of ventricular length)
- Shimming and frequency adjustment
- PVM mid ventricular short axis slice R2
- PVM mid ventricular short axis slice R3
- Frequency adjustment
- PVM basal short axis slice (25% of ventricular length) R2
- PVM basal short axis slice (25% of ventricular length) R3
- Frequency adjustment
- PVM apical short axis slice (75% of ventricular length) R2
- PVM apical short axis slice (75% of ventricular length) R3

In two volunteers a second scan was performed during which a full stack of nine short-axis slices were also acquired with R3 to allow a more comprehensive analysis of regional variations of motion through the left ventricle. Background phase errors due to uncorrected eddy current effects or field inhomogeneities were determined for each acquired dataset by scanning a large homogeneous stationary phantom (31cmx22cmx20cm, gelatine with 5mM concentration of Gadolinium to shorten the T_1) using the same sequence parameters and the same slice positions as in the volunteer study (see Section 3.2.4.1.4).

5.1.3 Analysis

The same MATLAB analysis used for the navigator data was used for the data acquired with the breath-hold sequence (see Section 3.4). The data was analysed globally and regionally with the myocardium being split both circumferentially and radially. As well as velocity-time curves, peak and TTP values were measured. For visualisation, each slice was also split into 24 regions circumferentially and velocities were colour coded to produce colour maps.

Statistical testing was performed using SPSS (SPSS 19, SPSS, Chicago, Ill). All parameters were checked for normality using the Shapiro-Wilk test. The mean $\pm$ SD of global longitudinal, radial and circumferential parameters was determined throughout the cardiac cycle for each slice (basal, mid and apical). Repeated measures analysis of variance (with Greenhouse-Geisser correction in the case of non-sphericity) and paired t-testing (with Bonferroni correction for multiple testing) were used to compare parameters between slices. Differences between endo, mid and epi-cardial velocities were similarly analysed. The values obtained with the accelerated sequences were also compared with those obtained with HighRes.

The right ventricle was analysed, but only longitudinal velocities were consid-

ered because of the asymmetrical nature of the RV. Results were compared with the left ventricle and with HighRes results.

5.2 Results

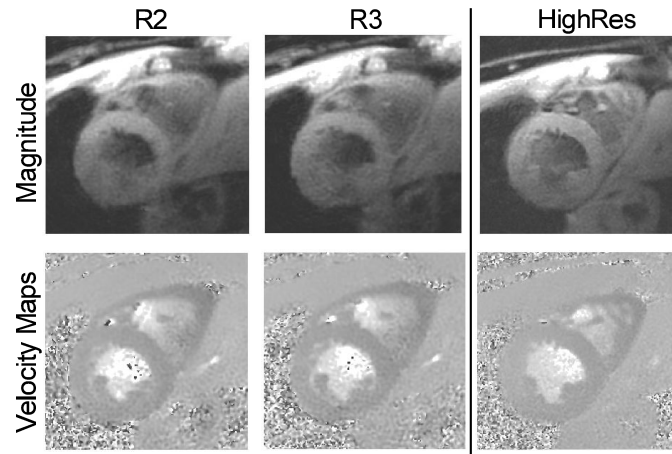


Figure 5.1: Example magnitude images and longitudinal velocity maps from the same volunteer for R2, R3 and the HighRes sequences.

All scans were performed successfully, with 3 slices acquired with both R2 and R3 in all ten volunteers. Example images can be seen in Figure 5.1. Equivalent images acquired with HighRes are included for comparison and show similar image quality and features of motion. The suppression of blood and fat signals is good and the spirals are short enough to prevent major off-resonance blurring. Mean RR duration for R2 acquisitions was $947 \pm 13\text{ms}$, for R3 was $953 \pm 13\text{ms}$. The average systolic and diastolic durations were $328 \pm 24\text{ms}$ and $619 \pm 120\text{ms}$ for R2 and $333 \pm 23\text{ms}$ and $620 \pm 122\text{ms}$ for R3.

Average global velocities over the cardiac cycle were not significantly different from zero (R3 values, for example, were $0.03 \pm 0.57\text{cm/s}$ for longitudinal, $-0.03 \pm 0.29\text{cm/s}$ for radial and $0.04 \pm 0.21\text{cm/s}$ for circumferential velocities, $P > 0.05$

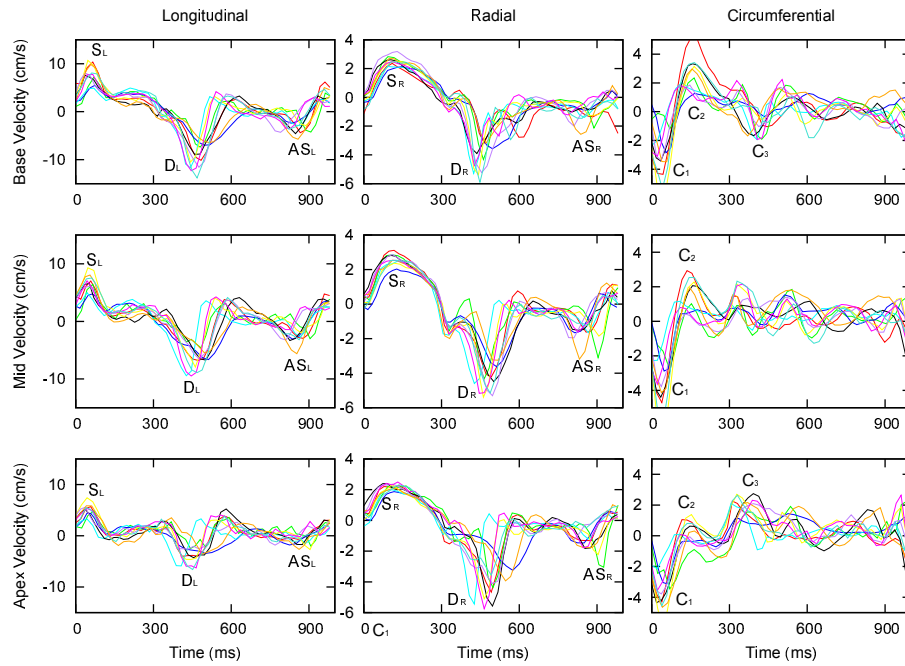


Figure 5.2: Velocity-time curves for R2 acquisitions in all volunteers, time normalised to end-systole to reduce the effect of different heart rates.

in a single sample t-test) indicating that velocity offsets caused by phase errors are effectively removed by the phantom subtraction.

5.2.1 LV

5.2.1.1 Global velocity curves

The main peaks through the cardiac cycle are labelled on the global velocity-time curves for all ten volunteers in Figures 5.2 and 5.3 for R2 and R3 acquisitions respectively. The curves are shown normalised to end systole and end diastole to reduce the effect of heart rate variation on the timing of the peaks. R2 and R3 curves are extremely similar in all cases and show the same patterns as previously seen in Chapter 4. In the longitudinal and radial directions there

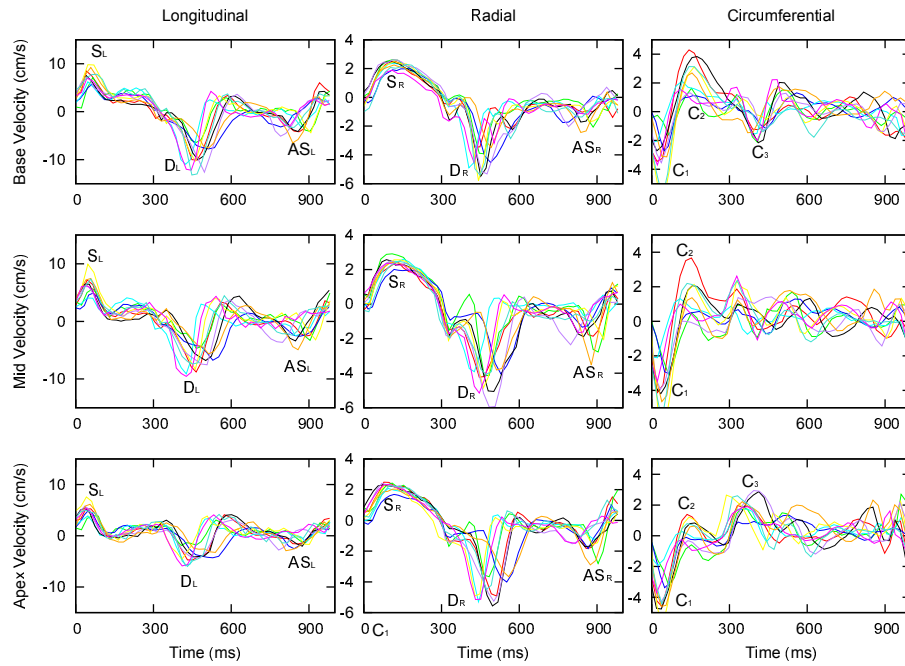


Figure 5.3: Velocity-time curves for R3 acquisitions in all volunteers, time normalised to end-systole to reduce the effect of different heart rates.

are three main peaks; the systolic peak (referred to as S_L and S_R for longitudinal and radial directions respectively), the early diastolic peak (D_L and D_R) and the atrial systolic peak (AS_L and AS_R). In the circumferential direction, there are two systolic peaks (C_1 and C_2) and one main diastolic peak (C_3). Qualitatively there are no obvious differences which can be seen between R2 and R3. The quantitative analysis of peak and TTP values measured by R2 and R3 can be found in the next section.

5.2.1.2 Global Peak and TTP values

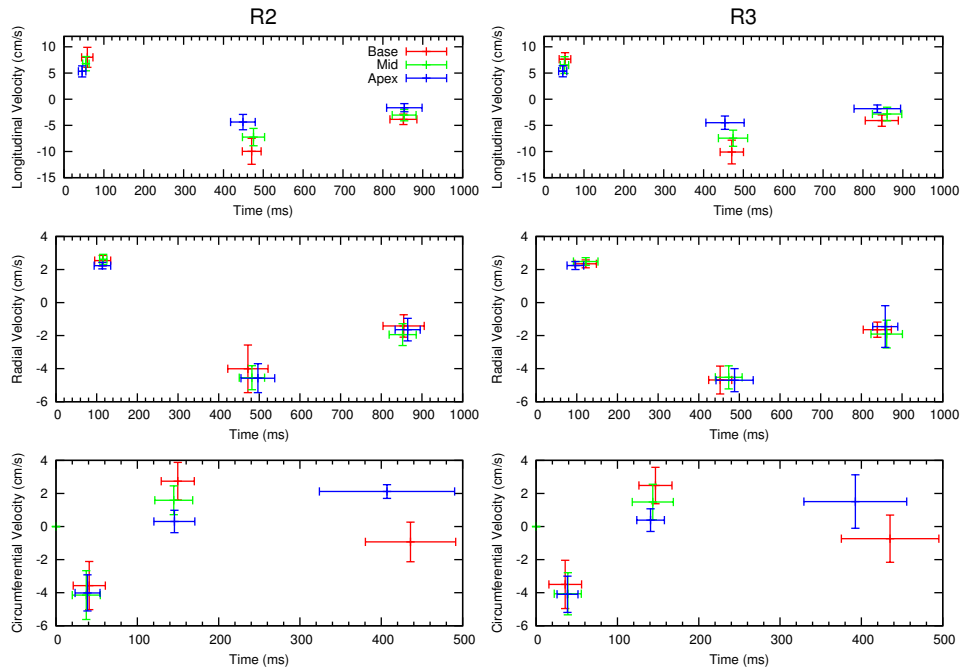


Figure 5.4: Mean $\pm$ SD peak and TTP velocity values for R2 (left) and R3 (right) acquisitions.

The global peak and time to peak velocity measurements for R2 and R3 acquisitions can be seen in Table 5.2 and are shown graphically in Figure 5.4. The quantitative analysis allows a statistical comparison between the values measured by R2 and R3. Paired analysis of R2 and R3 data show no significant differences for any of the peak or TTP values measured as shown in columns four and seven of the Table.

The pattern of velocities is the same as was found for the navigator acquisitions as described in the previous Chapter. Longitudinal velocities are significantly higher at base than mid levels and are higher at mid than apical levels (for example D_L values are -10.11 ± 2.27 cm/s at base, -7.46 ± 1.55 cm/s at mid and -4.50 ± 1.27 cm/s at apex, $p < 0.01$ for both, with significant differences between

	R2	R3	R2vsR3	TTP R2	TTP R3	R2vsR3
BASE						
S_L (cm/s)	8.00±1.91	7.63±1.25	NS	58.4±14.1	52.4±14.6	NS
D_L (cm/s)	-9.97±2.49	-10.11±2.27	NS	470.9±23.7	470.7±29.3	NS
AS_L (cm/s)	-3.86±0.99	-4.10±1.08	NS	851.4±33.9	847.3±41.5	NS
E/A_L	2.76±0.98	2.65±0.97	NS			
S_R (cm/s)	2.54±0.32	2.34±0.24	NS	114.8±19.6	121.9±26.4	NS
D_R (cm/s)	-4.01±1.44	-4.69±0.84	NS	472.0±49.4	452.7±28.4	NS
AS_R (cm/s)	-1.41±0.68	-1.64±0.46	NS	854.9±50.7	839.2±34.5	NS
E/A_R	3.32±1.28	3.06±0.92	NS			
C_1 (cm/s)	-3.57±1.46	-3.50±1.46	NS	40.9±19.7	35.8±20.1	NS
C_2 (cm/s)	2.74±1.13	2.48±1.10	NS	149.7±20.3	146.8±20.4	NS
C_3 (cm/s)	-0.93±1.20	-0.73±1.43	NS	436.0±55.5	435.3±60.0	NS
MID						
S_L (cm/s)	6.79±1.35	6.53±1.61	NS	54.8±8.9	51.1±10.6	NS
D_L (cm/s)	-7.24±1.66	-7.46±1.55	NS	475.5±27.7	473.9±36.8	NS
AS_L (cm/s)	-3.05±1.08	-2.83±1.30	NS	853.4±30.0	860.4±36.8	NS
E/A_L	2.79±1.62	2.45±0.86	NS			
S_R (cm/s)	2.62±0.31	2.48±0.70	NS	116.2±8.9	122.0±30.3	NS
D_R (cm/s)	-4.55±0.72	-4.52±0.84	NS	481.8±31.2	473.7±33.0	NS
AS_R (cm/s)	-1.94±0.66	-1.91±0.84	NS	852.6±33.2	862.4±38.7	NS
E/A_R	2.59±0.88	2.85±1.36	NS			
C_1 (cm/s)	-4.14±1.48	-4.07±1.27	NS	37.2±17.2	39.0±16.6	NS
C_2 (cm/s)	1.59±0.87	1.48±1.07	NS	144.8±23.3	143.5±25.2	NS
APEX						
S_L (cm/s)	5.31±1.06	5.34±1.06	NS	45.6±9.4	46.7±10.3	NS
D_L (cm/s)	-4.38±1.46	-4.50±1.27	NS	448.9±30.9	453.8±48.0	NS
AS_L (cm/s)	-1.63±0.78	-1.83±0.72	NS	853.9±44.5	835.9±58.3	NS
E/A_L	2.77±1.74*	2.69±2.79	NS			
S_R (cm/s)	2.24±0.19	2.24±0.24	NS	114.2±20.3	96.6±20.5	NS
D_R (cm/s)	-4.58±0.88	-4.70±0.70	NS	496.5±41.4	488.2±45.7	NS
AS_R (cm/s)	-1.64±0.68	-1.45±1.27	NS	864.8±30.8	858.7±30.9	NS
E/A_R	3.31±1.65	2.93±1.07	NS			
C_1 (cm/s)	-4.01±1.09	-4.09±1.10	NS	38.8±15.3	38.6±12.9	NS
C_2 (cm/s)	0.31±0.68	0.39±0.68	NS	145.5±25.2	140.8±17.0	NS
C_3 (cm/s)	2.12±0.42	2.09±0.56	NS	407.1±83.1	392.6±63.2	NS

Table 5.2: Peak and time to peak values for R2 and R3 acquisitions. Results of the statistical comparison are shown in columns four and seven and show no significant differences between R2 and R3 for any of the measured parameters. The starred value indicates that an outlier has been left out of the calculation.

all levels also being present for S_L and AS_L , $p < 0.02$ for all). As found previously, radial velocities do not show significant differences between slices, however, S_R occurs earlier at apex than base ($p = 0.011$) and D_R occurs earlier at base than apex ($p = 0.011$). S_R is less sharp than S_L and occurs later in the cardiac cycle. Circumferential velocities show many small peaks through the cardiac cycle, the timings of which are variable between subjects. However all subjects show the early systolic peaks C_1 and C_2 indicating a quick reversal of circumferential direction as the ventricle contracts. Basal and apical slices rotate in opposite directions during early diastole, shown by the opposite polarities of C_3 . As with the HighRes acquisitions, C_3 is not consistently seen in the mid slice.

Values of E/A (i.e. the ratio of diastolic and atrial systolic peaks) are also shown in Table 5.2. In the apical slice one value of E/A_L was a clear outlier (a value of 35.2) and was left out of the calculation of mean and standard deviation. This large value was due to a very small value of AS_L (-0.18cm/s). As was discussed in the previous chapter, the atrial systolic peak is perhaps not consistently present in all healthy subjects, leading to problems when calculating E/A_L in the apical slice.

5.2.1.3 Regional velocities

Figure 5.5 shows velocities in 6 circumferential regions for all volunteers, demonstrating some consistent regional variations, for example septal velocities are consistently lower than lateral velocities. However the plots are difficult to interpret and the averaging of large regions does not make use of the acquired spatial resolution.

Magnitude images at five points in the cardiac cycle with overlaid, colour-coded velocities for a single volunteer are shown in Figures 5.6 to 5.8. The time points shown have been chosen to correspond to interesting phases of the cardiac

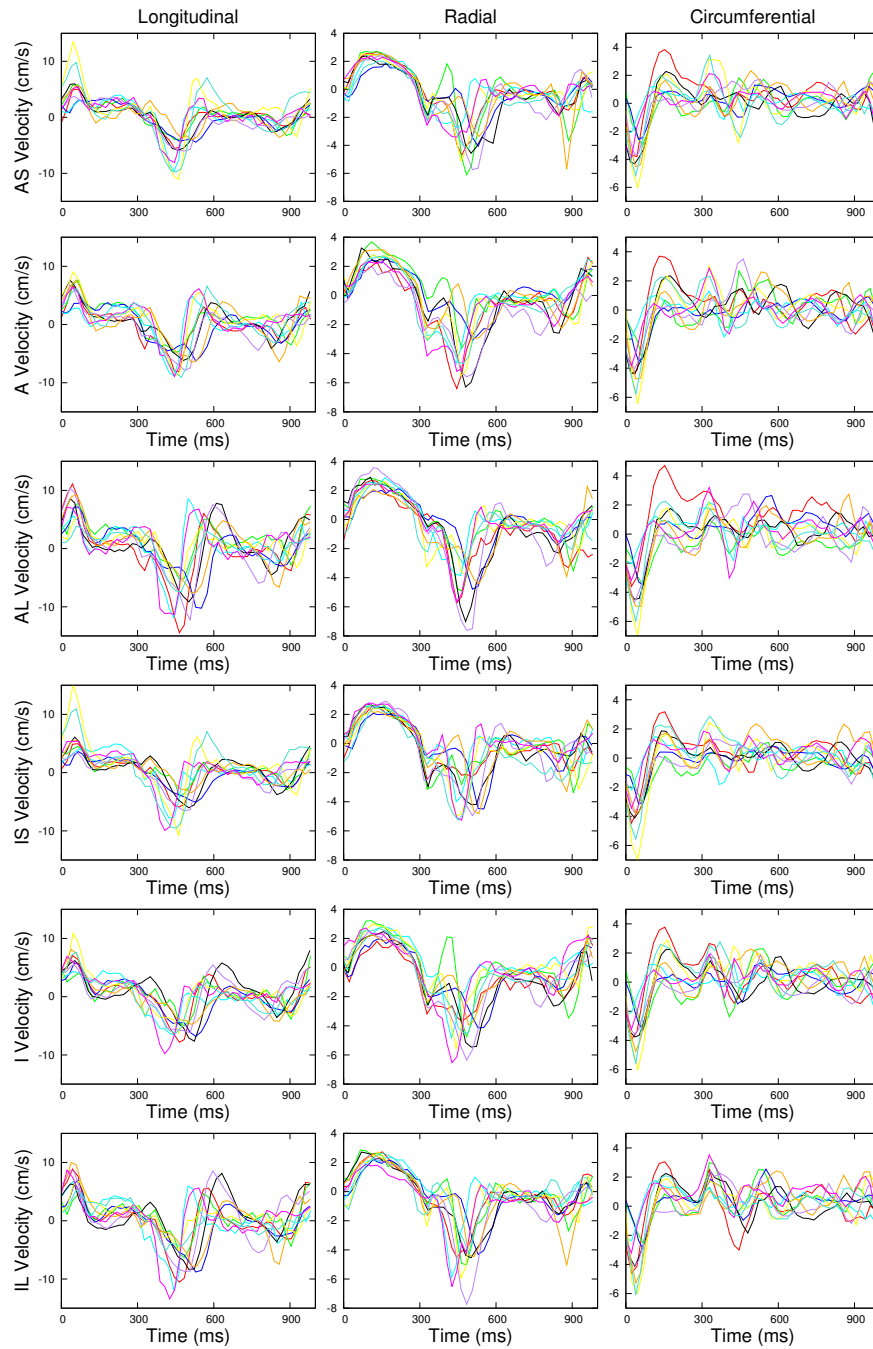


Figure 5.5: Regional longitudinal (left), radial (middle) and circumferential (right) velocity-time curves in the 6 mid slice regions for all volunteers

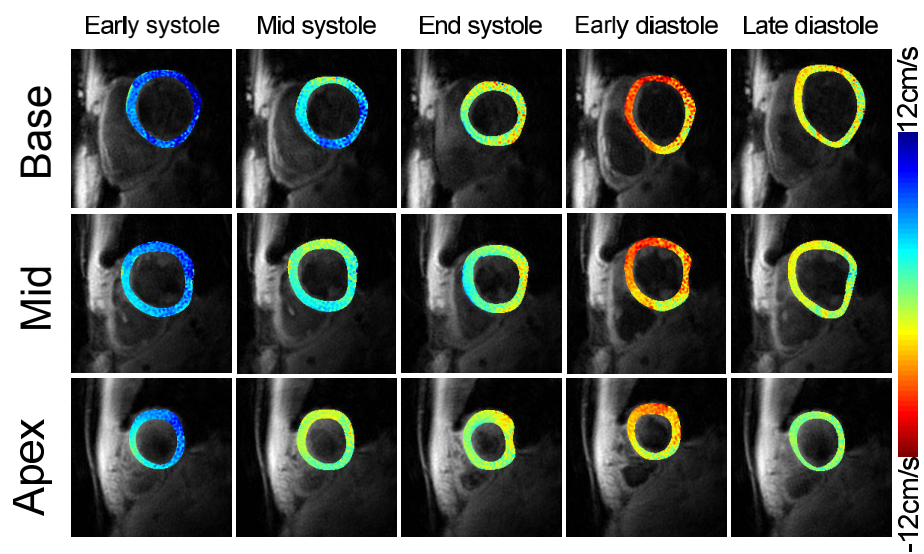


Figure 5.6: Longitudinal colour overlays

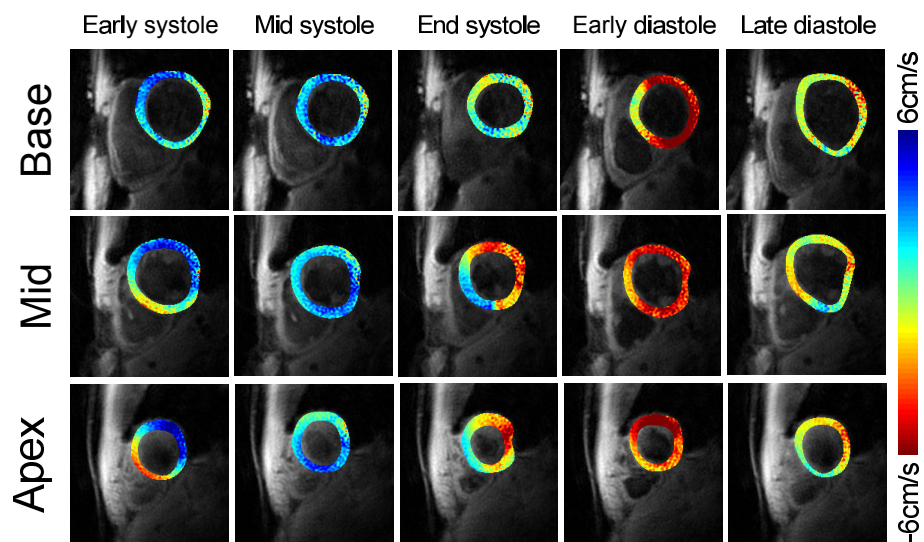


Figure 5.7: Radial colour overlays

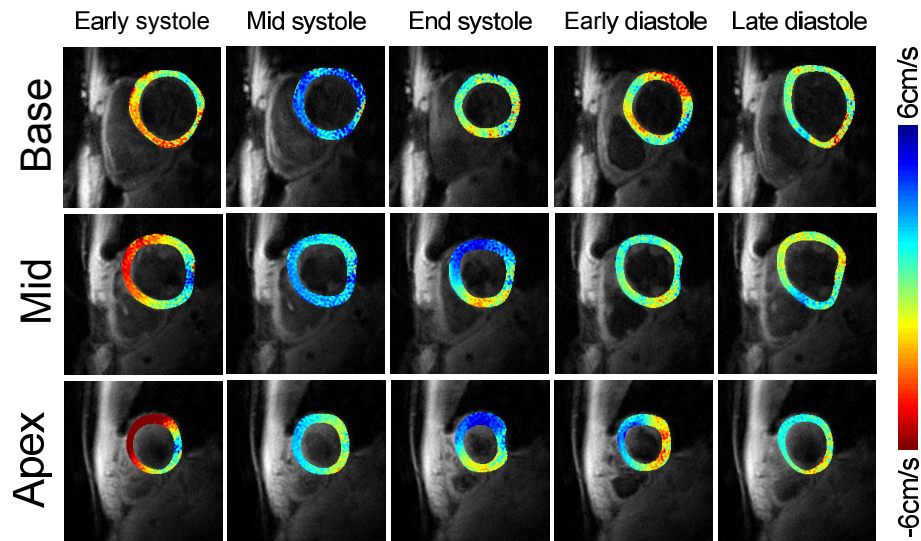


Figure 5.8: Circumferential colour overlays

cycle. The early systolic time point corresponds with the peak systolic longitudinal velocity (S_L) and with the first circumferential peak (C_1), while the mid systolic time point corresponds to S_R and C_1 . The early and late diastolic time points correspond to D_L/D_R and AS_L/AS_R respectively. End systole is also shown. While these show regional variation, it is difficult in a single figure to represent the entire cardiac cycle and the three directional motion of the myocardium. The colourplots which follow allow this regional information to be shown in an easily interpretable way.

5.2.1.4 Colour plots

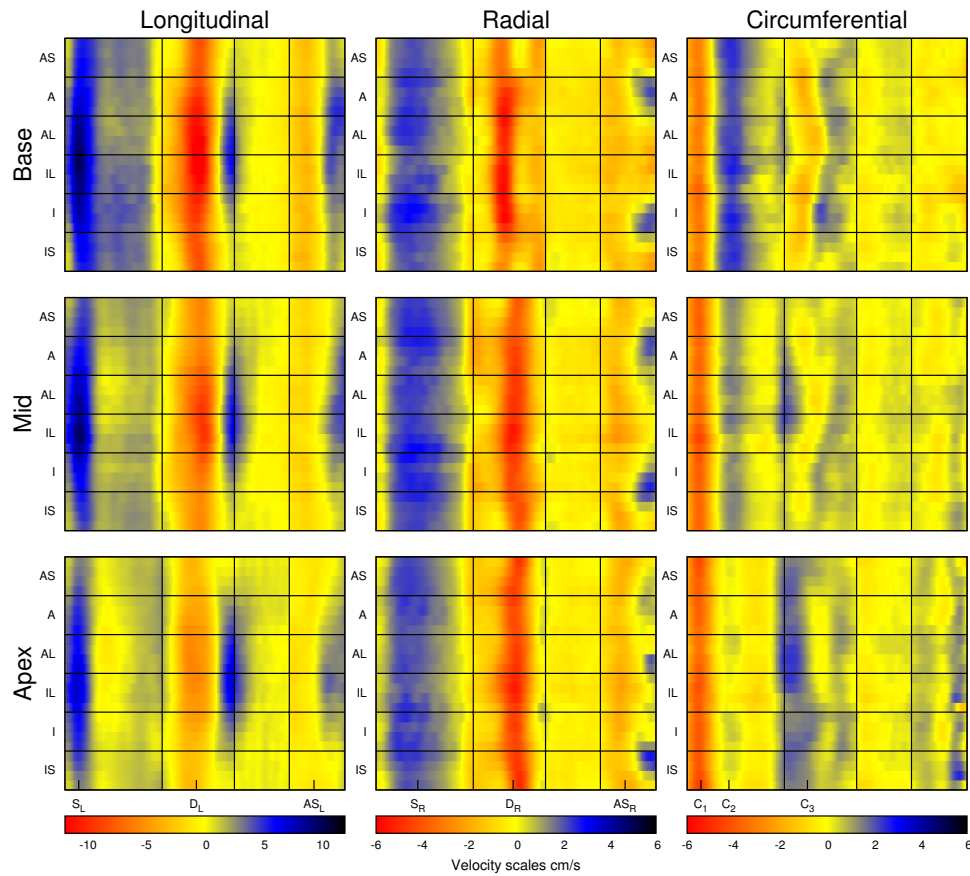


Figure 5.9: Longitudinal (left), radial (middle) and circumferential (right) colourplots averaged over all volunteers. The position of the main peaks are labelled beneath the apical plots.

Figure 5.9 shows colour plots as described in Section 4.10 averaged over all ten volunteers. The plots are formed by splitting the myocardium circumferentially into 24 regions, which are plotted on the y-axis against time on the x-axis. Velocities are then colour coded to allow quick interpretation of regional variations of motion throughout the cardiac cycle.

The plots show the same complicated regional patterns of motion as were seen

with the navigator acquisitions, for example the biphasic septal radial motion in the basal slice and the complicated patterns of circumferential motion in early diastole.

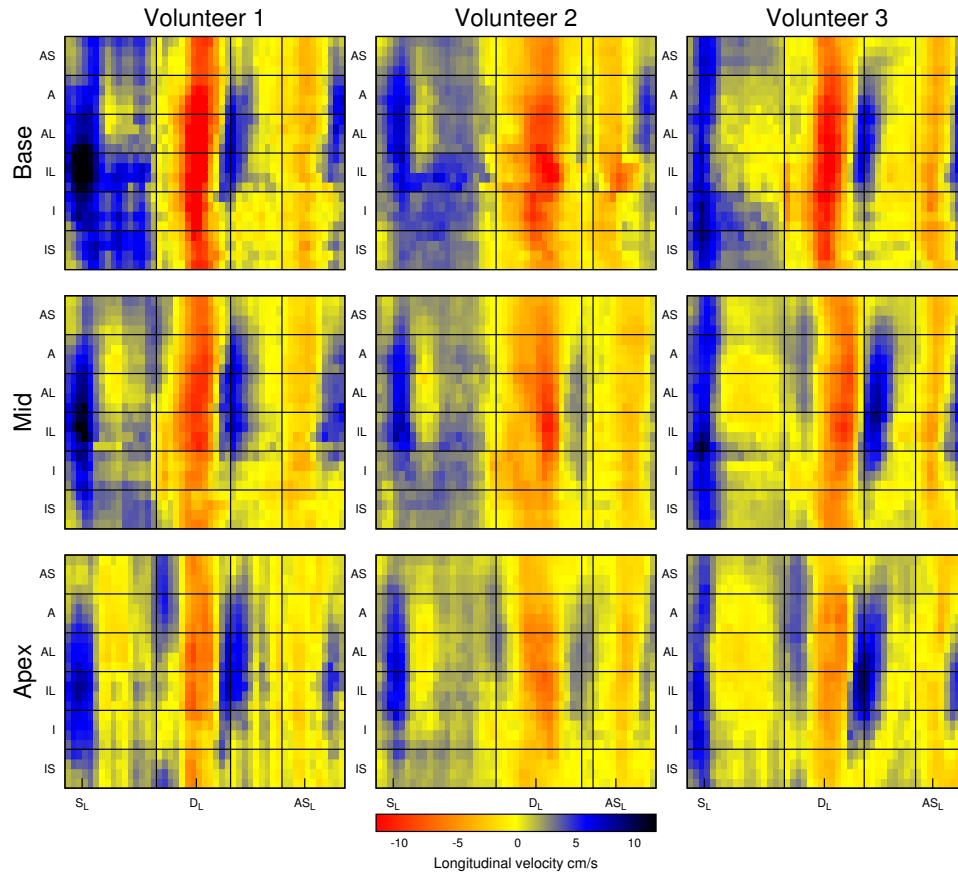


Figure 5.10: Longitudinal colourplots for three volunteers. Vertical lines represent the positions of end systole and the beginning and end of diastasis as measured from velocity-time curves.

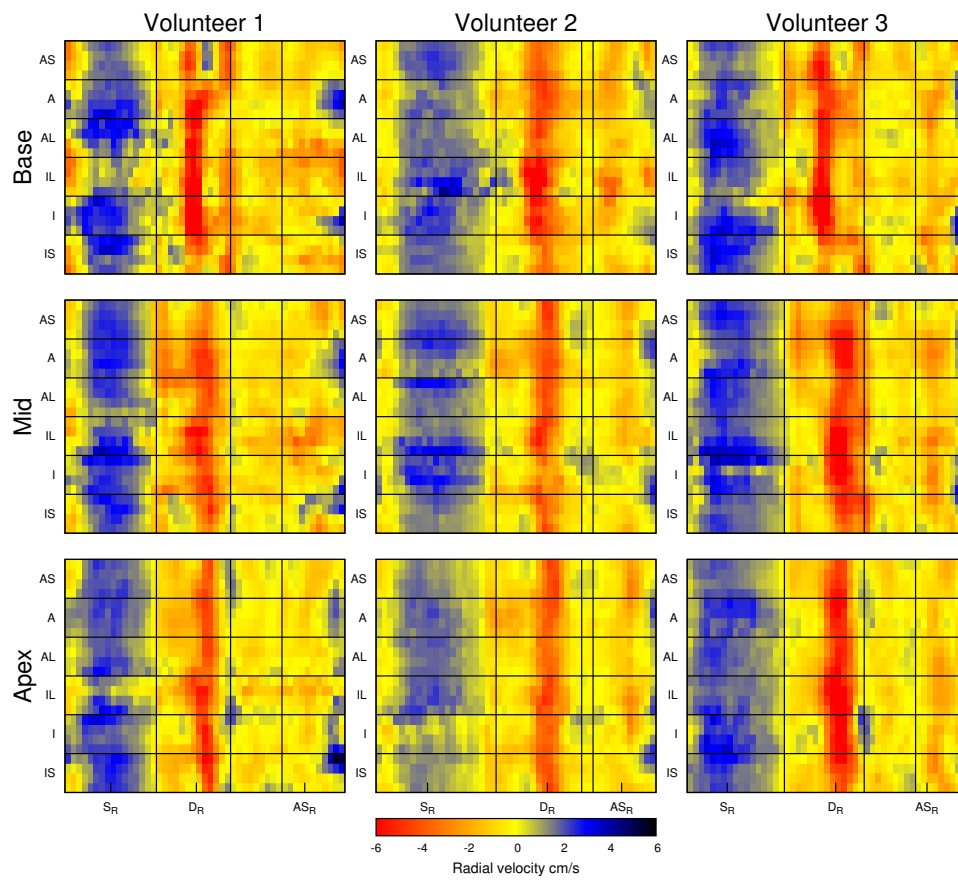


Figure 5.11: Radial colourplots for the same three volunteers.

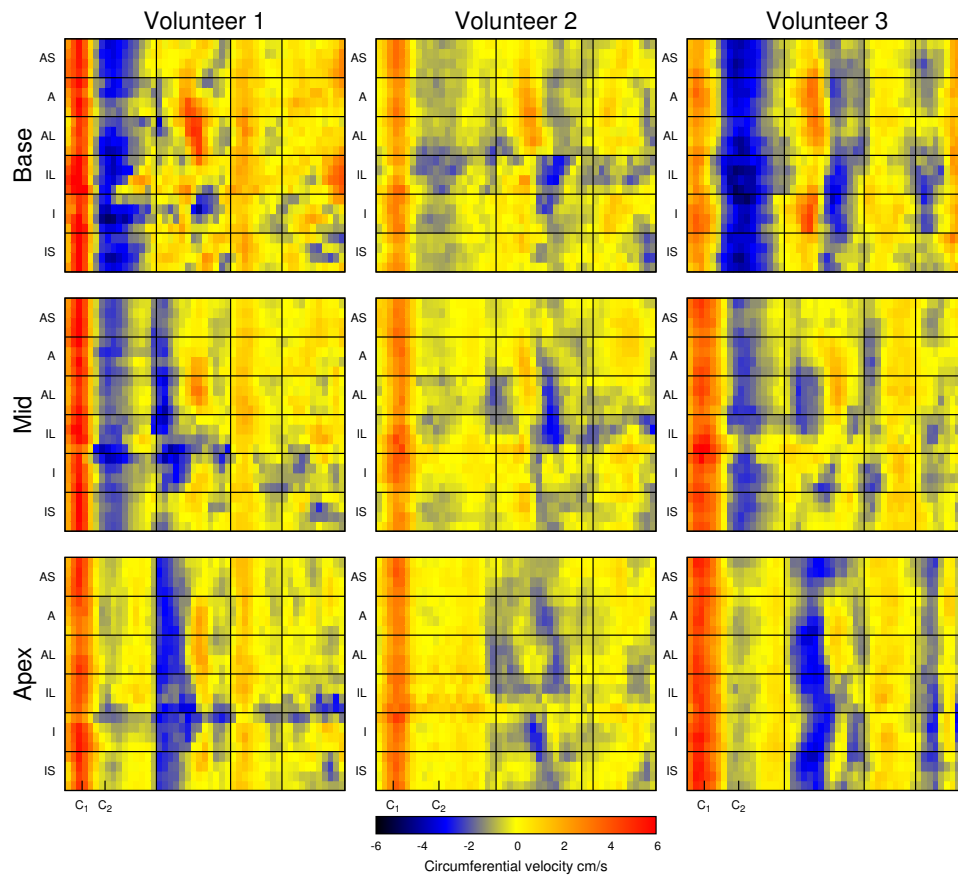


Figure 5.12: Circumferential colourplots for the same three volunteers.

Figures 5.10, 5.11 and 5.12 show individual colour plots for three of the volunteers in the longitudinal, radial and circumferential directions respectively. While the same overall patterns are seen for each of the volunteers, inter-volunteer variations in timing are obvious and subtle differences in the patterns can be seen. For example the positive longitudinal peak shortly after D_L is much less prominent in Volunteer 2 than in Volunteers 1 and 3, and S_L is more localised. Comparing these plots for individuals could allow detailed analysis of regional motion abnormalities.

5.2.1.5 Transmural velocities

Peak velocity(cm/s)	Endocardium	Mid	Epicardium	P(Endo-Mid)	P(Mid-Epi)
Base					
S_L	7.60±1.21	7.79±1.28	7.51±1.31	NS	NS
D_L	-10.33±2.40	-10.18±2.32	-9.86±2.16	NS	NS
AS_L	-4.13±1.08	-4.17±1.18	-4.01±1.02	NS	NS
S_R	2.89±0.32	2.36±0.25	1.92±0.22	<0.005	<0.005
D_R	-5.58±0.94	-4.71±0.88	-3.95±0.75	<0.005	<0.005
AS_R	-1.81±0.51	-1.65±0.48	-1.54±0.39	<0.005	NS
C_1	3.22±1.38	3.59±1.45	3.67±1.53	<0.005	NS
C_2	-2.49±1.14	-2.51±1.10	-2.46±1.09	NS	NS
C_3	1.23±1.07	1.19±1.09	1.13±1.25	NS	NS
Mid					
S_L	6.40±1.56	6.66±1.67	6.52±1.61	0.02	NS
D_L	-7.32±1.60	-7.56±1.56	-7.50±1.57	NS	NS
AS_L	-2.76±1.21	-2.88±1.38	-2.86±1.32	NS	NS
S_R	3.03±0.32	2.50±0.23	2.06±0.18	<0.005	<0.005
D_R	-5.28±0.77	-4.59±0.70	-3.89±0.65	<0.005	<0.005
AS_R	-2.11±0.94	-1.93±0.85	-1.73±0.76	0.02	0.01
C_1	3.86±1.11	4.16±1.30	4.16±1.39	0.02	NS
C_2	-1.24±1.08	-1.47±1.07	-1.71±1.07	<0.005	<0.005
Apex					
S_L	5.13±1.04	5.43±1.13	5.44±1.06	<0.005	NS
D_L	-4.50±1.31	-4.65±1.32	-4.47±1.12	NS	NS
AS_L	-1.51±1.02	-1.79±1.05	-1.79±0.95	<0.005	NS
S_R	2.67±0.32	2.26±0.25	1.92±0.20	<0.005	<0.005
D_R	-5.41±0.80	-4.74±0.70	-4.10±0.65	<0.005	<0.005
AS_R	-1.93±0.71	-1.84±0.60	-1.65±0.54	NS	<0.005
C_1	3.88±1.00	4.15±1.08	4.23±1.20	<0.005	NS
C_2	-0.17±0.68	-0.37±0.73	-0.57±0.66	<0.005	0.01
C_3	-2.17±0.51	-2.27±0.54	-2.24±0.53	NS	NS

Table 5.3: Transmural peak velocities in all three slices. Any significant differences between layers are also shown in the final two columns.

Table 5.3 shows the peak velocities calculated when the three transmural layers are treated separately. The last two columns show the statistical significance of any differences between the layers. The radial velocities show a consistent gradient across the myocardium with higher velocities at endocardium than epicardium. Longitudinal and circumferential velocities do not show such a

consistent gradient although occasional small statistical differences are seen.

5.2.1.6 Phantom offsets

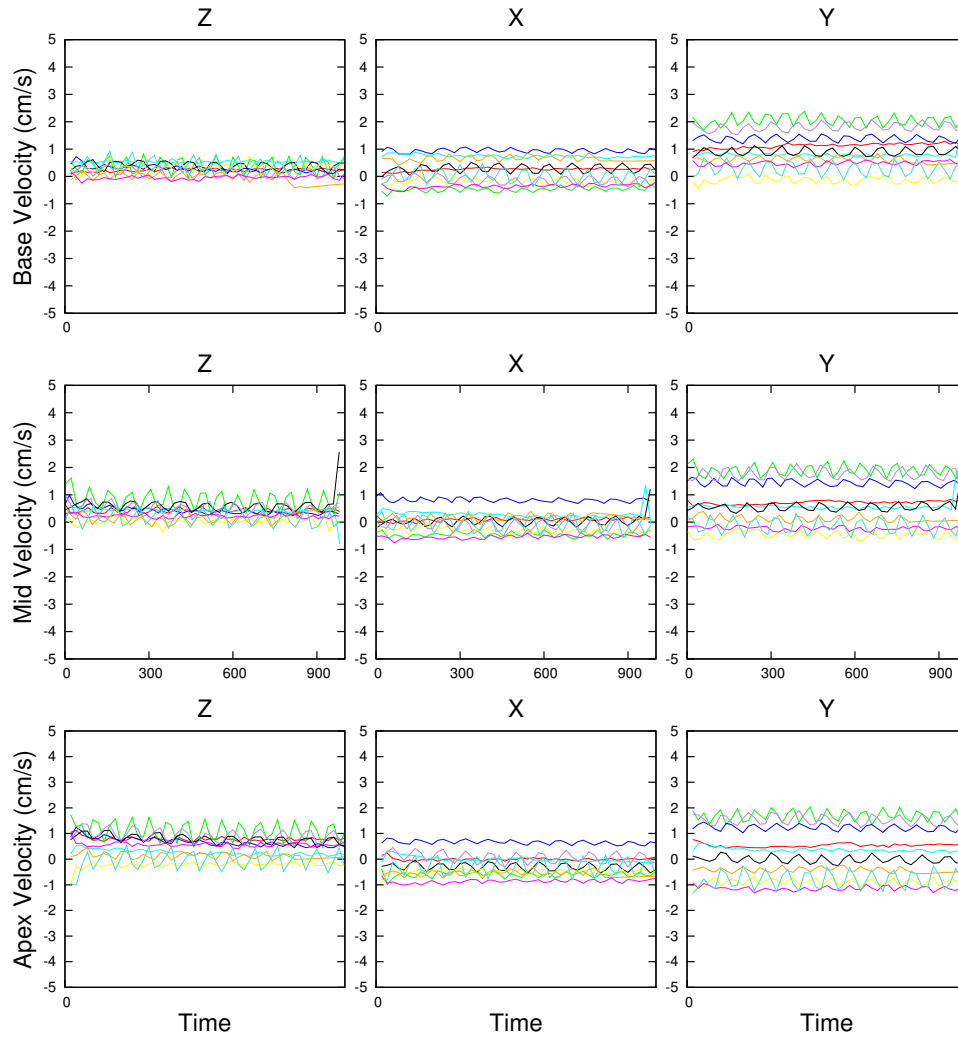


Figure 5.13: Background offsets over the cardiac cycle in basal (top), mid (middle) and apical (bottom) slices for all volunteers. Z (left), X (middle) and Y (right) directions are shown as measured, before conversion to longitudinal, radial and circumferential directions.

The average phantom velocities in the segmented area over time are shown in Figure 5.13 to show the necessity of the background correction. In all directions the offset is fairly stable over time (the bump at the beginning of the cardiac cycle seen in the navigator acquisitions shown in Section 4.2.1.6 is not seen) and the offset is between -1cm/s and 2cm/s . Regular oscillation is seen, perhaps due to the presence of the black blood pulses on every third phase.

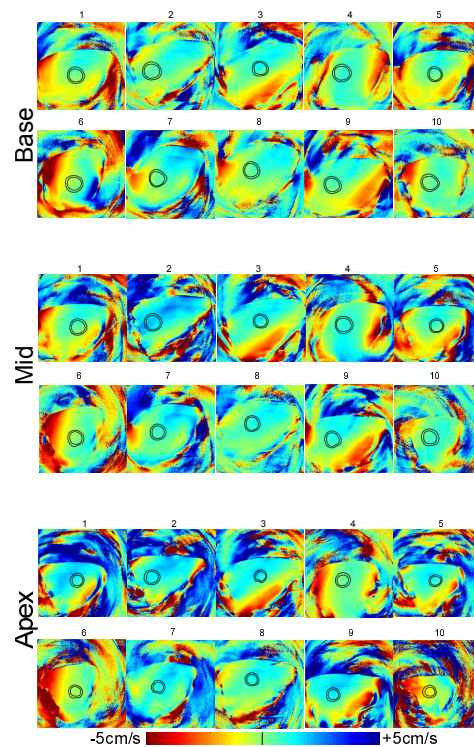


Figure 5.14: Regional background offsets in the Z direction for all ten volunteers (1-10) and in all three slices. The location and extent of the segmented left ventricle is overlaid as a black outline.

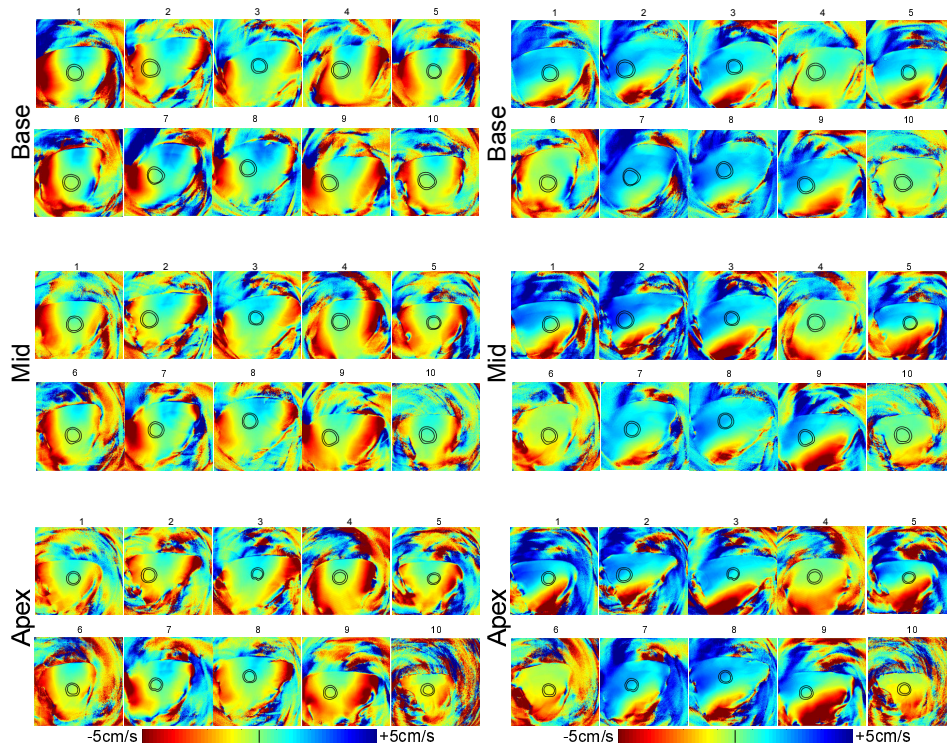


Figure 5.15: Regional background offsets in X (left) and Y (right) for all ten volunteers (1-10) and in all slices. The location and extent of the segmented left ventricle is overlaid as a black outline.

The regional background offsets for the first frames of the acquisitions are shown in Figures 5.14 and 5.15, with the position of the myocardium shown as a black ring. As with the navigator gated sequence, a non-linear offset is seen in all volunteers, all slices and all directions. Across the phantom the offsets are in the range of $\pm 5\text{cm/s}$, but in the region of the myocardium the offset is generally stable and closer to a range of $\pm 1\text{cm/s}$. However, in some cases (for example the Y offset in the mid slice of Volunteer 2) a larger and variable offset is seen across the myocardium, demonstrating the necessity of some sort of correction for background offsets.

5.2.1.7 Stack of slices

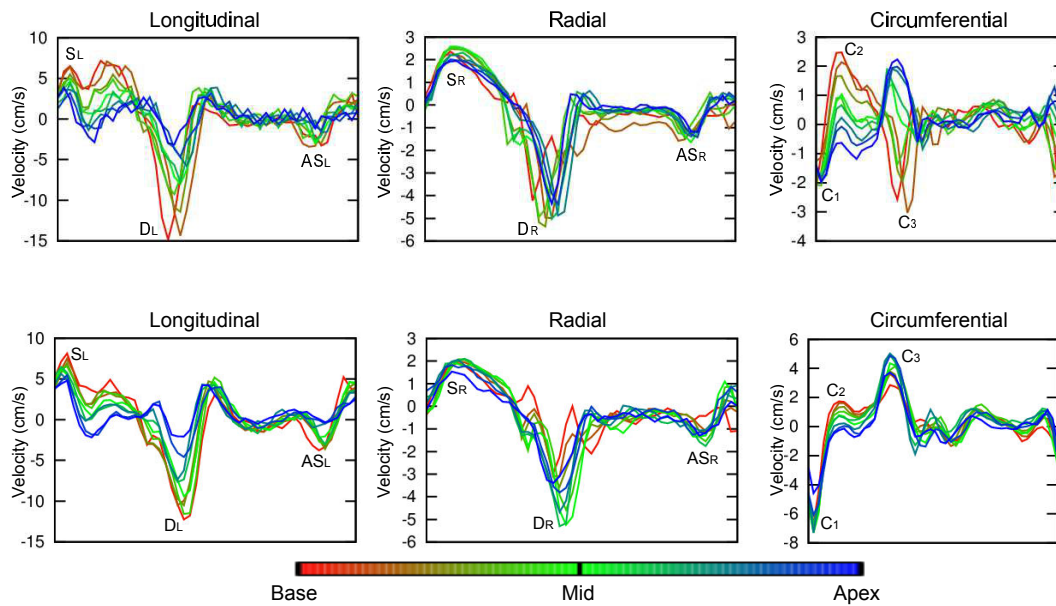


Figure 5.16: Longitudinal (left), radial (middle) and circumferential (right) velocities from a stack of nine slices acquired in two volunteers (one volunteer per row of graphs). While longitudinal and radial patterns are very similar, C_3 shows a different pattern between slices for the two examples.

The global velocity curves for the stack of nine slices acquired in two volunteers can be seen in Figure 5.16. The entire acquisition (including reconstruction time) takes less than thirty minutes. In the longitudinal curves, S_L and D_L both decrease in magnitude steadily from base to apex in both volunteers. This gradient is not seen consistently in the radial peaks, however the timing of D_R changes when moving from base to apex (as seen earlier in the global TTP values averaged over all volunteers). In the circumferential direction, C_1 is always negative and approximately the same magnitude at all levels. C_2 is positive at base but gradually decreases towards the apex. In the first volunteer C_3 does the opposite, starting negative at base and ending up positive (but with a similar magnitude) at apex. In the second volunteer this change from positive

to negative in C_3 is not seen. The reason for this difference is not yet clear but could be investigated by acquiring this many slices in more volunteers.

5.2.2 Comparison with HighRes

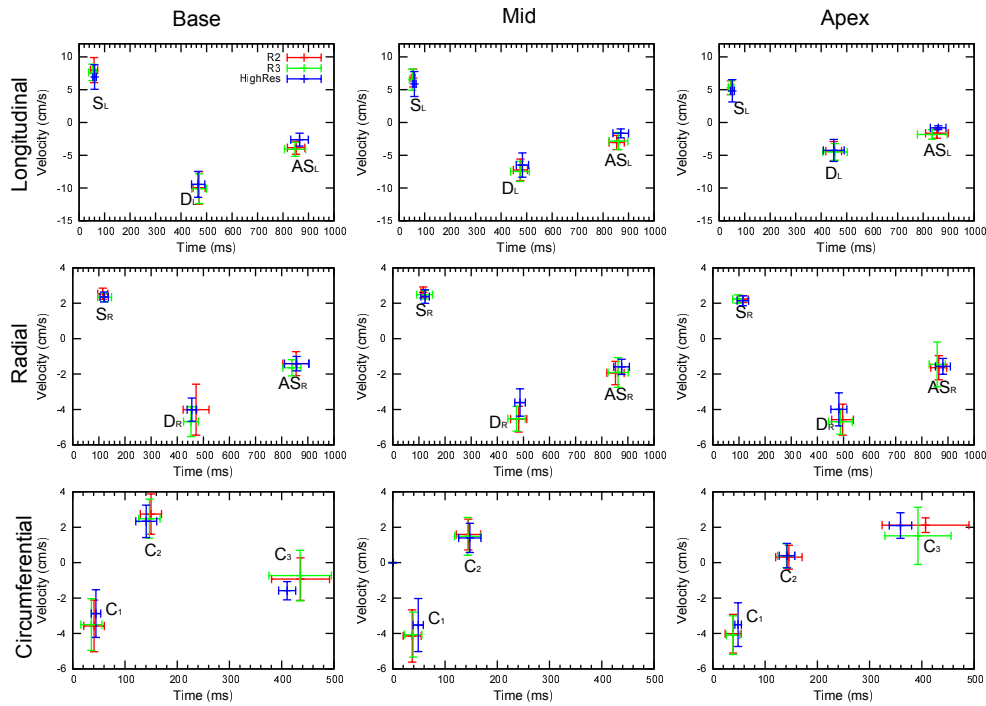


Figure 5.17: Mean $\pm$ SD values for R2, R3 and HighRes acquisitions in the basal (left), mid (middle) and apical (right) slices. Very little difference is seen between sequence versions.

Table 5.4 shows the results of the statistical analysis comparing the R2/R3 peak and TTP velocities with the HighRes measurements while Figure 5.17 shows graphically the mean $\pm$ SD values for the three acquisitions. In almost all cases there is no difference between the methods. However there are some small but significant differences in measurements of AS_L and C_1 . The possible reasons for this are discussed later.

Peak	R2vsHighRes	R3vsHighRes	TTP R2vsHighRes	TTP R3vsHighRes
BASE				
S_L (cm/s)	NS	NS	NS	NS
D_L (cm/s)	NS	NS	NS	NS
AS_L (cm/s)	0.05	0.02	0.02	0.02
S_R (cm/s)	NS	NS	NS	NS
D_R (cm/s)	NS	NS	NS	NS
AS_R (cm/s)	NS	NS	NS	NS
C_1 (cm/s)	0.03	0.03	NS	NS
C_2 (cm/s)	NS	NS	NS	NS
C_3 (cm/s)	NS	NS	NS	NS
MID				
S_L (cm/s)	NS	NS	NS	NS
D_L (cm/s)	NS	NS	NS	NS
AS_L (cm/s)	0.02	NS	NS	NS
S_R (cm/s)	NS	NS	NS	NS
D_R (cm/s)	NS	NS	NS	NS
AS_R (cm/s)	NS	NS	NS	NS
$C1$ (cm/s)	0.00	0.01	0.02	NS
$C2$ (cm/s)	NS	NS	NS	NS
APEX				
S_L (cm/s)	NS	NS	NS	NS
D_L (cm/s)	NS	NS	NS	NS
AS_L (cm/s)	0.00	0.01	NS	NS
S_R (cm/s)	NS	NS	NS	NS
D_R (cm/s)	NS	NS	NS	NS
AS_R (cm/s)	NS	NS	NS	0.01
C_1 (cm/s)	0.03	0.03	NS	NS
C_2 (cm/s)	NS	NS	NS	NS
C_3 (cm/s)	NS	NS	NS	NS

Table 5.4: Statistical comparison of measurements made with the different sequences. Very few statistical differences are seen ($P < 0.05$ is considered significant).

Figures 5.18, 5.19 and 5.20 show Bland Altman plots comparing the HighRes and R3 sequences for peak velocity measurements in the basal, mid and apical slices for all ten volunteers. HighRes measurements are treated as the ‘gold standard’ measurement and plotted along x, against the difference between measurements made with the two techniques on the y-axis.

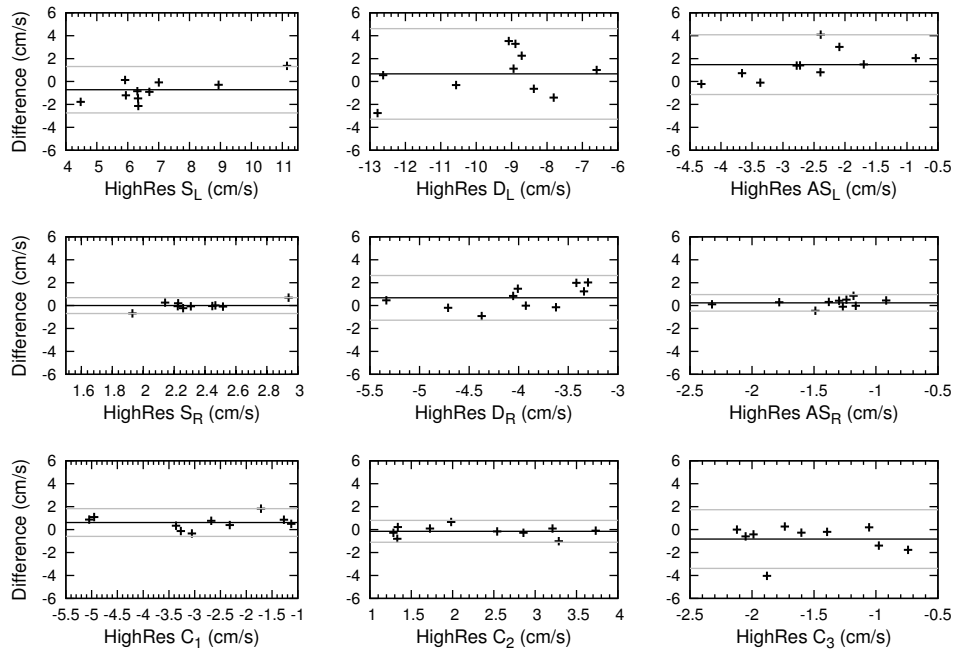


Figure 5.18: Bland Altman plots showing the HighRes measurements of peak velocities in the basal slice (x-axis) against the difference between HighRes and R3 (y-axis).

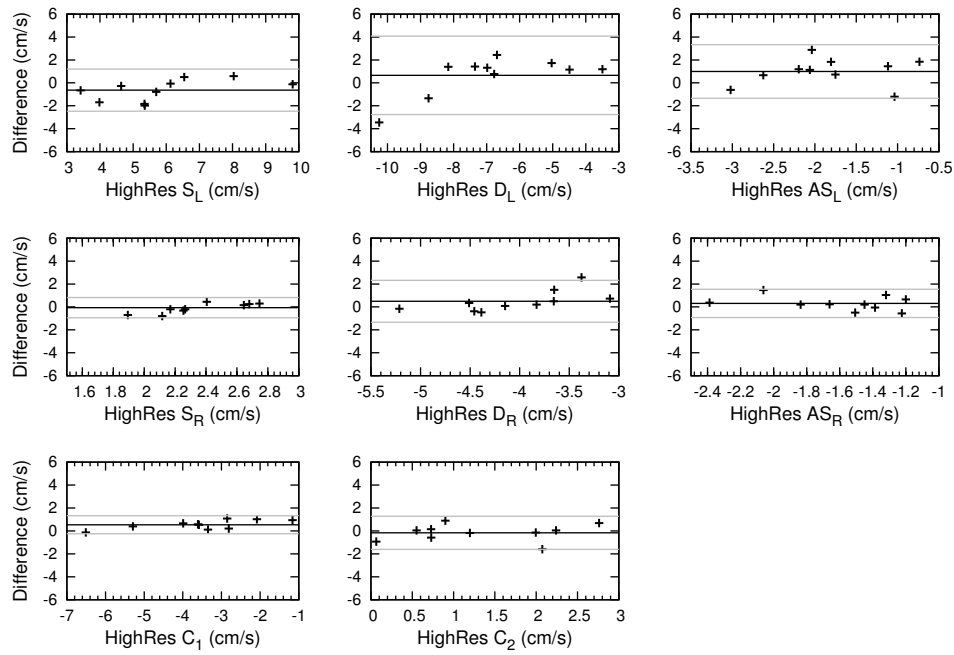


Figure 5.19: Bland Altman plots showing the HighRes measurements of peak velocities in the mid slice (x-axis) against the difference between HighRes and R3 (y-axis). A plot for C_3 is not shown as this peak is not consistently seen in the mid slice.

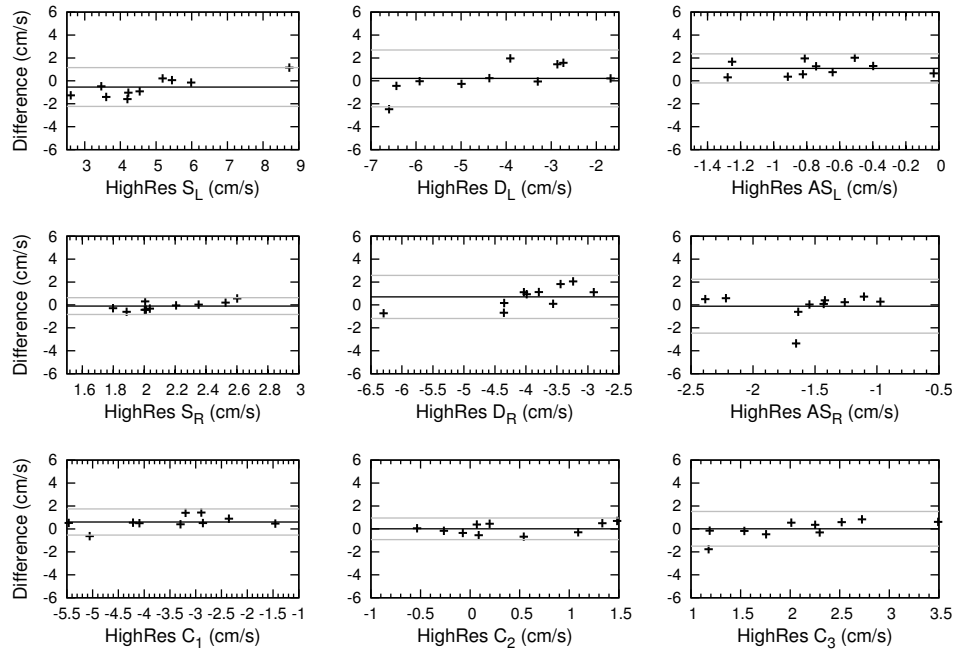


Figure 5.20: Bland Altman plots showing the HighRes measurements of peak velocities in the apical slice (x-axis) against the difference between HighRes and R3 (y-axis).

The limits of agreement are generally small and in all cases straddle zero. In the parameters for which a statistical difference was found between the techniques (AS_L and C_1 , see Table 5.4), R3 generally measures higher magnitude values than HighRes. For the diastolic parameters (D_L and D_R) a small trend towards higher values measured with R3 is seen, although this is not significant. The possible reasons for these trends are discussed later.

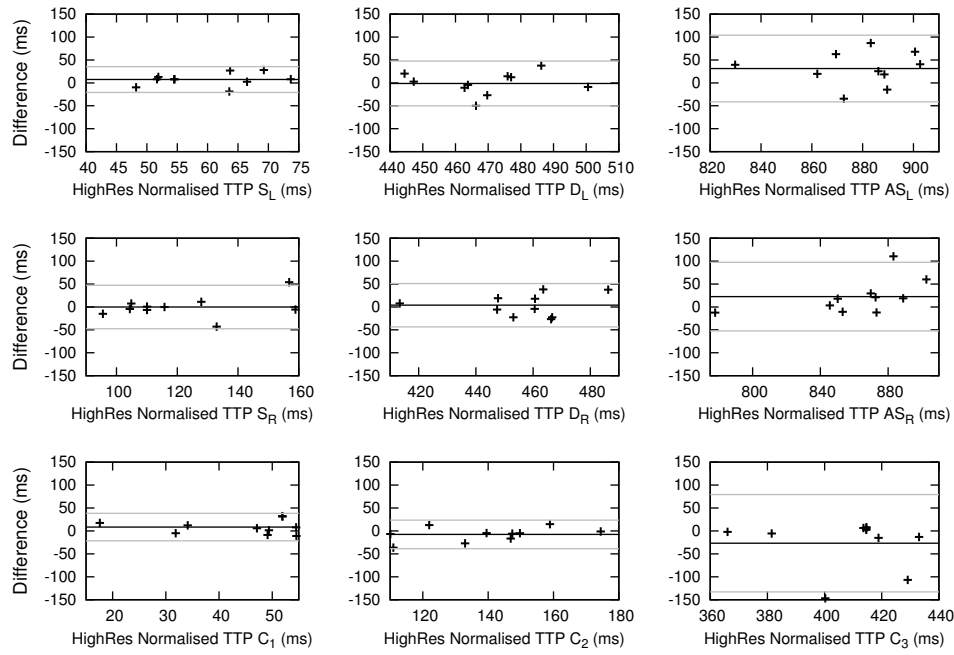


Figure 5.21: Bland Altman plots showing the HighRes measurements of TTP velocities in the basal slice (x-axis) against the difference between HighRes and R3 (y-axis).

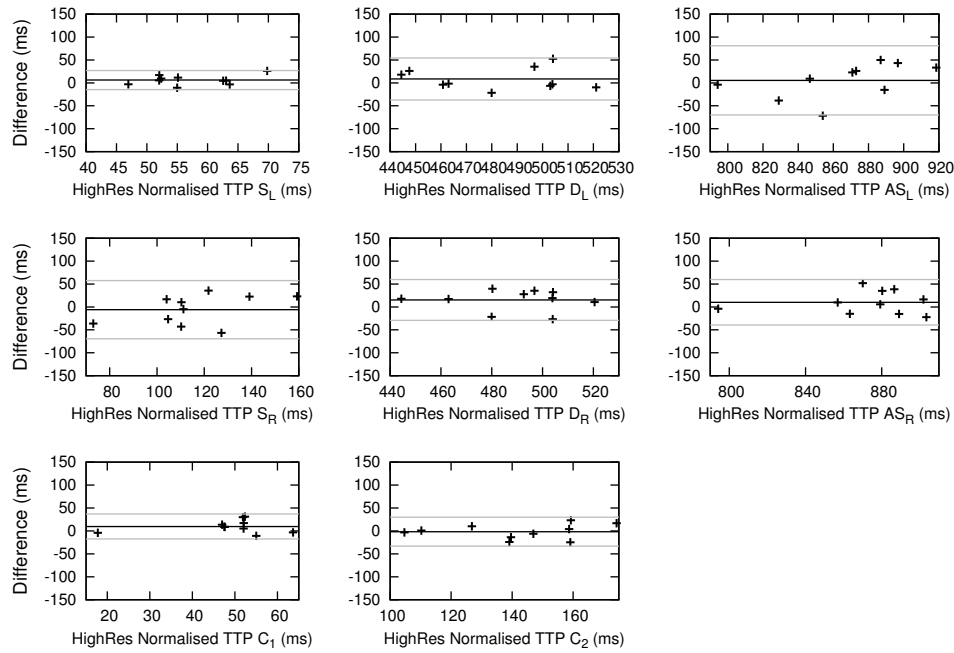


Figure 5.22: Bland Altman plots showing the HighRes measurements of TTP velocities in the mid slice (x-axis) against the difference between HighRes and R3 (y-axis).

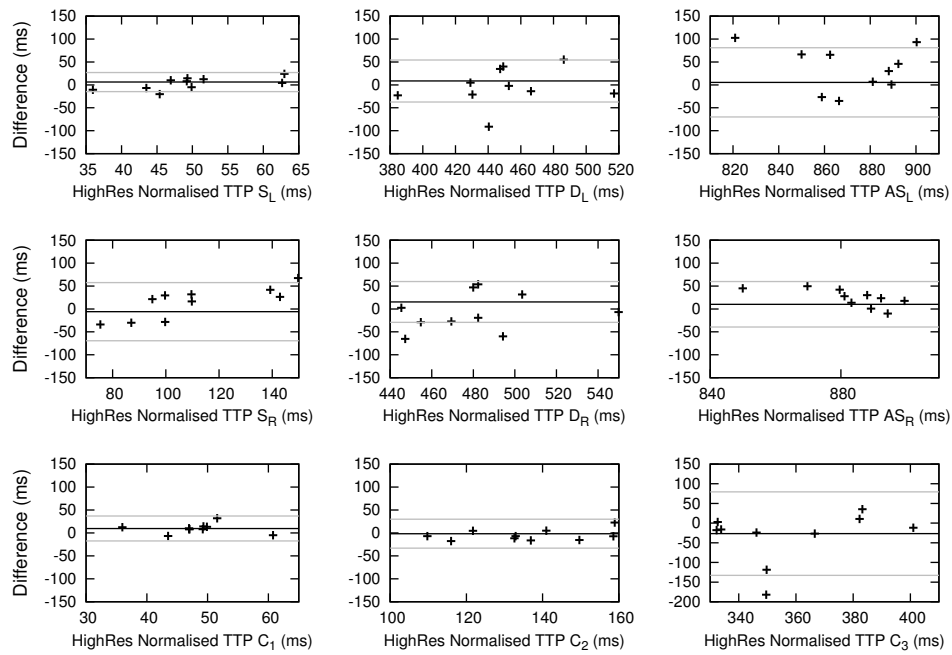


Figure 5.23: Bland Altman plots showing the HighRes measurements of TTP velocities in the apical slice (x-axis) against the difference between HighRes and R3 (y-axis).

Figures 5.21 to 5.23 show the Bland Altman plots for normalised TTP measurements for HighRes and R3 (again HighRes is treated as the gold standard). While most parameters show small limits of agreement, the limits for C_3 are larger than expected. This could be because in some subjects there are several peaks which could be interpreted as C_3 . It is possible that C_3 is not consistently identifiable in different subjects.

5.2.3 RV

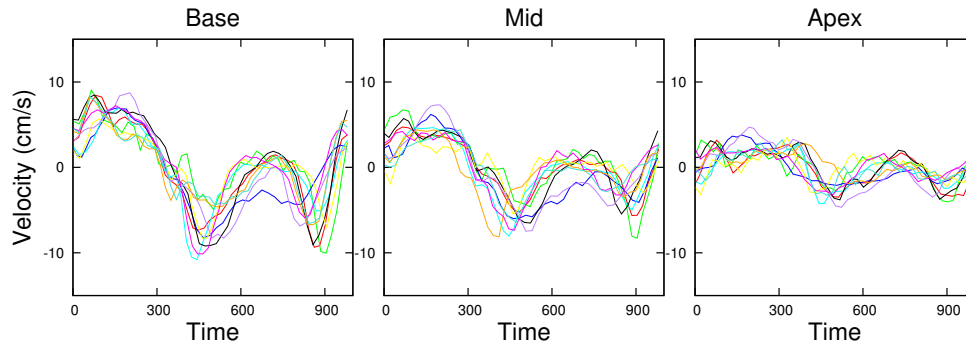


Figure 5.24: Longitudinal RV velocity-time curves in the basal (left), mid (middle) and apical (right) slices for all volunteers

	Peak	TTP (ms)	TTP (norm ms)	Peak R3vsHighRes	Normalised TTP R3vsHighRes
BASE					
S_L (cm/s)	7.80 ± 1.05	130.7 ± 53.4	139.2 ± 54.3	NS	NS
D_L (cm/s)	-7.62 ± 2.29	465.0 ± 40.0	495.6 ± 27.4	NS	NS
AS_L (cm/s)	-7.09 ± 1.86	838.0 ± 134.0	875.5 ± 32.2	<0.005	0.02
E/A	1.18 ± 0.56	-	-		
MID					
S_L (cm/s)	5.22 ± 1.20	137.0 ± 60.0	143.3 ± 58.9	NS	NS
D_L (cm/s)	-6.52 ± 1.21	468.7 ± 48.7	495.5 ± 35.5	NS	NS
AS_L (cm/s)	-4.55 ± 1.65	844.2 ± 143.3	844.2 ± 143.3	0.03	NS
E/A	1.61 ± 0.59	-	-		
APEX					
S_L (cm/s)	3.27 ± 0.65	213.3 ± 139.0	218.8 ± 140.9	NS	NS
D_L (cm/s)	-3.23 ± 0.87	490.9 ± 32.0	514.2 ± 36.3	NS	NS
AS_L (cm/s)	-2.59 ± 0.97	858.6 ± 137.2	897.6 ± 34.5	NS	NS
E/A	1.35 ± 0.43	-	-		

Table 5.5: Peak and TTP mean $\pm$ SD values in the RV

The peak and TTP longitudinal velocity values measured from the RV are shown in Table 5.5 and the global longitudinal velocity time curves for all volunteers are shown in Figure 5.24. As for the left ventricle, basal velocities in the RV are higher than mid velocities which are higher than apical velocities (statistically significant ($p < 0.001$) for all except D_L base-mid).

The results of paired t-tests between the R3 and HighRes values from the previous Chapter are shown in the last two columns of the table. Significant differences are seen for peak and TTP AS values measured with R3 and HighRes. This is similar to what is seen in the left ventricle and the possible reasons are discussed below.

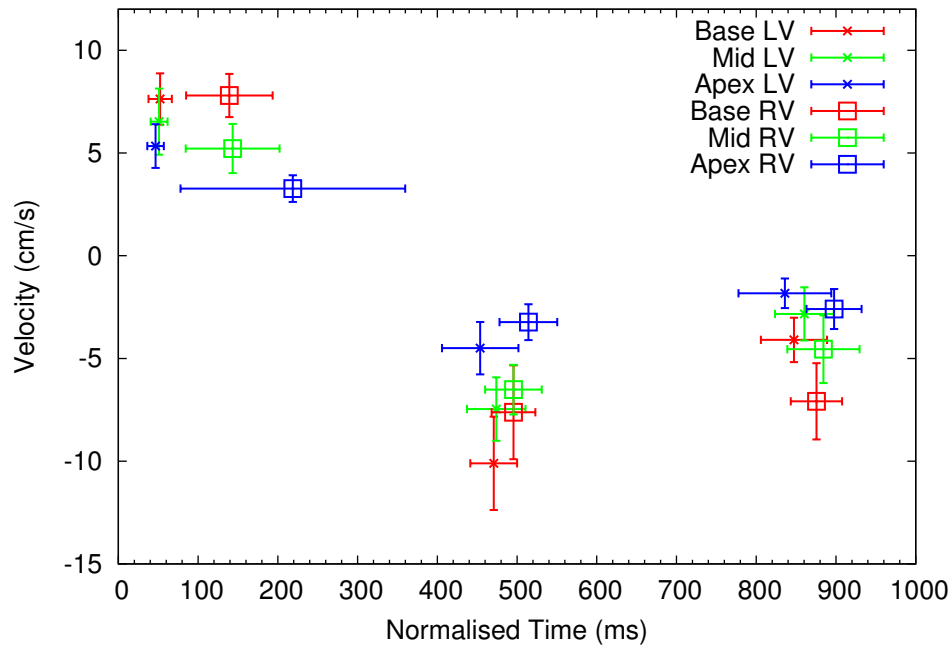


Figure 5.25: Average Peak and TTP values for LV and RV

The average $\pm$ SD values for the right and left ventricles are shown together in Figure 5.25 for comparison. S_L is later in the RV than in the LV ($p < 0.01$ for all levels). AS_L values are higher (ie more negative) in the RV than in the LV at all levels although only statistically significant for the base and mid slices.

5.3 Discussion

5.3.1 Data acquisition

By using efficient spiral trajectories and a non-Cartesian SENSE reconstruction, PVM data has been acquired within a clinically acceptable breath-hold duration (13 cardiac cycles) and with higher spatial and temporal resolution than has previously been possible. Despite using 14ms spirals at high field strength (3T) image quality in all acquisitions was high. As shown in Figure 5.1, image quality for R2 and R3 is extremely similar to HighRes which uses shorter spiral durations of 12ms. However it is possible that some off-resonance blurring remains in the images which could allow equivalent image quality to be obtained with shorter spirals, further increasing the temporal resolution. This will be investigated for future work.

The use of retrospective cardiac gating has allowed the analysis of the entire cardiac cycle, including atrial systole. The loss of SNR which is expected at increasing levels of acceleration can be seen in Figure 5.1, however the non-Cartesian SENSE reconstruction is not affecting quantitative measurements, as shown by comparisons between measurements made with R2 and R3. Comparing the results with HighRes results (with known inter-study reproducibility) shows that the resolution is still high enough to make accurate measurements of global and regional peak and TTP velocities.

Spatial and temporal resolution (1.7x1.7mm and 24ms) are better than previously reported Cartesian breath-hold sequences (for example 2.7x1.3mm and 37-87ms resolution acquired in 17-29 heartbeats (Petersen et al., 2006)) allowing the detection of fine features of motion which previously were not seen in images acquired within a breath-hold. Coverage of the entire cardiac cycle has recently also been achieved with a self navigated PVM sequence using golden

angle spirals, which allows the reconstruction of real time images from data acquired during free breathing (Steeden et al., 2013). However, despite the advantages gained by using real time imaging, the acquisition and reconstruction times are currently long (about 8.7 minutes and 1 hour per slice respectively) compared with R3 which is acquired in 13 seconds and reconstructed online at the time of imaging within one minute and twenty seconds.

5.3.2 Data analysis

5.3.2.1 Breath-hold acquisitions

R2 and R3 show no statistically significant differences in measured peak or TTP values, indicating that the level of acceleration is not affecting the accuracy of velocity measurements. Previous studies using Cartesian imaging and acceleration schemes that exploit temporal correlations (eg Lutz et al. (2011)) have found that accelerating PVM acquisitions by more than a factor of two has an effect on measured peak velocities due to temporal smoothing. This effect is not seen in R3 since temporal correlations are not exploited.

Peak and TTP velocity values from the R3 sequence show the same patterns as have previously been shown with PVM sequences; a significant decrease in peak longitudinal velocities is seen from base to apex, but peak radial velocities do not show this pattern, while a transmural gradient is seen in radial but not longitudinal velocities. Normalising the TTP values to take inter-subject heart rate variations into account allows easier comparison between subjects. The colour plots provide a way to quickly interpret the motion patterns of the myocardium and the application to patient data would potentially allow regional wall motion abnormalities to be easily identified.

Spiral images require more complicated reconstruction than Cartesian trajec-

ries and this often does not allow images to be reconstructed online at the scanner and seen at the time of scanning. However the use of the Gadgetron has meant that reconstruction time is not a limiting factor. All 50 phases are reconstructed in approximately one minute and twenty seconds on current hardware (HP Z800 Workstation with 4GB Asus GeForce GTX 670 graphics card) which does not delay the scan significantly. This has also allowed the acquisition of a full stack of nine short axis slices in around thirty minutes, showing features of regional variation that were previously only seen in full 3D acquisitions (Lutz et al., 2012). The reconstruction time could be further improved by the addition of further GPUs.

5.3.2.2 Comparison with navigator gated sequence

Small but statistically significant differences between R2/R3 and HighRes were found for C_1 and for AS_L in all three slices. C_1 occurs at the very beginning of the cardiac cycle, which is where the crossed-pairs navigator is being acquired in the HighRes sequence. The navigator sequence has been specifically adapted to make it as short as possible (just 9ms plus 10ms feedback time), however this interruption in the data acquisition may affect the accuracy of the retrospective reconstruction interpolation at this time and could explain the small differences seen.

The effect could be worsened by the fact that a different temporal resolution was used for R2/R3 than was used for HighRes (acquired temporal resolution was 24ms for R2/R3 and 21ms for HighRes, 50 phases were reconstructed for R2/R3 and 60 for HighRes). The small but significant difference seen in AS_L measurements in the apex may be due to the fact that AS_L is an inconsistent feature of motion between volunteers (this is also suggested by the high standard deviation relative to the mean peak size, see Table 5.2) and is less reproducible within volunteers as shown in the previous Chapter.

The long scan time for HighRes also introduces a higher level of natural heart rate variation during data acquisition (the mean $\pm$ SD of RR interval for all accepted heartbeats was 947 ± 13 ms for R2, 953 ± 13 ms for R3 and 966 ± 57 ms for HighRes). This could explain the trend towards lower D_L and D_R velocities measured with HighRes when compared with R3, and is investigated in more detail in Chapter 6.

Differences could also be caused by slice positioning. While R2 and R3 scans were performed within the same study (and are therefore well co-registered), the HighRes acquisitions were performed on a different day and some differences in positioning would be expected. However, the fact that the majority of the measured parameters show excellent agreement with different sequences and on different days suggests that PVM has very good interstudy reproducibility.

5.3.2.3 RV

Despite the slightly lower resolution of the breath-hold sequence, velocity values measured with R3 in the thin RV wall were very similar to those measured with HighRes, apart for AS_L values in the basal and mid levels. AS_L has been found to be the least reliable parameter in the LV so these differences could be due to natural variation rather than experimental issues.

5.3.3 Limitations

The image quality achieved with R2 and R3 is good and comparable with that obtained with HighRes despite using longer spiral durations (14ms for R2 and R3, 12ms for HighRes). However it is possible that some off-resonance blurring remains in the images which could allow equivalent image quality to be obtained with shorter spirals, increasing the temporal resolution. This will be

investigated for future work.

A limitation of this study in terms of clinical applicability is that a separate phantom acquisition is carried out to remove background phase errors. A correction based on static tissue has previously been used with PVM (Lutz et al., 2011) and would remove this inconvenience (see Chapter 7), although the accuracy of the correction could be lower than with a phantom subtraction (Gatehouse et al., 2010). The time consuming manual segmentation of the images is also a limitation of the technique. Future work will investigate the implementation of semi-automatic segmentation algorithms to improve this.

5.3.4 Conclusion

The accelerated sequence that has been produced allows the acquisition of high spatial and temporal resolution data with three directions of velocity encoding in a single, clinically acceptable breath-hold, overcoming some of the issues inherent in the navigator gated image discussed in the previous Chapter. This has been achieved without compromising accuracy as shown by quantitative measurements of peak and TTP velocities. The GPU reconstruction allows the images to be seen on the scanner without extending scan time, and hence the technique is now suitable for inclusion within a clinical workflow.

Chapter 6

Simulating the effect of natural heart rate variation

The velocity time curves measured in this project are acquired over multiple heartbeats, and consequently represent some combination of all the cardiac cycles during the acquisition. In an ideal situation each heartbeat would be exactly the same and so the final curves would accurately represent the motion of the heart. In reality this is not the case and changing heart rates could therefore affect the final velocities measured.

The comparison of the navigator and breath-hold versions of the sequence in Chapter 5 highlighted a trend towards higher D_L and D_R velocities measured with the breath-hold sequences although these did not reach statistical significance. This Chapter aims to investigate the effects of heart rate variation on the velocities measured during this thesis and whether these trends could be caused by the increased levels of heart rate variation in the navigator acquisitions during the long period (2-3 minutes) of acquisition (the mean $\pm$ SD of RR interval for all accepted heartbeats was $947 \pm 13\text{ms}$ for R2, $953 \pm 13\text{ms}$ for R3 and $966 \pm 57\text{ms}$ for HighRes). Any differences between prospective and retro-

spective gating will also be investigated to determine whether any differences between results measured in this thesis and previously published results with prospectively gated acquisitions should be expected.

The effect of ‘missed triggers’ is first investigated. This is where a QRS complex is not detected by the scanner software, leading to two heartbeats being treated as one, and is an issue which does not effect prospectively gated sequences (apart from an extension of scan time). This effect is seen in clinical practice, particularly in obese patients, and is more of an issue at high field strengths due to the enhanced magneto-hydrodynamic effect.

The simulations in this Chapter assume k-space is covered by 13 spiral interleaves as for the navigator version of the sequence.

6.1 Validation of simulation method

6.1.1 Introduction

For these simulations, it is assumed that each spiral interleaf contributes equally to the final measured velocities. The effects of heart rate variation through the acquisition can then simply be simulated by stretching and resampling the velocity time curves from individual spiral interleaves before combining to form a composite curve. This approach is much faster and easier than simulating the entire MR acquisition and is validated in the following sections.

6.1.2 Validation

A simulated phantom was produced as shown in Figure 6.1, representing the myocardium as a ring with constant magnitude and phase. The phantom is

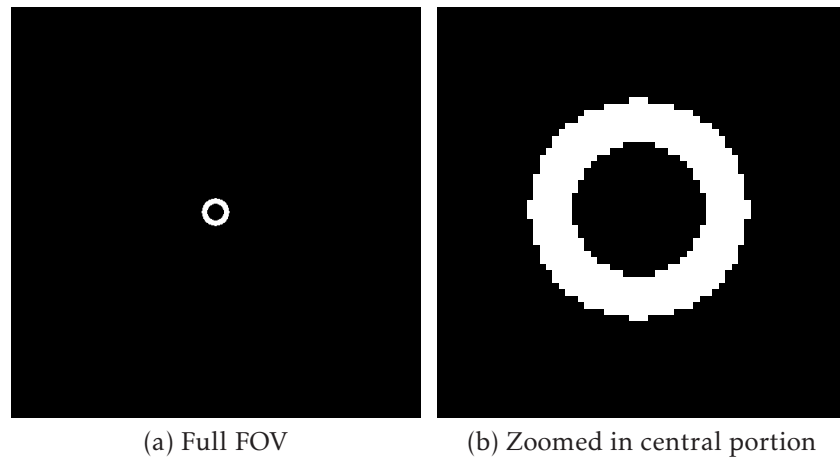


Figure 6.1: The simulated phantom used for validation

small enough to fit within the FOV of a single spiral to avoid wrapping artefacts that would occur when sampling a larger phantom with a single spiral at a time.

To compare the velocity measured by each interleaf individually to the velocity of the full reconstructed velocity map, the phantom was first sampled with all the spirals making up the full image (the high resolution spiral trajectories from Chapter 4 were used for this validation) and then separately for each interleaf on its own. The relationship between the phase values of the reconstructed phantom from each of the images formed from a single interleaf and the phase value of the image formed from all spirals together was investigated.

Several sets of phantom phase values were produced to be sampled by the individual interleaves, both in a geometric series and randomly over an interval. We hypothesised that the value measured in the fully sampled velocity map would be equal to the mean of the values measured by the individual spiral interleaves.

In each case, reference and velocity encoded images were produced (the reference images always had zero phase) and the phases of the final images were measured as the complex argument of the velocity-encoded image minus that

of the reference image for each pixel.

6.1.3 Results

6.1.3.1 Geometrically increasing phantom phase values

For this simulation the phase of the myocardium sampled by the n th spiral was equal to $0.05 \times \pi \times n$. The images formed from each of the single spirals accurately reproduced the simulated phantom as can be seen in Figure 6.2 (a) to (m). In each case the phase of the reconstructed phantom is equal to the phase of the phantom for that spiral as expected. The image formed from all spirals at once can be seen in Figure 6.2 (n). The value of the phase in this image is 0.3 which is equal to the mean of the individual phase values.

6.1.3.2 Random phantom phase values

For this simulation the phase of the myocardium sampled by the n th spiral was generated randomly over an interval of 0 to π , using the MATLAB command `pi * rand([1 13])`. The images formed from each of the single spirals accurately reproduced the simulated phantom as can be seen in Figure 6.3 (a) to (m). In each case the phase of the reconstructed phantom is equal to the phase of the phantom for that spiral as expected. The image formed from all spirals at once can be seen in Figure 6.3 (n). The value of the phase in this image is 0.94. This is again equal to the mean of the individual phase values.

6.1.4 Discussion

In each case the phase of the full image is equal to the average of the individual phases measured by single spirals. Each spiral covers the whole of k-space

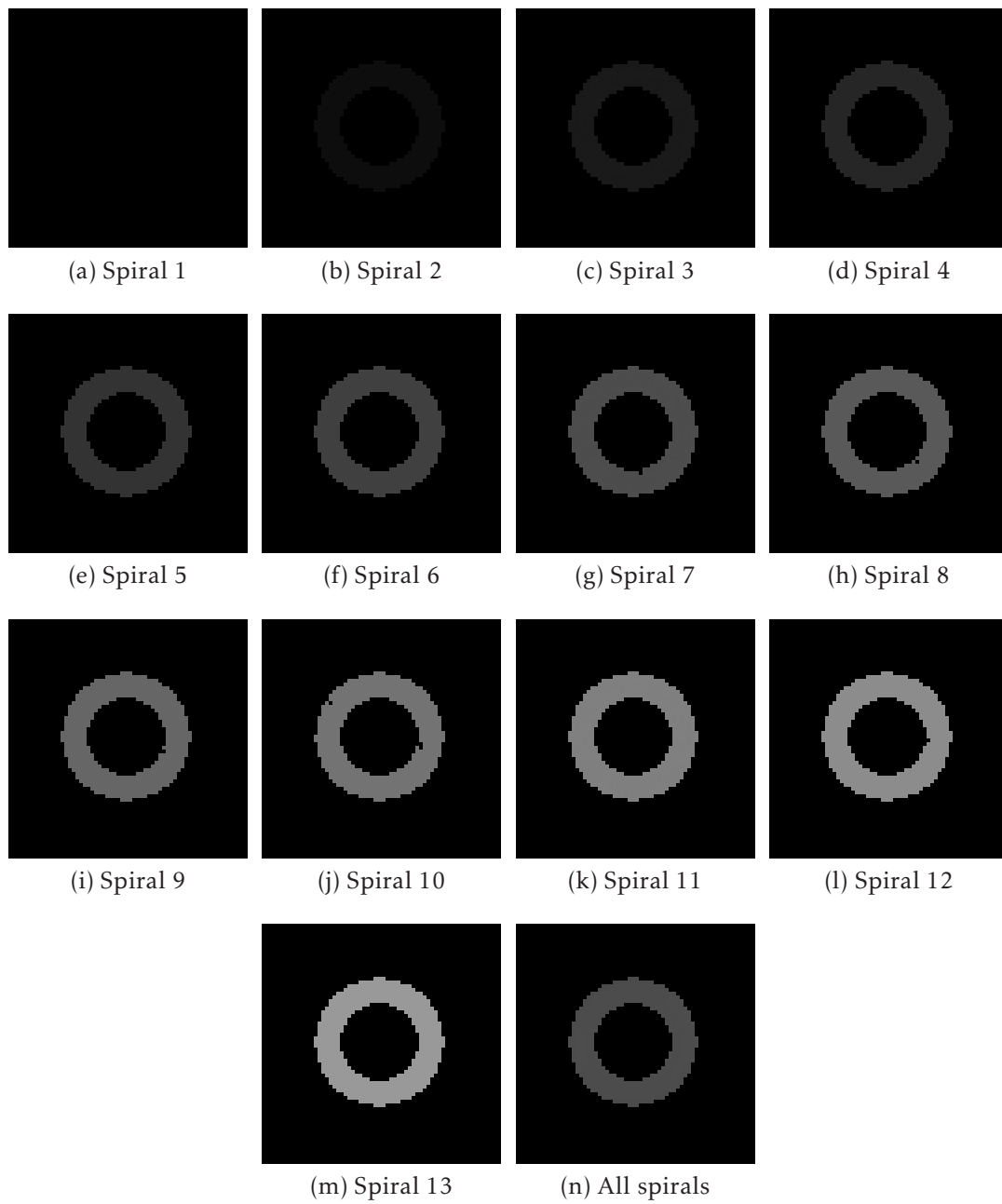


Figure 6.2: Phase images from each spiral individually with a geometrically increasing series of phases

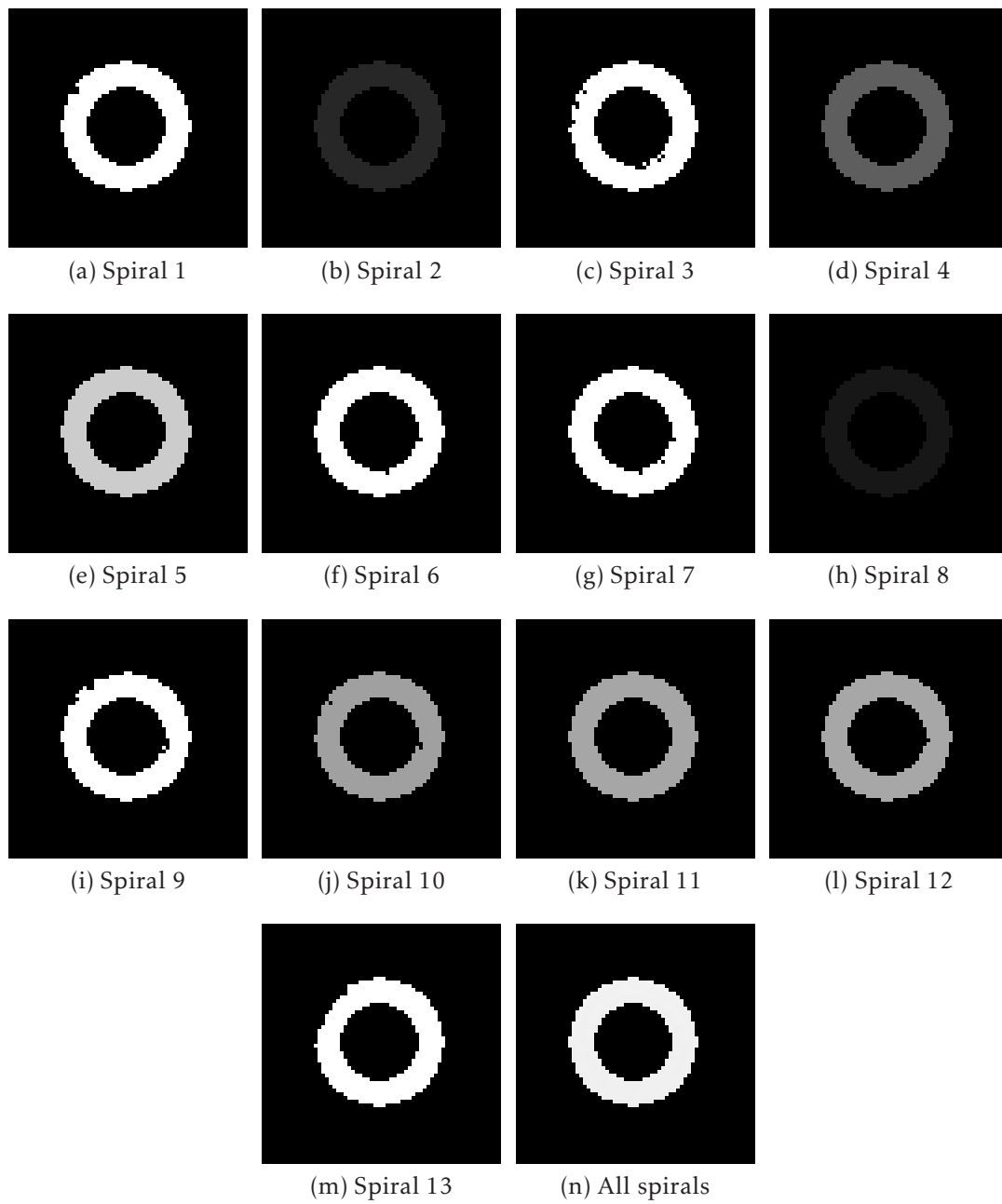


Figure 6.3: Phase images from each spiral individually with random phases for each spiral

and the paths are identical apart from a rotation of $\frac{2\pi}{n}$ where n is the number of spirals covering k-space. A rotation in k-space can be shown to result in a rotation in image space in the following way:

The discrete Fourier Transform $\hat{I}(\mathbf{k})$ of an image $I(\mathbf{x})$ can be written as

$$\hat{I}(\mathbf{k}) = \sum_{x=0}^N I(\mathbf{x}) \exp^{-2\pi i \mathbf{k}^T \mathbf{x}} / N \quad (6.1)$$

where N is the number of samples. If k-space is now rotated so that $\mathbf{k} \Rightarrow \mathbf{Rk}$, we can write

$$\hat{I}(\mathbf{Rk}) = \sum_{x=0}^N I(\mathbf{x}) \exp^{-2\pi i (\mathbf{Rk})^T \mathbf{x}} \quad (6.2)$$

The rotation matrix is orthogonal so $\mathbf{R}^T = \mathbf{R}^{-1}$. Inserting this into Equation 6.2:

$$\hat{I}(\mathbf{Rk}) = \sum_{x=0}^N I(\mathbf{x}) \exp^{-2\pi i \mathbf{k}^T (\mathbf{R}^{-1} \mathbf{x})} \quad (6.3)$$

Writing $\mathbf{x}' = \mathbf{R}^{-1} \mathbf{x}$, and using $\mathbf{R}\mathbf{R}^{-1} = \mathbf{1}$:

$$\hat{I}(\mathbf{Rk}) = \sum_{x'=0}^N I(\mathbf{R}\mathbf{x}') \exp^{-2\pi i \mathbf{k}^T \mathbf{x}'} \quad (6.4)$$

which is the discrete FT of a rotated image. So a rotation in k-space can be simulated by rotating image space. Since the simulated phantom is invariant under rotations, each spiral can effectively be thought to be following exactly the same path through k-space and hence the final phase is equal to the mean of all the equally contributing phases. This is clearly a simplification of the experimental situation as the myocardium is not generally invariant under rotation and there

is not a single phase value for the entire myocardium. However it should still give insight into the effect of heart rate variation on global velocities measured with the spiral sequences developed in this thesis.

All following simulations make use of this result by starting with velocity-time curves which are stretched and sampled appropriately, instead of starting with a simulated phantom and simulating the entire MR experiment.

6.2 Simulation Method

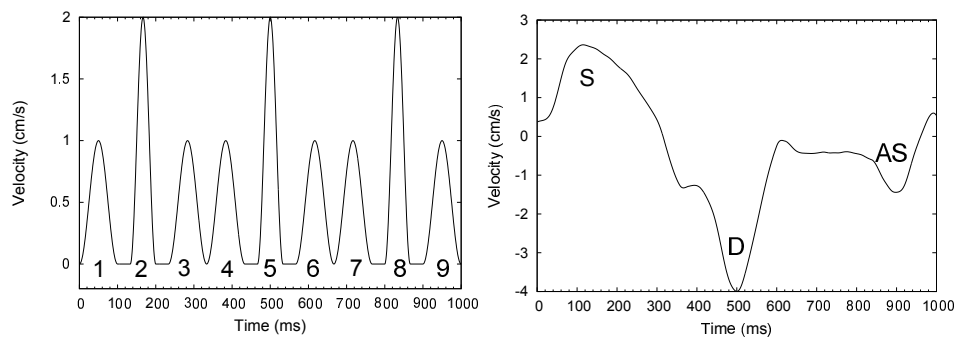


Figure 6.4: The two input curves used for simulations. The peak curve (left) has nine equally spaced peaks (1-9) while the real data curve (right) has three peaks labelled S, D and AS.

An input curve is used to represent the true motion of the myocardium which is then stretched and sampled in various ways to simulate the effect of heart rate variation. Two types of input curve have been used for the simulations: a series of sharp peaks throughout the cardiac cycle (referred to as the peaks curve) and a curve representing real data (referred to as the real data curve). The two input curves can be seen in Figure 6.4.

The peaks curve was designed to have nine sharp peaks through the cycle which would be expected to quickly lose fidelity in the presence of heart rate variation.

The magnitude of the peaks is not held constant to make differentiation of peaks easier.

The real data curve is the average radial velocity curve measured in the ten healthy volunteers scanned with the high resolution sequence (see Chapter 4). Using this curve provides a more realistic idea of how heart rate variation will affect the peak and TTP measurements that have been quoted in this thesis.

The effect of missed triggers and heart rate variation on both prospective and retrospective gating has been simulated using both input curves. The methods used for the two techniques can be seen schematically in Figure 6.5 and are explained below. The heartbeats were produced by random variations of a given size around an average duration (1000ms unless stated otherwise). In all cases where an experiment has been simulated with both prospective and retrospective gating, the same set of heartbeat durations have been used for both simulations. Peak and TTP velocity values given in tables are the percentage difference between the value measured for a given simulation and the value measured for the control simulation (i.e. with 0 missed triggers or with 0% variation in heart rate). This is done to isolate the effect of the parameter being investigated.

6.2.1 Prospective gating

Prospectively gated acquisitions collect data continuously for a period of time known as the acquisition window, which is set to cover approximately 90 % of the R-R duration. The different spirals acquired in different heartbeats are then binned according to the time after the R-wave at which they were acquired. If the heart rate changes between interleaves, interleaves acquired at the same time after the R-wave will sample different parts of the cardiac cycle, but will still be binned together. The process is shown schematically on the left hand side of Figure 6.5.

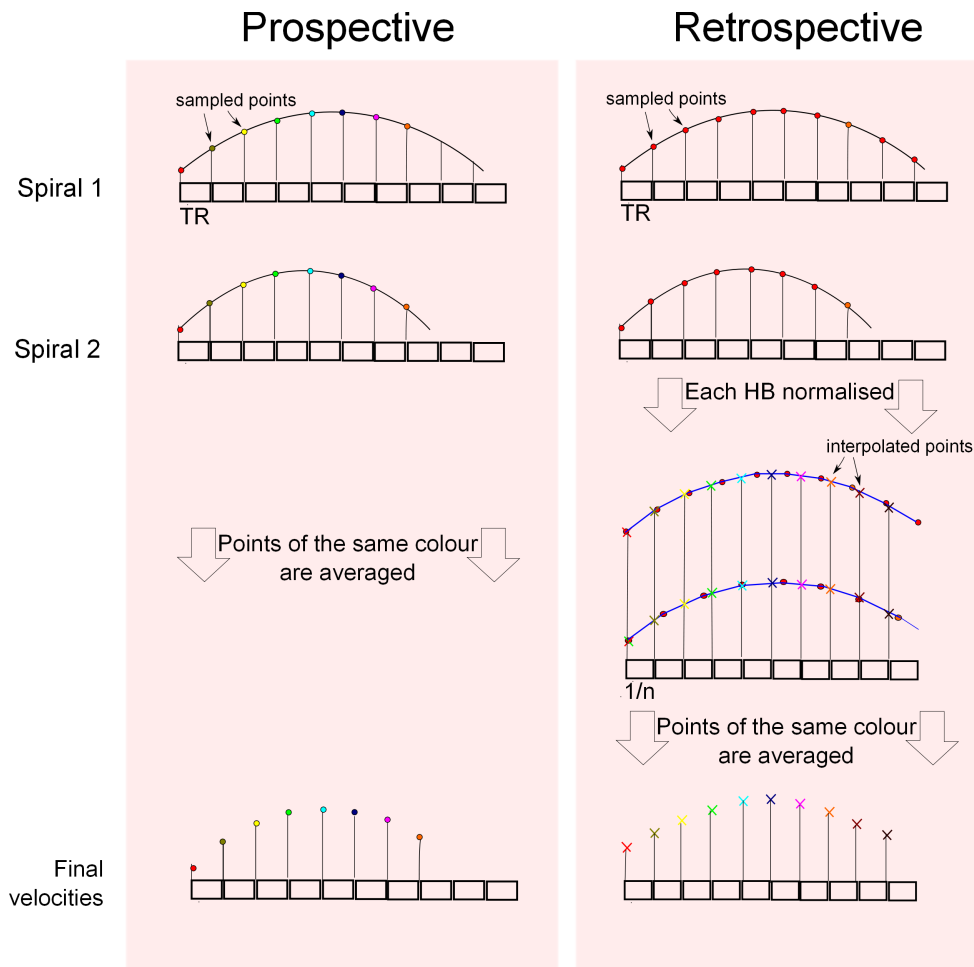


Figure 6.5: Schematic showing how the prospective (left) and retrospective (right) simulations are carried out. For both types of simulation the input curves are first stretched according to the duration of each heartbeat and then the values at multiples of TR are measured. For prospective gating the p^{th} values in each heartbeat are simply averaged to give the p^{th} value in the final curve. For retrospective gating each heartbeat is normalised to the same duration and the values at sixty equally spaced points through the normalised heartbeats are interpolated from the measured values. These interpolated values are then averaged to produce the values for the final curve.

6.2.2 Retrospective gating

Retrospectively gated acquisitions collect data continuously, along with ECG information, and data is binned once the scan is complete. Each heartbeat is then normalised to unit length. Linear interpolation is performed between the collected data points (represented by the straight blue lines connecting red circles in Figure 6.5) and the interpolated values at intervals of $\frac{1}{n}$ (where n is the number of phases to be reconstructed) are calculated. In reality this interpolation is done between raw data points, whereas in these simulations the interpolation is performed between velocity values. After interpolation, each heartbeat has the same number of reconstructed points which can be binned together and averaged to produce the simulated velocity value at n equally spaced time points. The process is shown schematically on the right hand side of Figure 6.5. For these simulations TR was 21ms and 60 phases were reconstructed in the retrospective reconstruction to match the parameters in Chapter 4.

6.3 Missed triggers

6.3.1 Introduction

Occasionally when scanning a patient an ECG trigger will be missed and the data from two heartbeats are treated by the reconstruction as a single heartbeat. This will make no difference to a prospectively gated sequence (apart from extending the scan time by one heartbeat) since the acquisition window will have been set to be less than the expected duration of a single heartbeat - by the time the trigger is missed, the sequence has already stopped collecting data. However for retrospectively gated sequences, two heartbeats will be normalised as one which will potentially cause the resulting velocity-time curves to be inaccurate. In the following sections the number of missed triggers refers to

	1 missed	2 missed	3 missed
1	7.22	14.44	20.93
2	7.48	15.02	22.55
3	7.69	15.38	19.82
4	7.24	14.49	21.75
5	7.27	14.54	21.81
6	7.50	15.00	19.51
7	7.52	15.05	22.58
8	7.22	14.44	21.65
9	7.23	14.48	19.62

Table 6.1: The percentage difference of the peak velocities measured in the peaks curve with 1,2 and 3 missed triggers from the peak velocities measured with no missed triggers. The table shows values for 1000ms heart rate.

the number of occasions during a scan where, because of a missed ECG trigger, two heartbeats are treated as one by the retrospective reconstruction.

6.3.2 Methods

To isolate the effect of missing ECG triggers, no random natural heart rate variation was simulated. Instead the effect of different numbers of missed triggers (0, 1, 2, and 3) on different resting heart rates (600ms, 800ms, 1000ms and 1200ms) was investigated. Both input curves were used. Only retrospective gating was simulated for the reasons outlined above.

6.3.3 Results

6.3.3.1 Peaks curve

Simulated velocity-time curves for the peaks curve can be seen in Figure 6.6, whereas a table showing peak values measured for the various numbers of missed triggers is shown in Table 6.1. Values are shown as the percentage dif-

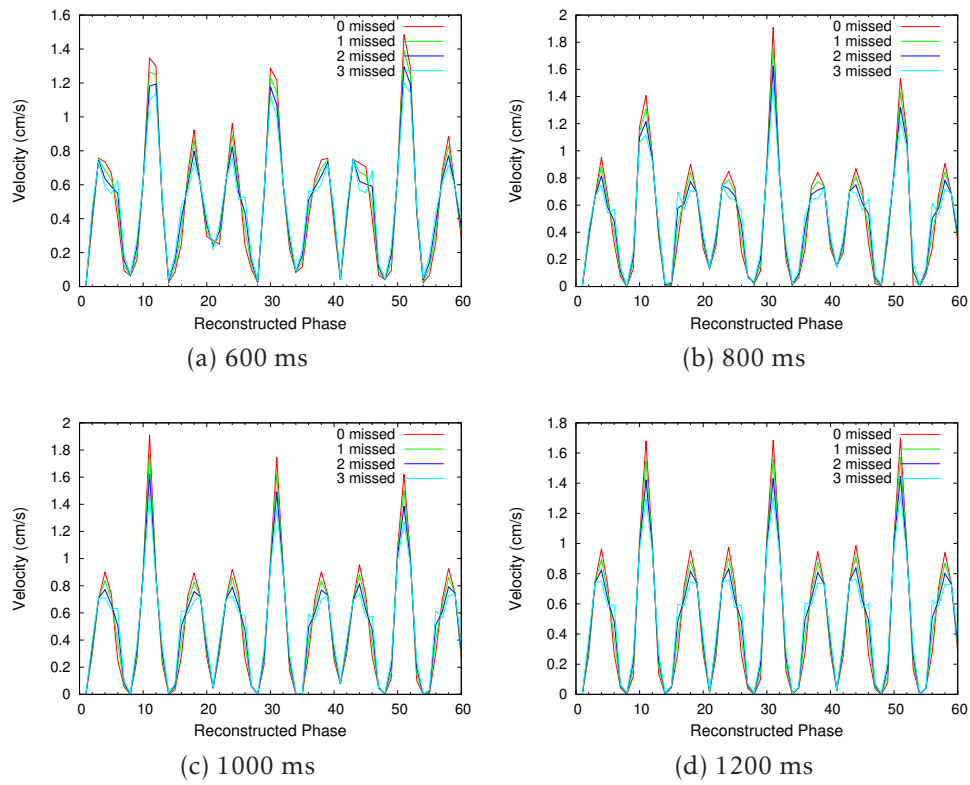


Figure 6.6: The effect of 0 to 3 missed triggers on the peaks curve for various heart rates.

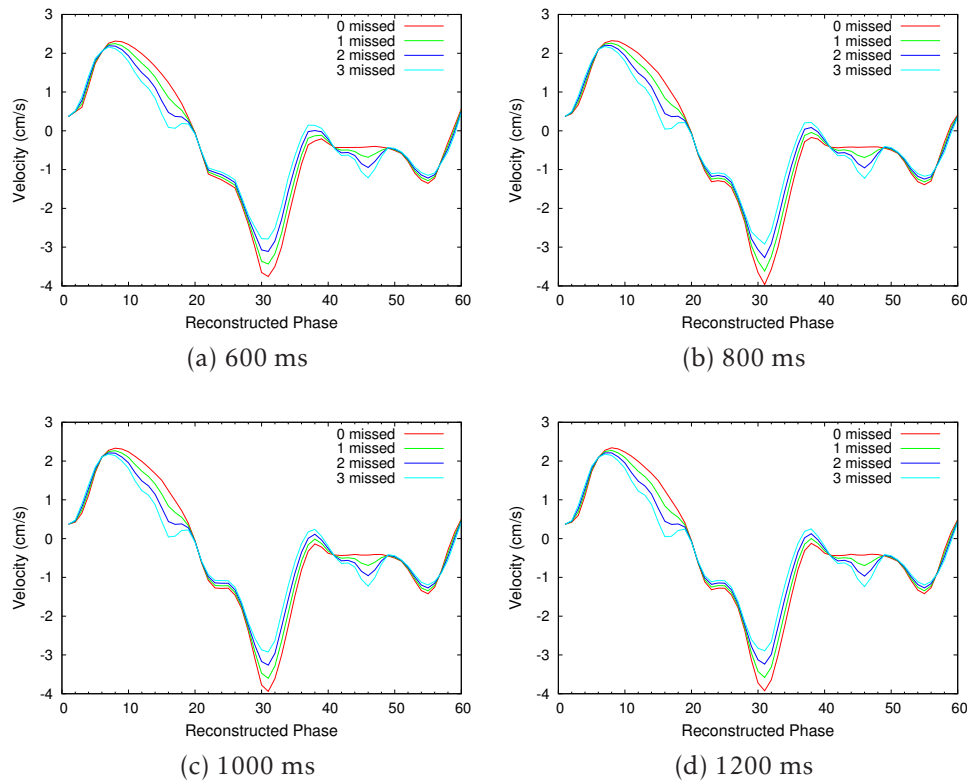


Figure 6.7: (a) to (d) The effect of missed triggers on the peak velocities measured with the curve based on real data for various heart rates.

ference from the values measured from the simulation where no triggers are missed. The effect is fairly constant through the cardiac cycle and gets worse as the number of missed triggers increases.

6.3.3.2 Curve based on real data

Simulated velocity-time curves for the curve based on real data can be seen in Figure 6.7, whereas the percentage differences as defined above are shown in Table 6.2. Measured peak velocities are reduced by missed triggers and the effect is worst for the main diastolic peak. The effect increases for all peaks as the number of missed triggers increases. New peaks also start to appear as the

	1 missed	2 missed	3 missed
Peak S	2.74	5.23	6.69
Peak D	8.60	17.21	25.81
Peak AS	5.27	10.62	15.89

Table 6.2: Percentage differences for the three main peaks in the real data curve when compared with the simulation with no missed triggers (values shown for 1000ms heart rate).

number of missed triggers increases. In particular a new peak between the main diastolic and atrial systolic peaks appears due to the main diastolic peak of the second heartbeat measured in those interleaves when a trigger was missed. For 3 missed triggers this peak is comparable to the actual atrial systolic peak and could cause the wrong TTP to be measured.

6.3.4 Discussion

The effect of missed triggers is that peak velocities can be underestimated by this technique. Two or more missed triggers for the same velocity encoding direction during an acquisition can reduce the size of the main diastolic peak by nearly 20%. While TTP values are not affected, the emergence of new peaks could cause inaccurate identification of peaks and hence could cause the wrong TTP to be measured. This is a particular problem for atrial systole.

An *in vivo* example of this effect can be seen in Figure 6.8. On the left two curves are shown from two acquisitions using the HighRes sequence (see Chapter 4) in the same patient. In one of the acquisitions two missed triggers occurred for data that was accepted into the final images, whereas in the other acquisition no missed triggers occurred. The reduction in peak diastolic and atrial systolic velocities is similar to that in the simulated data for no missed triggers and for two missed triggers. The systolic peak is also affected in a similar way (phases 10 to 20).

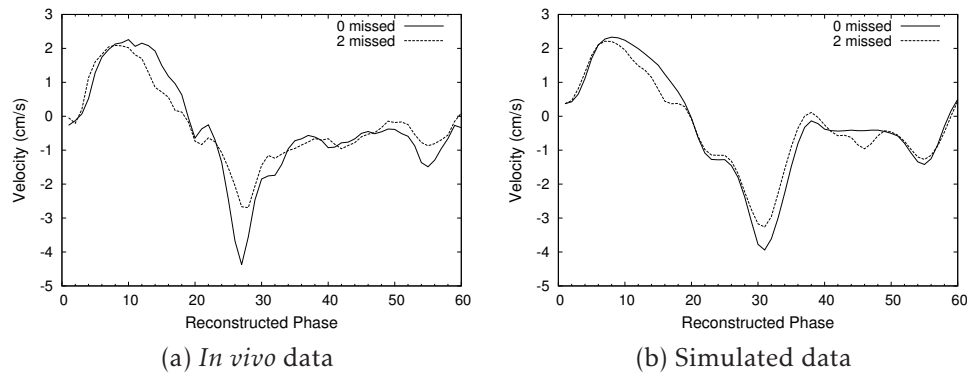


Figure 6.8: Comparison of the effect of missed triggers between *in vivo* and simulated data

6.4 Heart rate variation

A subject's heart rate will never be entirely steady throughout an MR scan, particularly for high resolution scans which may last several minutes. Even small changes in the duration of heart beats will change the timing of peaks and hence could affect the peak and TTP velocities that are measured. In the scans from Chapter 4, the level of heart rate variation (calculated for each acquisition as 2 times the standard deviation of RR duration divided by the average RR duration) was 15% on average whereas for the breathhold acquisitions of Chapter 5 the level of variation was just 6% on average. This section will simulate this effect using several magnitudes of variation (0%, 5%, 10%, 15% and 20%) around a base heart rate of 60bpm to cover the variation seen in both types of acquisition.

Four methods of stretching the cardiac cycle are also used. Firstly the entire cycle is stretched linearly as if all stages of the cardiac cycle were affected equally by changes in heart rate (this is effectively the assumption made by the retrospective gating algorithm). Secondly, systole is assumed to have a constant duration while diastole stretches to account for any heart rate variation. Then sys-

tole and diastole are each stretched separately and by different amounts based on a formula for heart-rate-dependent systolic duration derived from simultaneous electrocardiogram, phonocardiogram and carotid arterial pulsation measurements (Weissler et al., 1968). Finally the cycle is split into systole, early diastole, late diastole and atrial systole and each section is stretched separately according to ECG measurements on 25 healthy volunteers (Chung et al., 2004).

6.4.1 Linear

6.4.1.1 Methods

For these simulations it is assumed that the cardiac cycle is stretched linearly, according to the RR duration for each heartbeat. While it is not a particularly realistic assumption to make, it is a good first step to see the effect that changing heart rates could have on measured velocities and TTPs.

6.4.1.2 Results

Results for the peaks curve and the real data curve can be seen in Figures 6.9 and 6.10 respectively with percentage differences of peak measurements from the values with no heart rate variation shown in Tables 6.3 and 6.4. It is immediately obvious that the retrospective reconstruction deals almost perfectly with this kind of variation. TTPs are unaffected and only very small changes in peak velocities are observed. In contrast, the accuracy of prospective gating decreases rapidly as the level of variation increases. The effect also tends to worsen throughout the cardiac cycle, for example in the peaks curve at 5% variation peak 1 is underestimated by 1.08% while peak 9 is underestimated by nearly 54%. TTPs are accurate until the peak is reduced so much that it can no longer be accurately identified, a particular problem for AS in the real data

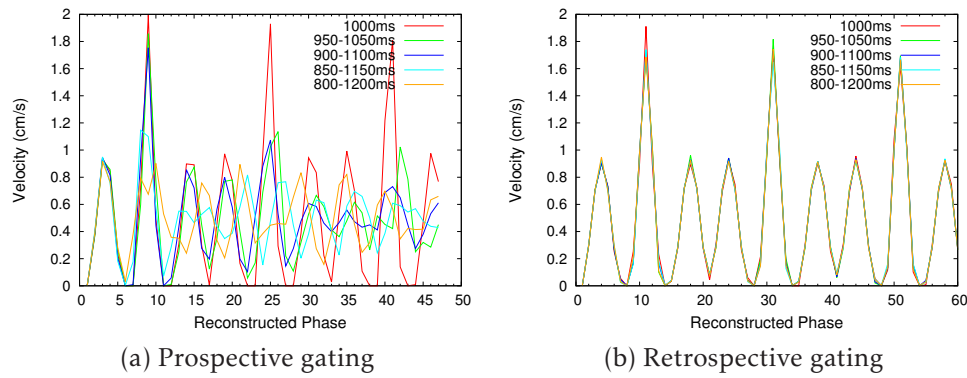


Figure 6.9: The effect of linear stretching of the cardiac cycle on the peaks curve for prospective gating (left) and retrospective gating (right). Curves are shown for 5 increasing levels of heart rate variation. Prospective gating performs worse as the variation increases whereas retrospective gating is unaffected even by a large amount of variation.

	5%	10%	15%	20%		5%	10%	15%	20%
1	1.08	-0.75	-1.24	2.27	1	-0.30	-0.70	-3.22	-5.22
2	6.73	11.95	42.42	60.19	2	11.15	9.89	8.90	11.83
3	2.77	4.76	35.81	15.66	3	-7.42	-3.75	-2.73	-3.21
4	19.77	17.74	15.95	7.94	4	-2.05	-2.04	0.12	0.57
5	41.14	44.35	60.27	76.23	5	-3.95	0.97	5.61	0.17
6	29.36	35.68	33.03	11.65	6	-1.39	-1.41	-1.64	-1.21
7	38.03	43.74	29.88	17.41	7	3.49	1.92	3.35	2.74
8	43.45	59.58	66.36	61.46	8	-4.57	-3.76	-3.76	-2.71
9	53.80	37.34	41.71	32.40	9	0.59	0.09	-1.04	0.12
TTP					TTP				
1	0.00	0.00	0.00	0.00	1	0.00	0.00	0.00	0.00
2	0.00	0.00	11.11	11.11	2	0.00	0.00	0.00	0.00
3	-7.14	0.00	-21.43	-14.29	3	0.00	0.00	0.00	0.00
4	-5.26	0.00	-15.79	-10.53	1	0.00	0.00	0.00	0.00
5	-4.00	0.00	-8.00	-4.00	2	0.00	0.00	0.00	0.00
6	-3.33	0.00	-3.33	3.33	3	0.00	0.00	0.00	0.00
7	-2.86	0.00	-2.86	0.00	1	0.00	0.00	0.00	0.00
8	-2.44	0.00	0.00	2.44	2	0.00	0.00	0.00	0.00
9	-2.17	-2.17	4.35	-2.17	3	0.00	0.00	0.00	0.00

(a) Prospective gating

(b) Retrospective gating

Table 6.3: Percentage underestimation of peak velocities measured in the peaks curve in the presence of increasing levels of linear heart rate variation for prospective (left) and retrospective (right) gating.

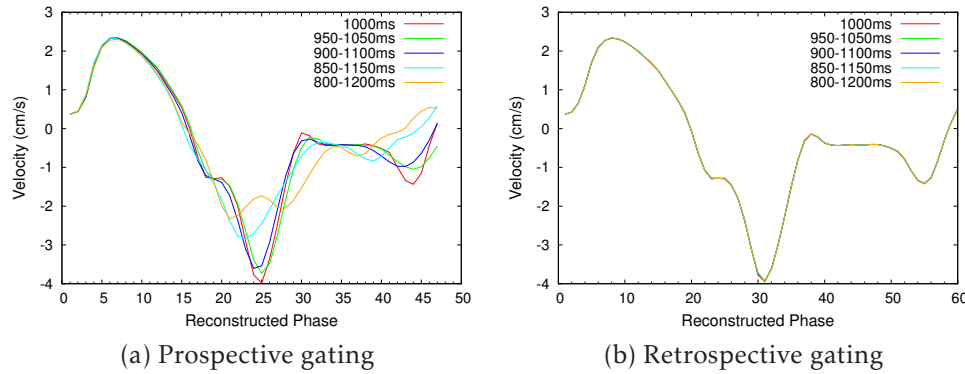


Figure 6.10: The effect of linear stretching of the cardiac cycle on the real data curve for prospective gating (left) and retrospective gating (right). Curves are shown for 5 increasing levels of heart rate variation. As with the peaks curve, the performance of prospective gating worsens through the cardiac cycle and as the variation increases whereas retrospective gating is unaffected even by a large amount of variation.

	5 %	10 %	15 %	20 %
Peak S	-0.21	0.21	0.56	1.33
Peak D	6.38	9.50	28.74	41.68
Peak AS	26.95	32.08	41.72	50.70
TTP S	0.00	16.67	16.67	0.00
TTP D	-0.08	4.36	8.26	10.09
TTP AS	1.91	2.38	13.32	15.09

(a) Prospective gating

	5 %	10 %	15 %	20 %
Peak S	-0.26	-0.30	-0.56	-0.17
Peak D	-0.30	0.25	0.79	0.23
Peak AS	0.28	0.49	0.28	0.28
TTP S	0.00	0.00	0.00	0.00
TTP D	0.00	0.00	0.00	0.00
TTP AS	0.00	0.00	0.00	0.00

(b) Retrospective gating

Table 6.4: Percentage underestimation of peak velocities measured in the real data curve in the presence of increasing levels of linear heart rate variation.

curve.

6.4.1.3 Discussion

The retrospective reconstruction deals almost perfectly with this type of variation. This is because the normalisation step in the reconstruction (see Figure 6.5) linearly stretches each curve to the same duration, perfectly compensating for the variation. Any remaining differences between the curves are due to interpolation and different initial sampling rates. It is also easy to understand why prospective gating deals badly with this kind of variation - different parts of the cardiac cycle overlap when there is variation and so the final curve gets smeared out by the averaging. The effect worsens through the cardiac cycle because the amount a phase of the cardiac cycle is affected by the variation is linearly dependent on its time after the R-wave.

6.4.2 Constant systole

6.4.2.1 Methods

For this section, systole is assumed to have a constant duration of 350ms while the length of diastole changes as the heart rate varies. While this is still not physiologically accurate, the length of diastole is generally considered to be more sensitive to heart rate changes than the length of systole.

6.4.2.2 Results

Results for the peaks curve and real data curve can be seen in Figures 6.11 and 6.12 respectively while percentage underestimations are shown in Tables 6.5

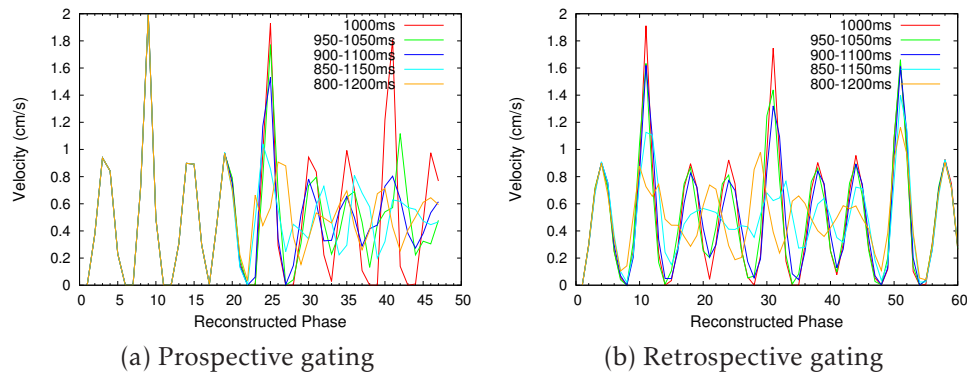


Figure 6.11: The effect of keeping the duration of systole constant on the peaks curve for prospective gating (left) and retrospective gating (right). Curves are shown for 5 increasing levels of heart rate variation. Prospective gating performs perfectly during systole but poorly towards the end of the cardiac cycle, even at low levels of variation. Retrospective gating is most affected in the middle of the cardiac cycle.

	5%	10%	15%	20%		5%	10%	15%	20%
1	0.00	0.00	0.00	0.00	1	0.35	-0.35	-0.88	0.50
2	0.00	0.00	0.00	0.00	2	14.50	67.56	41.03	54.22
3	0.00	0.00	0.00	0.00	3	3.26	7.68	36.85	50.64
4	0.28	-0.27	-0.60	0.19	4	12.00	16.36	52.49	19.98
5	8.19	72.49	46.06	52.99	5	17.63	24.38	56.18	43.88
6	15.67	17.07	22.75	43.51	6	4.60	7.01	29.18	27.17
7	30.48	34.18	18.51	30.00	7	6.37	6.70	24.41	38.73
8	38.25	55.60	65.26	60.56	8	-2.47	0.62	13.57	28.25
9	50.98	37.02	52.18	33.94	9	0.60	0.46	0.12	2.41
TTP					TTP				
1	0.00	0.00	0.00	0.00	1	0.00	0.00	0.00	0.00
2	0.00	0.00	0.00	0.00	2	0.00	0.00	0.00	9.09
3	0.00	0.00	0.00	0.00	3	0.00	0.00	-11.11	11.11
4	0.00	0.00	0.00	0.00	4	0.00	0.00	-8.33	12.50
5	0.00	0.00	4.00	-4.00	5	0.00	0.00	-6.45	6.45
6	-3.33	0.00	-6.67	-3.33	6	0.00	0.00	-2.63	7.89
7	-2.86	0.00	-2.86	0.00	7	0.00	0.00	0.00	4.55
8	-2.44	0.00	0.00	2.44	8	0.00	0.00	0.00	0.00
9	-2.17	-2.17	-2.17	0.00	9	0.00	0.00	0.00	0.00

(a) Prospective gating

(b) Retrospective gating

Table 6.5: The effect of linear stretching of diastole only (constant systole) on the peak velocities measured from the peaks curve with prospective (left) and retrospective (right) gating.

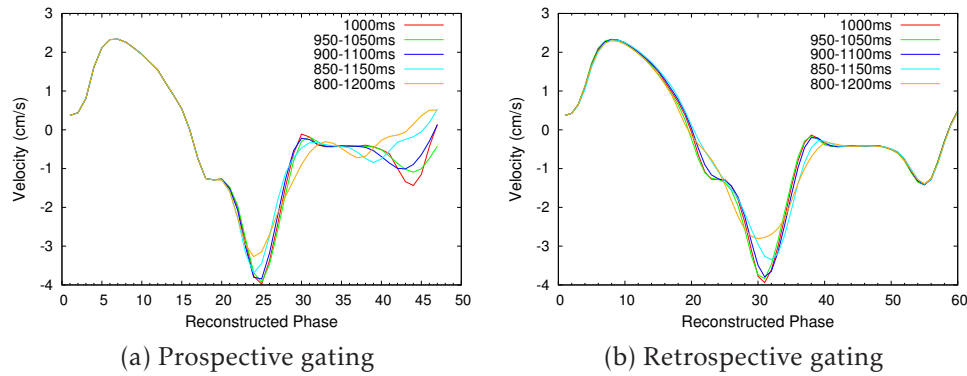


Figure 6.12: The effect of linear stretching of diastole only (constant systole) on the real data curve. Prospective gating performs well for S and D but less well for AS. Retrospective gating performs almost perfectly for S and AS and comparably to prospective gating for D.

	5%	10%	15%	20%
Peak S	0.00	0.00	0.00	0.00
Peak D	1.13	3.39	7.19	17.86
Peak AS	23.96	29.81	41.44	49.79
TTP S	0.00	0.00	0.00	0.00
TTP D	-3.65	-3.65	0.67	0.67
TTP AS	1.61	3.90	13.05	17.63

(a) Prospective gating

	5%	10%	15%	20%
Peak S	-0.04	0.04	0.56	1.63
Peak D	2.61	3.76	15.00	28.71
Peak AS	0.28	0.56	1.20	2.32
TTP S	0.00	0.00	4.00	-9.09
TTP D	0.00	0.00	-0.76	-2.19
TTP AS	0.00	0.00	0.28	-0.52

(b) Retrospective gating

Table 6.6: The effect of linear stretching of diastole only (constant systole) on the peak velocities measured on the real data curve.

and 6.6. Prospective gating now deals perfectly with systole (peaks 1-3 in the peaks curve and S in the real data curve). However, diastole is affected by the variation, with the effect getting worse towards the end of the cycle. For the real data curve this means that D is quite well preserved (less than 20% underestimation at 20% heart rate variation), while AS is badly affected (23% underestimation even at 5% heart rate variation). In contrast retrospective gating deals well with the beginning and end of the cycle (peaks 1 and 9 for the peaks curve and S and AS for the real data curve), but the middle of the cardiac cycle is affected - peak 5 is underestimated by 17.6% even at 5% variation. TTPs are not affected much by this kind of variation.

6.4.2.3 Discussion

Prospective gating deals well with this type of variation in systole because, unlike retrospective gating which assumes each heartbeat is stretched linearly, prospective gating assumes each heartbeat is the same. However diastole is affected in the same way as for linear stretching of the entire cycle, except the effect is not as bad because it is now proportional to the time after the beginning of diastole rather than the time since the R-wave. Retrospective gating deals well with the beginning and end of the cycle because during normalisation of the each heartbeat, the beginning and end of the cycle are fixed. However the middle of the cycle is not fixed and so peaks 4-6 in the peaks curve and D in the real data are progressively underestimated as heart rate variation increases.

6.4.3 Changing systole and diastole

6.4.3.1 Methods

This section uses a method of stretching the cardiac cycle based on physiological measurements of the length of systole in relation to heart rate (double rate stretching). Various studies have investigated the relationship between systolic intervals and heart rate (Bombardini et al., 2011; Hassan and Turner, 1983; Weissler et al., 1968; Wikstrand et al., 1978). The formula chosen for these simulations relates the time (in ms) between the two heart sounds (t_{syst}) with the heart rate measured in bpm (HR) (Weissler et al., 1968). This has been chosen because it most closely resembles the systolic duration measured from tissue phase velocity mapping curves (Jung et al., 2006a). The formula is:

$$t_{syst}(ms) = 456ms - 1.8 \times HR(bpm). \quad (6.5)$$

6.4.3.2 Results

Results for the peaks curve and real data curve can be seen in Figures 6.13 and 6.14 respectively, while underestimation of peak velocities is shown in Tables 6.7 and 6.8. The results are similar to the constant systole case except systole is no longer perfectly preserved by prospective gating. For the real data curves, S is well preserved for prospective and retrospective gating even with large heart rate variation. However retrospective gating performs better than prospective gating for both D and AS.

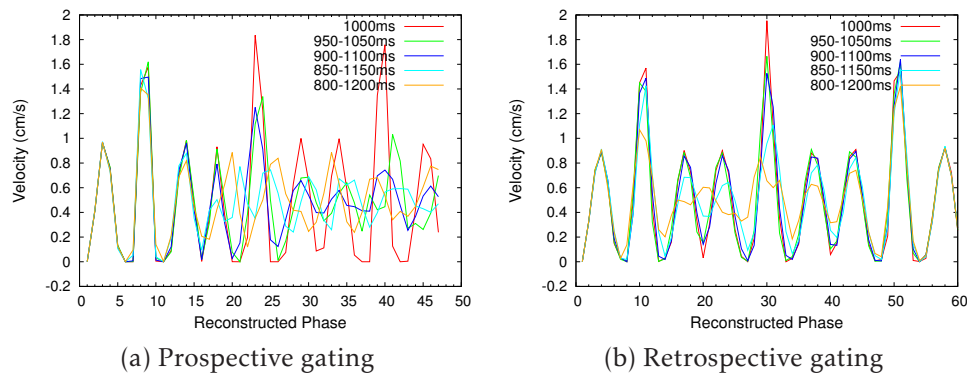


Figure 6.13: The effect of double scale stretching on the peaks curve. Curves are shown for 5 increasing levels of heart rate variation. Prospective gating performs well during systole but poorly towards the end of the cardiac cycle, even at low levels of variation. Retrospective gating is most affected in the middle of the cardiac cycle.

Peak	5%	10%	15%	20%	Peak	5%	10%	15%	20%
1	0.2	-0.2	-0.5	0	1	0.4	-0.9	-2.9	-2.4
2	-2.6	5.3	1.4	10.9	2	7.6	5.2	9.1	31.9
3	0.1	2.6	10.8	16.9	3	1.7	4.9	24.0	44.5
4	1.9	15.0	46.0	4.9	4	2.0	4.6	28.4	33.0
5	27.1	31.95	58.0	54.3	5	14.8	21.9	43.23	56.6
6	31.5	34.2	25.5	59.3	6	-3.3	3.6	10.8	28.8
7	35.7	42.0	30.9	11.2	7	2.0	1.7	7.2	18.5
8	41.3	57.7	61.7	61.2	8	-4.9	-6.22	-1.2	8.0
9	26.6	35.6	37.7	18.5	9	0.7	0.3	-0.6	1.1
TTP					TTP				
1	0	0	0	0	1	0	0	0	0
2	0	0	11.1	11.1	2	9.1	0	0	9.1
3	0	0	0	0	3	0	0	0	5.93
4	0	0	0	-11.1	4	0	0	-4.3	13.0
5	-4.3	0	8.7	-13.0	5	0	0	-3.3	3.3
6	-3.4	0	13.8	0	6	0	0	-2.7	0
7	-2.9	0	11.8	2.9	7	2.3	0	0	0
8	-2.5	0	15	2.5	8	0	0	0	0
9	-4.4	-2.2	6.7	-2.2	9	0	0	0	0

(a) Prospective gating

(b) Retrospective gating

Table 6.7: The effect of double scale stretching on the peak velocities measured with the peaks curve with prospective (left) and retrospective (right) gating.

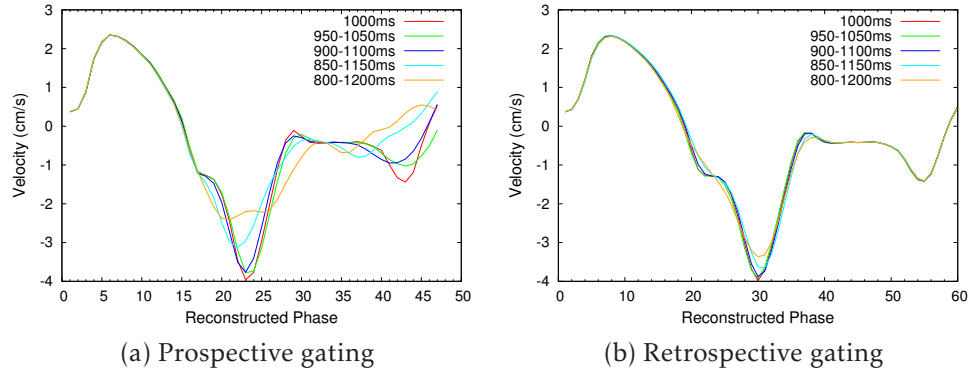


Figure 6.14: The effect of double scale stretching on the real data curve. Curves are shown for 5 increasing levels of heart rate variation. Prospective gating performs well for S but poorly for D and AS for the higher levels of variation. Retrospective gating deals very well with all levels of variation but is most affected in the middle of the cardiac cycle.

	5%	10%	15%	20%
Peak S	0.08	-0.04	-0.04	0.25
Peak D	4.59	4.92	21.10	39.15
Peak AS	28.58	34.12	44.30	52.61
TTP S	0.00	0.00	0.00	0.00
TTP D	-0.49	-0.49	4.07	8.64
TTP AS	1.85	6.52	15.87	18.21

(a) Prospective gating

	5%	10%	15%	20%
Peak S	0.04	-0.17	-0.17	0.77
Peak D	1.73	2.69	8.31	15.54
Peak AS	0.49	0.63	0.56	1.13
TTP S	-4.55	0.00	0.00	-9.52
TTP D	-2.93	0.00	-3.71	-5.71
TTP AS	-0.25	0.00	0.00	-0.49

(b) Retrospective gating

Table 6.8: The effect of double scale stretching on the peak velocities measured with the real data curve with prospective (left) and retrospective (right) gating.

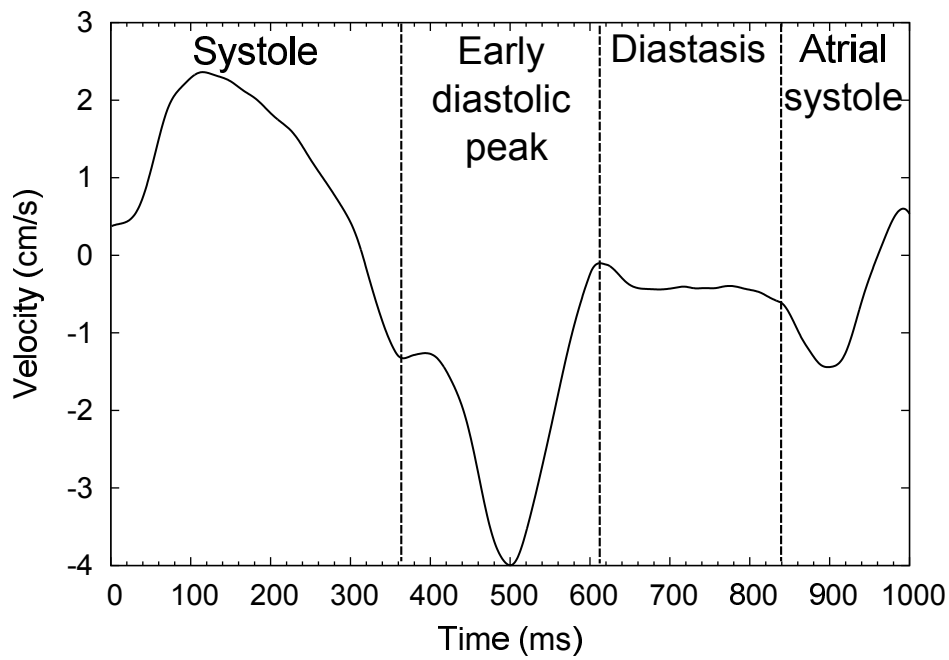


Figure 6.15: Method of splitting cycle based on diastolic intervals

6.4.3.3 Discussion

With this method of stretching the cycle, similar results to the constant systole case are seen. This is because Equation 6.5 means that systole is stretched less than diastole. Consequently the results are somewhere between the linear stretching case and the constant systole case.

6.4.4 Splitting the cardiac cycle based on diastolic intervals

6.4.4.1 Methods

For this section a more complicated method of stretching the cardiac cycle has been used. Instead of splitting the cardiac cycle into systole and diastole, the cycle has been split into four sections: systole, the early diastolic peak, diastasis

and atrial systole. The sections can be seen in Figure 6.15. The durations of the sections as a function of heart rate (HR) are based on the following diastolic intervals (in ms) as calculated from ECG measurements on 25 healthy volunteers (Chung et al., 2004):

$$\text{Early diastolic peak}(ms) = 313ms - 0.957 \times \text{HR}(\text{bpm}) \quad (6.6)$$

$$\text{Diastasis}(ms) = 600ms - 6.82 \times \text{HR}(\text{bpm}) \quad (6.7)$$

$$\text{Atrial systole}(ms) = 166ms - 0.454 \times \text{HR}(\text{bpm}) \quad (6.8)$$

$$\text{Systole}(ms) = \text{RR duration} - \text{Early diastolic peak} - \text{Diastasis} - \text{Atrial systole} \quad (6.9)$$

This takes into account the fact that as heart rate increases, diastasis shortens in length and eventually disappears altogether with the two diastolic peaks merging. Using Equation 6.7 this would happen at a heartrate of around 90bpm.

6.4.4.2 Results

Results for the peaks curve and real data can be seen in Figures 6.16 and 6.17 respectively while underestimations of peak velocities are shown in Tables 6.9 and 6.10. The results for prospectively gated acquisitions are again similar to the constant systole case, with the accuracy decreasing through the cardiac cycle and with increasing heart rate variation. However, very little decrease in accuracy is seen for retrospective gating in the presence of this kind of heart

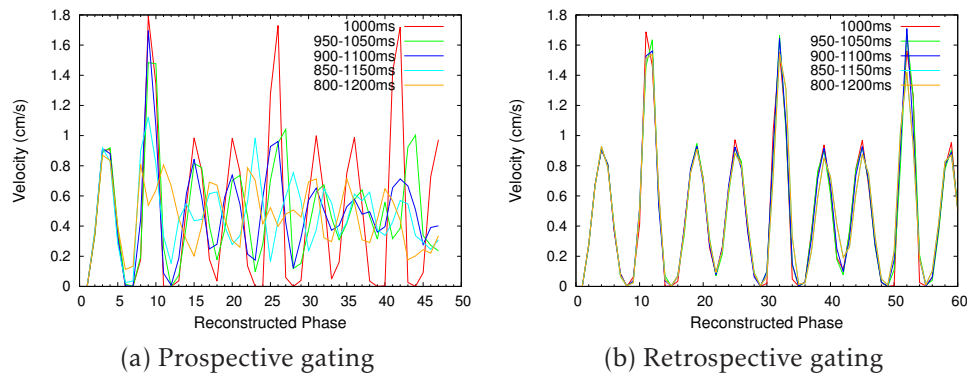


Figure 6.16: The effect of stretching based on diastolic intervals on the peaks curve. Curves are shown for 5 increasing levels of heart rate variation. Prospective gating performs well only for peak 1 while retrospective gating performs well throughout the cycle.

Peak	0.05	0.10	0.15	0.20	Peak	5%	10%	15%	20%
1	-1.36	-0.63	-1.26	3.94	1	-0.30	-0.61	-2.87	-4.42
2	17.14	5.30	37.24	54.99	2	3.14	7.58	8.83	3.50
3	17.27	14.42	44.50	29.82	3	-2.70	-0.85	1.31	3.64
4	25.12	24.96	36.29	20.02	4	5.85	4.89	9.30	12.41
5	39.83	44.44	43.09	69.84	5	-7.29	-6.06	0.39	0.26
6	32.60	34.76	35.12	28.65	6	3.89	2.29	9.22	20.39
7	35.27	41.44	36.65	27.47	7	4.79	4.25	9.55	18.76
8	41.69	58.56	66.88	62.37	8	-7.23	-9.40	9.28	23.86
9	46.06	58.68	68.26	54.75	9	5.27	7.04	8.85	7.49
TTP					TTP				
1	0.00	25.00	25.00	25.00	1	0.00	0.00	0.00	0.00
2	0.00	0.00	0.00	-22.22	2	-9.09	-9.09	-9.09	-9.09
3	0.00	0.00	6.67	-13.33	3	0.00	0.00	0.00	0.00
4	-5.00	0.00	10.00	-10.00	4	0.00	0.00	0.00	-4.00
5	-3.85	0.00	11.54	3.85	5	0.00	0.00	0.00	-3.13
6	-3.23	0.00	-3.23	0.00	6	0.00	0.00	0.00	0.00
7	-2.78	0.00	-5.56	2.78	7	0.00	0.00	0.00	0.00
8	-4.76	0.00	0.00	4.76	8	0.00	0.00	0.00	0.00
9	-4.26	0.00	0.00	-4.26	9	0.00	0.00	0.00	0.00

(a) Prospective gating

(b) Retrospective gating

Table 6.9: The effect of stretching based on diastolic intervals on the peak velocities measured with the peaks curve for prospective (left) and retrospective (right) gating.

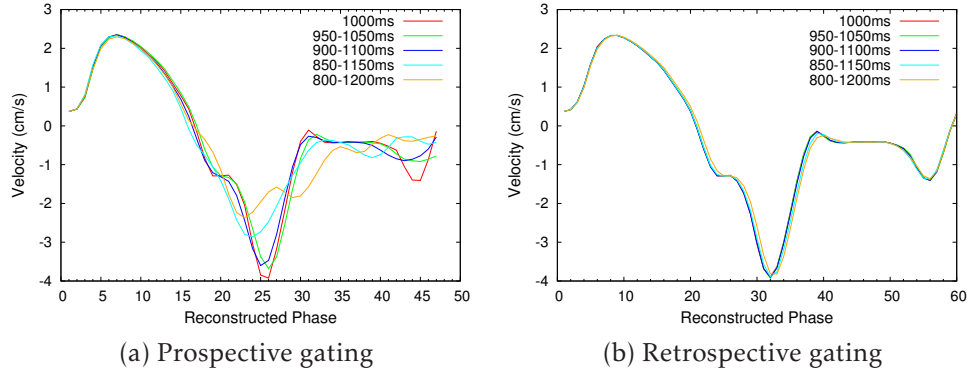


Figure 6.17: The effect of stretching based on diastolic intervals on the real data curve. Curves are shown for 5 increasing levels of heart rate variation. Both algorithms perform well for S and retrospective gating performs almost perfectly throughout the cycle.

	5%	10%	15%	20%
Peak S	0.08	0.42	1.27	2.63
Peak D	6.29	8.23	27.18	39.67
Peak AS	34.73	36.12	41.74	51.04
TTP S	0.00	0.00	0.00	0.00
TTP D	-6.88	-2.60	1.67	5.95
TTP AS	1.53	6.01	14.96	19.43

(a) Prospective gating

	5%	10%	15%	20%
Peak S	0.04	0.13	-0.21	-0.21
Peak D	-0.67	-0.46	0.08	1.90
Peak AS	-0.43	-0.21	1.92	2.92
TTP S	4.00	4.00	14.67	4.00
TTP D	2.92	2.92	2.92	-0.83
TTP AS	0.22	0.22	0.22	0.22

(b) Retrospective gating

Table 6.10: The effect of stretching based on diastolic intervals on the peak velocities measured with the real data curve for prospective (left) and retrospective (right) gating.

rate variation.

6.4.4.3 Discussion

This method aims to most closely simulate the real-life effect of heart rate variation on the timings of the various peaks through the cardiac cycle, although there will clearly be some inter-subject variations. The results from this kind of stretching are very similar to the linear stretching results, with retrospective gating dealing very well with all levels of variation, while prospective gating does not deal well even with low levels of variation.

6.4.5 Heart rate variation discussion

The effect of heart rate variation on the timing of peaks and hence on the measured peak velocity values is complicated. The four methods of stretching the cardiac cycle here start simply and aim to get more physiologically accurate through to the method which stretches the four sections of the cycle separately. However even these simulations are greatly simplified when compared with the real life situation. The exact timings with different heart rates will change between volunteers and no attempt was made to change the amplitude of the velocity peaks with different heart rates.

The simulations show that peak velocities in the middle of the cardiac cycle (i.e. D on the real data curve) are most affected by heart rate variation when using retrospective gating. Therefore this effect could explain the trend towards higher D_L and D_R velocities measured with R2 and R3 in the previous Chapter when compared with velocities measured with HighRes, due to the lower level of heart rate variation during the short breath-hold scans (percentage variation defined as twice the standard deviation of heart rate divided by average heart rate during the scan was 15% for HighRes acquisitions but just 6% for R2 and

R3 acquisitions).

In general, prospective cardiac gating leads to more serious underestimation of peak velocities than retrospective cardiac gating in the presence of heart rate variation. The retrospective gating algorithm effectively assumes that the cardiac cycle is stretched linearly by heart rate variation which explains why the algorithm performs perfectly with linear stretching of the cycle. Prospective gating on the other hand assumes that each heart beat is of exactly the same duration and hence does not perform well when heart rate variation is introduced.

The method of stretching the cycle according to diastolic intervals was intended to be the most physiologically accurate and led to very good performance of the retrospective algorithm (maximum peak underestimation in the real data curve was less than 3%). The performance of prospective gating was poor at levels of variation greater than around 10%. The navigator scans from Chapter 4 had heart rate variation (defined as 2 times standard deviation of RR durations during the acquisition divided by the average RR duration) of around 15% which would lead to significant underestimation of D_R in prospectively gated scans of 27%, indicating that retrospective cardiac gating should be used for long spiral PVM acquisitions even if atrial systole is not being considered.

Chapter 7

Discussion

Myocardial phase velocity mapping is one of several emerging MRI techniques which can be used to measure regional myocardial mechanics. However the sequences used in the past have been slow due to the use of inefficient Cartesian k-space trajectories, and have provided incomplete coverage of the cardiac cycle due to the use of prospective cardiac gating. This has limited the technique both in terms of research into healthy motion of the heart, and in terms of application in clinical practice.

This thesis has described the development of phase velocity mapping sequences which are capable of overcoming the current limitations of myocardial phase velocity mapping. This is achieved by using spiral k-space coverage to increase the imaging efficiency of the technique, and by using retrospective cardiac gating to cover the entire cardiac cycle.

7.1 Summary of findings

The need for an improved technique for measuring regional myocardial mechanics was made clear by an extensive literature review (Chapters 1 and 2) parts of which were published as a detailed review article in JMRI (Simpson et al., 2013b). The advantages and disadvantages of the available techniques which are capable of measuring regional myocardial mechanics were discussed, and the theory behind the MRI techniques was explained. From this discussion, tissue phase velocity mapping emerges as the only available MRI technique capable of measuring regional myocardial mechanics which does not suffer from tag fading and can therefore cover the entire cardiac cycle. It can also be used to measure three directions of velocity from a single slice, and is therefore the obvious choice for a comprehensive technique to measure regional myocardial mechanics. However, the use of prospective cardiac gating in previous sequences has limited the technique, as have long scan times due to inefficient coverage of k-space.

It was hypothesised that the use of retrospective gating (to allow coverage of the entire cardiac cycle) and spiral k-space coverage (to reduce scan time) would allow tissue phase velocity mapping to be routinely acquired in clinical practice. The development of the new sequences is described in detail in Chapter 3. Two final sequence versions were produced and have been used for healthy volunteer studies, establishing the technique as reproducible (this has not previously been comprehensively shown) and helping establish normal ranges of motion. Analysis tools were also developed for segmentation of the images and data analysis and display. In particular colour plots have been used to present a large amount of velocity information in an easily interpretable way.

The first sequence version that has been developed is navigator gated, taking 53 heartbeats (with 100% respiratory efficiency) to acquire data with 1.4x1.4mm spatial resolution and 21ms temporal resolution. However with the modified

acceptance algorithm necessary to suppress motion over the entire cycle, biofeedback is needed to keep scan times reasonable. While this is well tolerated by healthy volunteers, it may well provide difficulties for scanning patients. Results from scans in ten healthy volunteers are presented in Chapter 4. The reproducibility of the technique was found to be very good and measured quantitative parameters agree with results from previous studies by other groups. Results from this study have been published in JCMR (Simpson et al., 2013a) and presented at international MRI conferences.

The second is a version which uses a non-Cartesian SENSE reconstruction implemented on the Gadgetron GPU system to reconstruct undersampled data which can be acquired within a short breath-hold. This version acquires data with 1.7x1.7mm spatial resolution and 24ms temporal resolution in just 13 heartbeats using a SENSE factor of 2.67. By acquiring data within a breath-hold many of the limitations of the navigator sequence have been overcome, and the results from scanning the same ten healthy volunteers as in Chapter 4 are presented in Chapter 5, where results from the two versions of the sequence are compared. The two sequences achieve very similar results despite the large difference in scan time. It was even found that the accelerated sequence shows a tendency towards measuring higher peak velocities despite having slightly lower resolution.

It was proposed that some of the differences between the navigator and breath-hold sequence versions could be caused by heart rate variation over the scan duration, which may affect the longer navigator sequence more than the breath-hold sequence. The effect of heart rate variation on these scans was therefore investigated via simulations in Chapter 6. It was found that with retrospective cardiac gating, an increasing level of heart rate variation leads to underestimation of peak velocity values, particularly for early diastolic velocities. The simulations also found that retrospective cardiac gating deals much better in general with natural heart rate variation than prospective gating.

7.2 Limitations

The limitations of the two sequence versions can be found in the discussion sections of Chapters 4 and 5 and are summarised here. Some of the limitations of the navigator technique have been overcome by acquiring the data within a breath-hold. Namely, the biofeedback mechanism (which is difficult to apply in patients) is no longer necessary, the scan time is greatly reduced, and the reconstruction time is no longer a limiting factor due to the use of GPU reconstruction.

Both versions currently require an additional phantom scan to remove background phase errors. Background phase errors are inherent to phase velocity mapping and the most accurate way to deal with them is to use a phantom subtraction. However it is extremely inconvenient, particularly in clinical practice. A background offset modelling method to remove the errors has been used previously with myocardial phase velocity mapping (Lutz et al., 2011) but its accuracy when compared with a phantom subtraction has not yet been established (see Section 7.3).

The segmentation of the images is required for extracting regional velocity information but is time consuming and is currently carried out using custom software in MATLAB. This too makes the technique difficult to incorporate clinically as MATLAB is not widely available to clinicians and the process is too time consuming to be done regularly. This could be overcome by semi automatic segmentation algorithms and incorporation of the analysis into software which is already used by clinicians (see Section 7.3).

The use of long spiral durations means that off resonance artefacts could be an issue in clinical practice. The images acquired in the healthy patient studies are of high quality and largely free from off resonance issues due to careful shimming and frequency adjustment. However this is not routinely carried out

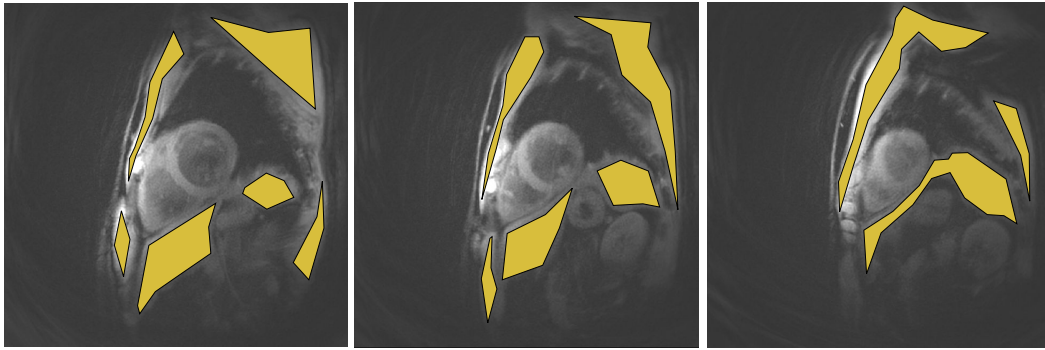


Figure 7.1: Possible segmentation of stationary tissue from basal (left), mid (middle) and apical (right) slices in a single volunteer.

in clinical practice and would require extra time and extra training. If higher levels of acceleration were possible, shorter spirals could be used and the technique could be made more robust (see Section 7.3). An off resonance correction could also be implemented to increase robustness (Ahunbay and Pipe, 2000; Man et al., 1997; Nayak et al., 2001).

7.3 Future work

The future work for this project falls into two main categories; further improvements to the technique and further studies to be carried out.

7.3.1 Improvements to the technique

7.3.1.1 Background offset modelling

Being able to accurately model the background phase offset based on static tissue within the images would remove the need for additional time consuming and inconvenient phantom scans. However before this can be done it must first

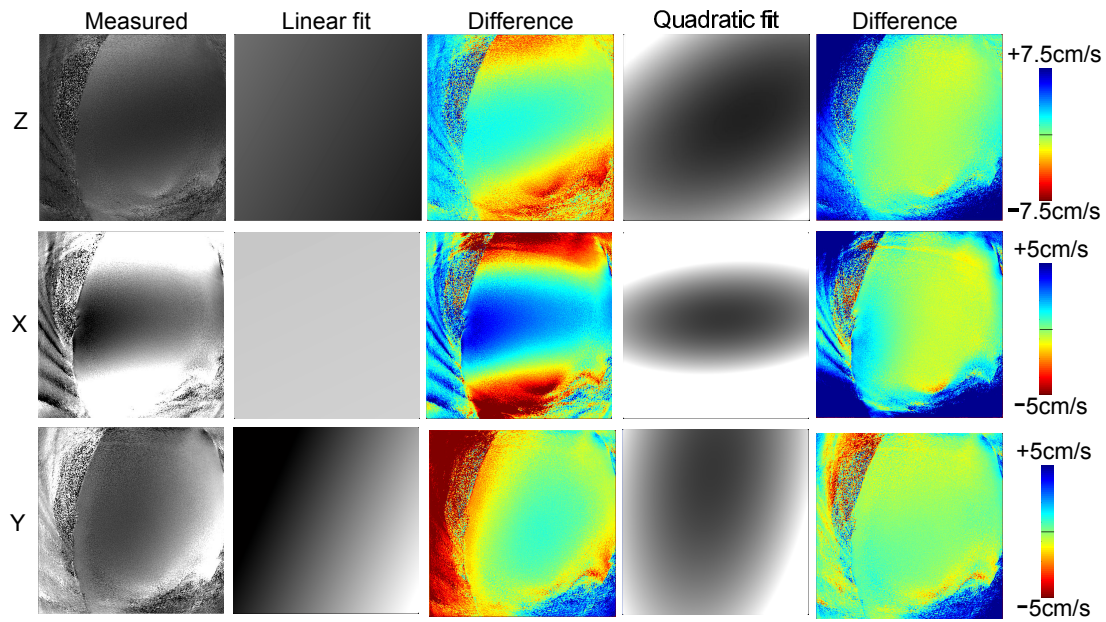


Figure 7.2: Example results obtained by background modelling on the mid ventricular short axis slice shown in Figure 7.1. The results of linear and quadratic fits, and the difference between them and the phantom measurement are displayed for all three directions.

be properly validated. Figure 7.1 shows that there is a large area of static tissue in a short axis slice that could be used to perform the modelling. This tissue only has to be manually segmented once for each cine since the tissue is stationary and so the process will not greatly extend processing time.

Previous studies have used linear modelling to remove background phase errors (Delfino et al., 2006; Lutz et al., 2011), as this is the standard method when correcting for scans measuring blood flow in the great arteries. In the case of great artery scans, not much stationary tissue is available for accurate polynomial correction, which is why a linear fit is used. However from Section 4.2.1.6 it is clear that the background offset is not linear, and in the case of measuring regional myocardial velocities, the difference between a linear and polynomial fit could affect the measured regional variation.

Figure 7.2 shows the results of fitting the background offset by segmenting stationary tissue in the mid ventricular short axis slice as shown in Figure 7.1. Both linear and quadratic fits were performed using the MATLAB command ‘fit’ with options ‘poly11’ and ‘poly22’. The results were subtracted from the phantom background measurement to assess their effectiveness. While the linear fit does not closely match the measured background offsets (in the X direction particularly there are large differences), the quadratic fit achieves a reasonable estimation of the measured offsets, with differences close to 0cm/s over the position of the heart.

A full study will be performed for future work to determine the accuracy of various methods of modelling the background offset based on static tissue segmented using short axis myocardial phase velocity mapping images. This can be done retrospectively on all scans that have so far been performed during this project.

7.3.1.2 Improved segmentation

The time consuming segmentation is one of the main remaining limitations of the technique and future work will aim to speed up the process. This could involve segmenting only key frames within the heart cycle and interpolating between them, or developing a fully automatic segmentation algorithm such as the one described in Lutz et al. (2011) which uses active contour techniques incorporating a shape model to segment the first phase, and then tracks profile intensities to propagate the segmentation through the cycle.

Future work will also investigate carrying out the analysis using CMRTools (Cardiovascular Imaging Solutions Ltd.) which is a commercial tool developed at Imperial College used by clinicians to analyse clinical MR scans at the Royal Brompton Hospital. This package is currently used to calculate volumes in all

clinical scans by segmenting the epicardial and endocardial layers. If volumes calculated from the magnitude images of the phase velocity mapping sequence developed from this project could be validated against the current clinical acquisitions, the phase velocity mapping sequence could be used instead. The velocity information would then be gained without any additional processing time. Alternatively the segmentation tools available in CMRTools could be used and the segmentation exported for further processing in MATLAB.

7.3.1.3 GRAPPA

While the SENSE algorithm implemented to reconstruct the undersampled data in Chapter 5 has allowed high quality images to be acquired within a clinically acceptable breath-hold, the spiral duration could lead to issues in clinical use in some patients. If higher acceleration factors were possible, shorter spiral durations could be used, increasing the robustness of the technique. Further investigation into other acceleration techniques could be carried out for future work. In particular the through-time spiral GRAPPA algorithm developed at Case Northwestern University (presented in the study by Seiberlich et al. (2011)) has been applied in collaboration with Dr Nicole Seiberlich to the data acquired during this project and can be used without any change to the acquisition. The fully sampled data acquired during the first heartbeat is used as the calibration lines in the GRAPPA reconstruction. Due to the use of temporal correlations in the data there is the potential for higher acceleration factors than is possible with the SENSE algorithm used in this thesis. However previous Cartesian work that has exploited temporal correlations in PVM data has found that high acceleration factors can cause peak velocities to be underestimated due to temporal smoothing (Lutz et al., 2011).

7.3.1.4 Strain-rate

While velocities are a good way of showing myocardial mechanics, strain-rate provides a more specific way of investigating myocardial contraction (bulk tissue motion does not contribute). Previous studies have shown strain-rate information from velocity data (eg (Beache et al., 1995; Delfino et al., 2008a)) but without obtaining the complete strain-rate tensor, and while one study performed 3D imaging in order to get the full strain-rate tensor (Selskog et al., 2002), the temporal resolution was low (108ms) and the scan time was long (around 40 minutes). The breath-hold sequence described in Chapter 5 allows the acquisition of short axis stacks of cines (see Section 5.2.1.7) from which strain-rate tensor information can be derived (although with low resolution in the through plane direction).

Figure 7.3 shows example data produced by Dr Robert Merrifield of the Department of Computing at Imperial College, visualising strain-rate data derived from one of the acquired stacks of velocity data presented in Chapter 5. The longitudinal, radial and circumferential components of the full strain-rate tensor in the mid slice are shown through time with the various stages of the cardiac cycle marked ('ejection', 'clockwise' etc.). On the right the velocity maps are also shown for comparison and on the far right interesting frames in the cycle are shown enlarged and with velocity information overlaid as arrows.

This is a preliminary example showing initial attempts at deriving this information from the velocity data acquired. Future work will include developing this processing and further analysis of strain-rate measurements in collaboration with Prof Guang-Zhong Yang's group at Imperial College.

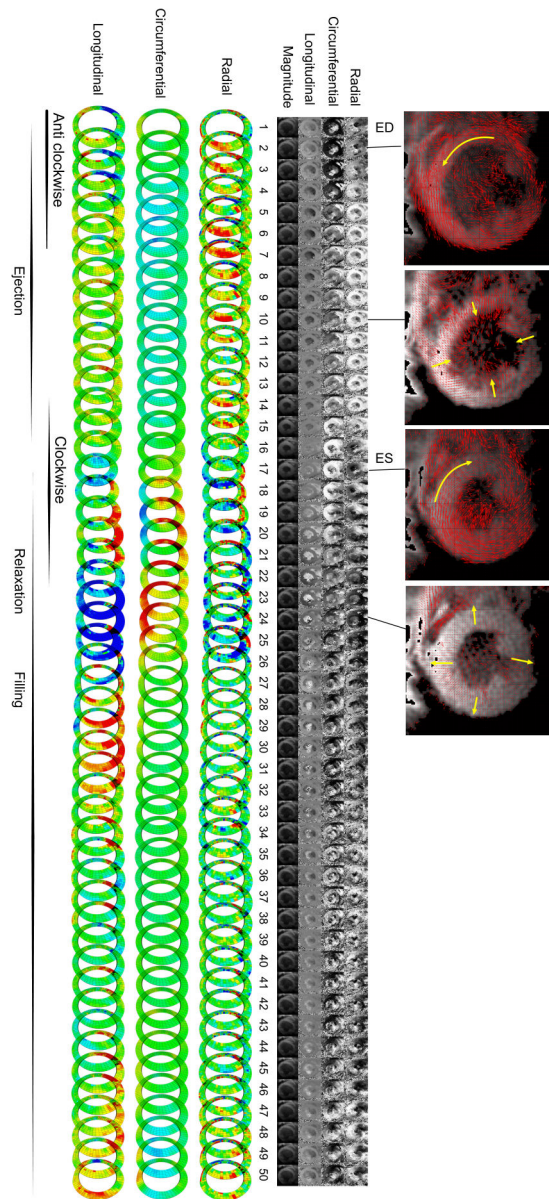


Figure 7.3: Example strain rate plots, with various stages of the heart cycle marked. Also shown are the magnitude images and velocity maps for all 50 phases. On the right are magnitude images from four time points of interest with in plane velocities overlaid as arrows.

7.3.2 Future studies

7.3.2.1 Comparison with Echocardiography

Echocardiography is routinely used in clinical practice and is an obvious modality to compare PVM with as it also can be used to measure myocardial velocities via TDI. Comparing the two techniques is not trivial as they work in different ways and have different advantages and disadvantages. Previous studies comparing the techniques have used different views for the two techniques (short axis for MRI and four chamber for TDI) (Delfino et al., 2006; Jung et al., 2004) but have attempted to analyse velocities from the same region of interest with both techniques. This is clearly difficult to achieve and could lead to different parts of the heart being compared. Despite this, good correlation has been found for both radial (correlation of velocity data $R=0.97$ in twenty nine volunteers, Jung et al. (2004)) and longitudinal ($R=0.86$ for longitudinal velocities in ten healthy subjects and ten patients with dyssynchrony, Delfino et al. (2006)) velocities. In both cases peak velocities were found to be higher when measured with PVM than with TDI, possibly because of the angle dependence of TDI measurements.

Speckle tracking presents a possible method of comparing the two techniques which is less prone to misregistration issues and which is not angle dependent. A comparison study of strain-rate values measured with PVM and speckle tracking will be carried out in healthy volunteers and in patients in collaboration with Professor Roxy Senior at the Royal Brompton Hospital and Professor Guang-Zhong Yang at Imperial College. The MRI acquisitions will emulate an echocardiographic clinical exam with both modalities acquiring three long axis views (two, three and four chamber) as well as short axis views. In this way all three components of strain-rate can be investigated and a full comparison of the techniques can be made.

7.3.2.2 Patient studies

So far only healthy subject data has been presented in this thesis. The navigator gated sequence presented in Chapter 4 is difficult to apply to patients as it requires cooperation and understanding in order for the biofeedback to work efficiently. Despite this, images have been acquired in three patients with HCM, although with reduced image quality. Colour plots for the three acquisitions can be seen in Figure 7.4 along with a healthy example for comparison.

As well as general lowering of velocities in all directions and throughout the cardiac cycle, some regional differences between these plots and the healthy colour plots can be seen. In particular S_R is highly homogeneous in the healthy subject example, with similar peak values across the whole myocardium. For the patients however this is not the case with lowered velocities seen in the hypertrophied regions (for example the anterior region of the third example). It is not clear how much of the remaining differences are due to the reduced image quality.

Unlike the navigator version, the breath-hold sequence allows the acquisition of PVM data without greatly extending scan time. Results from the mid slice of a DCM patient with a mildly dilated ventricle (end systolic volume (ESV) 96mL, end diastolic volume (EDV) 188mL, normal values for this age group 29-66mL and 99-179mL respectively (Manning and Pennell, 2010)) and slightly lowered ejection fraction of 49% (normal range 56-75% (Manning and Pennell, 2010)) and the mid slice of a DCM patient with a greatly dilated ventricle (ejection fraction 21%, ESV 258mL, EDV 326mL, age matched ranges are 58-76%, 29-74mL and 113-196mL respectively Manning and Pennell (2010)) have been analysed. Global peak velocities can be seen in Table 7.1 (basal and apical values for the early DCM patient are also shown) and Figure 7.5.

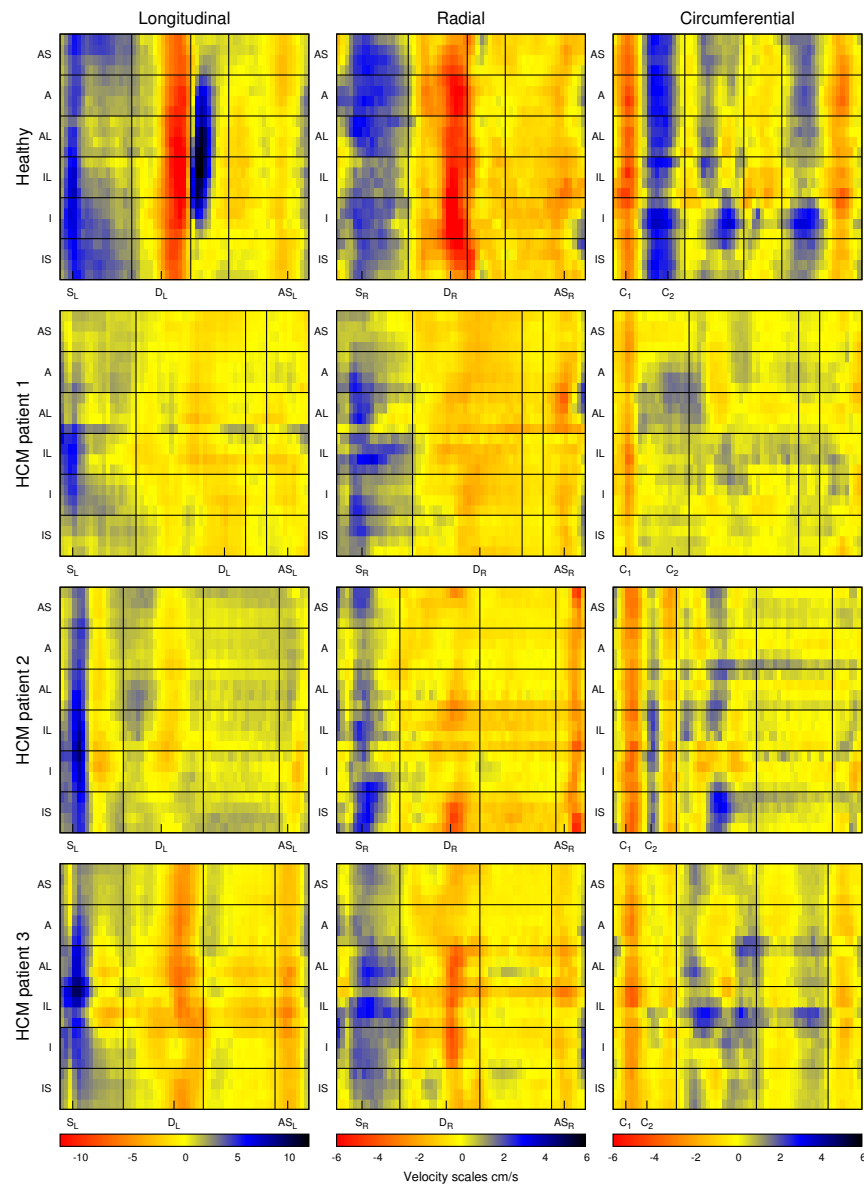


Figure 7.4: Example HCM colourplots acquired with the navigator gated sequence, with a healthy example for comparison.

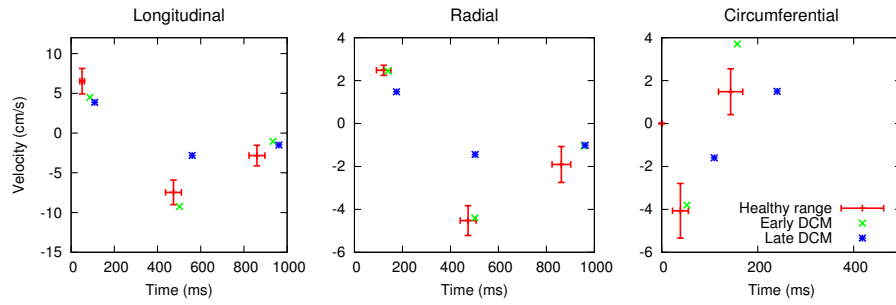


Figure 7.5: Peak and TTP values for DCM patients and healthy volunteers (mean $\pm$ SD shown).

	Early DCM base	Early DCM mid	Early DCM apex	Late DCM mid
S_L (cm/s)	6.42 (5.13 to 10.13)	4.50 (3.31 to 9.74)	5.63 (3.21 to 7.47)	3.87 (3.31 to 9.74)
D_L (cm/s)	-9.69 (-14.65 to -5.56)	-9.24 (-10.55 to -4.37)	-5.34 (-7.05 to -1.95)	-2.82 (-10.55 to -4.37)
AS_L (cm/s)	-2.22 (-6.26 to -1.93)	-0.64 (-5.42 to -0.24)	-0.30 (-3.27 to -0.39)	-1.5 (-5.42 to -0.24)
S_R (cm/s)	1.96 (1.86 to 2.82)	2.46 (2.01 to 2.96)	1.78 (1.76 to 2.72)	1.48 (2.01 to 2.96)
D_R (cm/s)	-5.24 (-6.38 to -3.00)	-4.40 (-5.92 to -3.13)	-4.56 (-6.09 to -3.31)	-1.44 (-5.92 to -3.13)
AS_R (cm/s)	-1.28 (-2.52 to -0.37)	-1.04 (-3.59 to -0.24)	-1.46 (-3.01 to -0.58)	-1.10 (-3.59 to -0.24)
C_1 (cm/s)	-4.90 (-6.41 to -0.58)	-3.82 (-6.61 to -1.52)	-4.64 (-6.29 to -1.90)	-1.60 (-6.61 to -1.52)
C_2 (cm/s)	3.58 (0.28 to 4.68)	3.74 (-0.66 to 3.62)	1.70 (-0.98 to 1.75)	1.52 (-0.66 to 3.62)
C_3 (cm/s)	-2.86 (-2.53 to -0.37)		2.48 (0.97 to 3.20)	

Table 7.1: Peak velocities in three slices from a DCM patient with a mildly dilated ventricle (early DCM) and the mid slice of a DCM patient with a greatly dilated ventricle (late DCM). 95% confidence intervals (ie mean healthy value $\pm$ 2SD) are shown in brackets and values outside those ranges are shown in bold.

Global peak velocities are within the healthy range for the early DCM patient while the late DCM patient shows reduced values (ie outside of the 95% confidence interval) in the longitudinal and radial directions.

Figure 7.6 shows regional colour plots for the two DCM patients alongside a healthy volunteer for comparison. While the early stage plots look fairly similar to the healthy example, the late stage DCM patient clearly has reduced veloci-

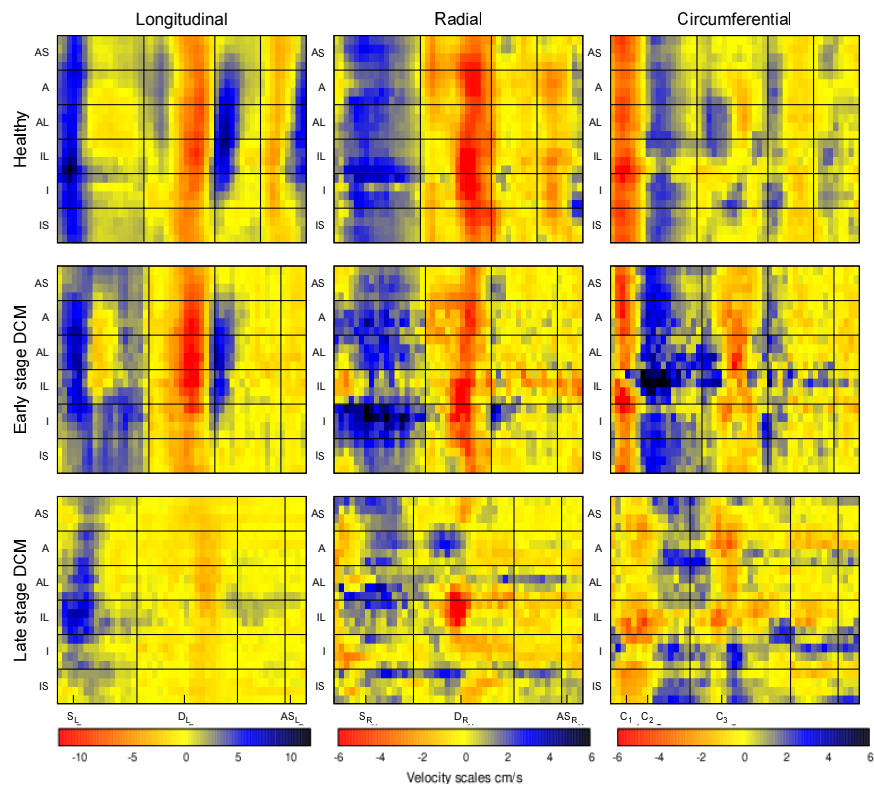


Figure 7.6: Colourmaps acquired in a patient with early DCM and a patient with late DCM, compared with a healthy volunteer.

ties in all directions. Diastolic radial relaxation is restricted to a small region in the lateral wall. This comparison also makes clearer the regional abnormalities of the early DCM patient, especially in the radial direction. Comparing colour plots side-by-side in this way could allow easy analysis of regional dysfunction.

A full study will be carried out on a suitable patient cohort. Sufferers of cardiomyopathies (DCM or HCM) are an obvious choice as they suffer from diastolic dysfunction in the early stages of disease and this technique could pick up dysfunction earlier than is currently possible in otherwise asymptomatic subjects who are likely to develop the disease.

7.4 Conclusion

The breath-hold technique presented in this thesis represents a step forward for tissue phase velocity mapping. Images can be acquired within an easily achievable breath-hold with good spatial and temporal resolution, and are reconstructed at the time of scanning. This allows the inclusion of three short axis slice acquisitions within a clinical workflow, and opens up the possibility of acquiring a full stack of short axis slices in a reasonable time. Tissue phase velocity mapping now has the potential to be included routinely in future clinical practice.

References

- Khaled Z. Abd-Elmoniem, Matthias Stuber, Nael F. Osman, and Jerry L. Prince. ZHARP: three-dimensional motion tracking from a single image plane. *Inf Process Med Imaging*, 19:639–651, 2005.
- C. B. Ahn, J. H. Kim, and Z. H. Cho. High-speed spiral-scan echo planar NMR imaging-I. *IEEE Trans Med Imaging*, 5(1):2–7, 1986. doi: 10.1109/TMI.1986.4307732. URL <http://dx.doi.org/10.1109/TMI.1986.4307732>.
- E. Ahunbay and J. G. Pipe. Rapid method for deblurring spiral MR images. *Magn Reson Med*, 44(3):491–494, Sep 2000.
- A. H. Aletras and H. Wen. Mixed echo train acquisition displacement encoding with stimulated echoes: an optimized DENSE method for in vivo functional imaging of the human heart. *Magn Reson Med*, 46(3):523–534, Sep 2001.
- A. H. Aletras, R. S. Balaban, and H. Wen. High-resolution strain analysis of the human heart with fast-DENSE. *J Magn Reson*, 140(1):41–57, Sep 1999a. doi: 10.1006/jmre.1999.1821. URL <http://dx.doi.org/10.1006/jmre.1999.1821>.
- A. H. Aletras, S. Ding, R. S. Balaban, and H. Wen. DENSE: displacement encoding with stimulated echoes in cardiac functional MRI. *J Magn Reson*, 137(1):247–252, Mar 1999b. doi: 10.1006/jmre.1998.1676. URL <http://dx.doi.org/10.1006/jmre.1998.1676>.

- Anthony H Aletras and Andrew E Arai. meta-DENSE complex acquisition for reduced intravoxel dephasing. *J Magn Reson*, 169 (2):246–249, Aug 2004. doi: 10.1016/j.jmr.2004.05.008. URL <http://dx.doi.org/10.1016/j.jmr.2004.05.008>.
- Anthony H Aletras, W. Patricia Ingkanisorn, Christine Mancini, and Andrew E Arai. DENSE with SENSE. *J Magn Reson*, 176 (1):99–106, Sep 2005. doi: 10.1016/j.jmr.2005.05.010. URL <http://dx.doi.org/10.1016/j.jmr.2005.05.010>.
- Anthony H Aletras, Gauri S Tilak, Alex Natanzon, Li-Yueh Hsu, Felix M Gonzalez, Robert F Hoyt, and Andrew E Arai. Retrospective determination of the area at risk for reperfused acute myocardial infarction with T2-weighted cardiac magnetic resonance imaging: histopathological and displacement encoding with stimulated echoes (DENSE) functional validations. *Circulation*, 113(15):1865–1870, Apr 2006. doi: 10.1161/CIRCULATIONAHA.105.576025. URL <http://dx.doi.org/10.1161/CIRCULATIONAHA.105.576025>.
- Renske Altena, Patrick J. Perik, Dirk J. van Veldhuisen, Elisabeth Ge de Vries, and Jourik A. Gietema. Cardiovascular toxicity caused by cancer treatment: strategies for early detection. *Lancet Oncol*, 10 (4):391–399, Apr 2009. doi: 10.1016/S1470-2045(09)70042-7. URL [http://dx.doi.org/10.1016/S1470-2045\(09\)70042-7](http://dx.doi.org/10.1016/S1470-2045(09)70042-7).
- Ertunc Altıok, Mirja Neizel, Sonja Tiemann, Vitali Krass, Kathrin Kuhr, Michael Becker, Christian Zwicker, Ralf Koos, Walter Lehmacher, Malte Kelm, Nikolaus Marx, and Rainer Hoffmann. Quantitative analysis of endocardial and epicardial left ventricular myocardial deformation-comparison of strain-encoded cardiac magnetic resonance imaging with two-dimensional speckle-tracking echocardiography. *J Am Soc Echocardiogr*, 25(11):1179–1188, Nov 2012. doi: 10.1016/j.echo.2012.07.019. URL <http://dx.doi.org/10.1016/j.echo.2012.07.019>.

- A. A. Amini, Y. Chen, R. W. Curwen, V. Mani, and J. Sun. Coupled B-snake grids and constrained thin-plate splines for analysis of 2-D tissue deformations from tagged MRI. *IEEE Trans Med Imaging*, 17(3):344–356, Jun 1998. doi: 10.1109/42.712124. URL <http://dx.doi.org/10.1109/42.712124>.
- A. A. Amini, Y. Chen, M. Elayyadi, and P. Radeva. Tag surface reconstruction and tracking of myocardial beads from SPAMM-MRI with parametric B-spline surfaces. *IEEE Trans Med Imaging*, 20(2):94–103, Feb 2001. doi: 10.1109/42.913176. URL <http://dx.doi.org/10.1109/42.913176>.
- Christopher P Appleton, Liv K Hatle, and Richard L Popp. Relation of transmitral flow velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. *Journal of the American College of Cardiology*, 12(2):426–440, 1988.
- A. E. Arai, C. C. Gaither, F. H. Epstein, R. S. Balaban, and S. D. Wolff. Myocardial velocity gradient imaging by phase contrast MRI with application to regional function in myocardial ischemia. *Magn Reson Med*, 42(1):98–109, Jul 1999. URL <http://onlinelibrary.wiley.com/doi/10.1002/%28SICI%291522-2594%28199907%2942:1>
- M. W. Ashford, W. Liu, S. J. Lin, P. Abraszewski, S. D. Caruthers, A. M. Connolly, X. Yu, and S. A. Wickline. Occult cardiac contractile dysfunction in dystrophin-deficient children revealed by cardiac magnetic resonance strain imaging. *Circulation*, 112(16):2462–2467, Oct 2005. doi: 10.1161/CIRCULATIONAHA.104.516716. URL <http://dx.doi.org/10.1161/CIRCULATIONAHA.104.516716>.
- D. J. Atkinson and R. R. Edelman. Cineangiography of the heart in a single breath hold with a segmented turboFLASH sequence. *Radiology*, 178(2):357–360, Feb 1991.

- L. Axel and L. Dougherty. MR imaging of motion with spatial modulation of magnetization. *Radiology*, 171(3):841–845, Jun 1989.
- L. Axel, R. C. Goncalves, and D. Bloomgarden. Regional heart wall motion: two-dimensional analysis and functional imaging with MR imaging. *Radiology*, 183(3):745–750, Jun 1992.
- Leon Axel, Albert Montillo, and Daniel Kim. Tagged magnetic resonance imaging of the heart: a survey. *Med Image Anal*, 9(4):376–393, Aug 2005. doi: 10.1016/j.media.2005.01.003. URL <http://dx.doi.org/10.1016/j.media.2005.01.003>.
- Jeroen J. Bax, Gabe B. Bleeker, Thomas H. Marwick, Sander G. Molhoek, Eric Boersma, Paul Steendijk, Ernst E. van der Wall, and Martin J. Schalij. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol*, 44(9):1834–1840, Nov 2004. doi: 10.1016/j.jacc.2004.08.016. URL <http://dx.doi.org/10.1016/j.jacc.2004.08.016>.
- G. M. Beache, V. J. Wedeen, R. M. Weisskoff, P. T. O’Gara, B. P. Poncelet, D. A. Chesler, T. J. Brady, B. R. Rosen, and R. E. Dinsmore. Intramural mechanics in hypertrophic cardiomyopathy: functional mapping with strain-rate MR imaging. *Radiology*, 197(1):117–124, Oct 1995. URL <http://radiology.rsna.org/content/197/1/117.long>.
- Philip J Beatty, Dwight G Nishimura, and John M Pauly. Rapid gridding reconstruction with a minimal oversampling ratio. *IEEE Trans Med Imaging*, 24(6):799–808, Jun 2005. doi: 10.1109/TMI.2005.848376. URL <http://dx.doi.org/10.1109/TMI.2005.848376>.
- N. G. Bellenger, M. I. Burgess, S. G. Ray, A. Lahiri, A. J. Coats, J. G. Cleland, and D. J. Pennell. Comparison of left ventricular ejection fraction and

- volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? *Eur Heart J*, 21(16):1387–1396, Aug 2000. doi: 10.1053/euhj.2000.2011. URL <http://dx.doi.org/10.1053/euhj.2000.2011>.
- King K. F. Zhou X. J. Bernstein, M. A. *Handbook of MRI Pulse Sequences*. Elsevier, 2004.
- M. A. Bernstein and Y. Ikezaki. Comparison of phase-difference and complex-difference processing in phase-contrast MR angiography. *J Magn Reson Imaging*, 1(6):725–729, 1991.
- M. A. Bernstein, M. Grgic, T. J. Brosnan, and N. J. Pelc. Reconstructions of phase contrast, phased array multicoil data. *Magn Reson Med*, 32(3):330–334, Sep 1994.
- M. A. Bernstein, X. J. Zhou, J. A. Polzin, K. F. King, A. Ganin, N. J. Pelc, and G. H. Glover. Concomitant gradient terms in phase contrast MR: analysis and correction. *Magn Reson Med*, 39(2):300–308, Feb 1998.
- Thorsten A. Bley, Oliver Wieben, Christopher J. Francois, Jean H. Brittain, and Scott B. Reeder. Fat and water magnetic resonance imaging. *J Magn Reson Imaging*, 31(1):4–18, Jan 2010. doi: 10.1002/jmri.21895. URL <http://dx.doi.org/10.1002/jmri.21895>.
- BD Bolster, Jr, E. R. McVeigh, and E. A. Zerhouni. Myocardial tagging in polar coordinates with use of striped tags. *Radiology*, 177(3):769–772, Dec 1990.
- Tonino Bombardini, Rosa Sicari, Elisabetta Bianchini, and Eugenio Picano. Abnormal shortened diastolic time length at increasing heart rates in patients with abnormal exercise-induced increase in pulmonary artery pressure. *Cardiovasc Ultrasound*, 9:36, 2011. doi: 10.1186/1476-7120-9-36. URL <http://dx.doi.org/10.1186/1476-7120-9-36>.

- R. O. Bonow, E. Lakatos, B. J. Maron, and S. E. Epstein. Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. *Circulation*, 84(4): 1625–1635, Oct 1991.
- D. J. Bryant, J. A. Payne, D. N. Firmin, and D. B. Longmore. Measurement of flow with NMR imaging using a gradient pulse and phase difference technique. *J Comput Assist Tomogr*, 8(4):588–593, Aug 1984.
- Gerald D Buckberg, Aman Mahajan, Bernd Jung, Michael Markl, Juergen Hennig, and Manel Ballester-Rodes. MRI myocardial motion and fiber tracking: a confirmation of knowledge from different imaging modalities. *Eur J Cardiothorac Surg*, 29 Suppl 1:S165–S177, Apr 2006. doi: 10.1016/j.ejcts.2006.02.064. URL <http://dx.doi.org/10.1016/j.ejcts.2006.02.064>.
- Loren P. Budge, Adam S. Helms, Michael Salerno, Christopher M. Kramer, Frederick H. Epstein, and Kenneth C. Bilchick. MR cine DENSE dyssynchrony parameters for the evaluation of heart failure: comparison with myocardial tissue tagging. *JACC Cardiovasc Imaging*, 5(8):789–797, Aug 2012. doi: 10.1016/j.jcmg.2011.12.024. URL <http://dx.doi.org/10.1016/j.jcmg.2011.12.024>.
- G. M. Bydder, J. M. Pennock, R. E. Steiner, S. Khenia, J. A. Payne, and I. R. Young. The short TI inversion recovery sequence—an approach to MR imaging of the abdomen. *Magn Reson Imaging*, 3(3):251–254, 1985.
- A. Caprihan, S. A. Altobelli, and E. Benitez-Read. Flow-velocity imaging from linear regression of phase images with techniques for reducing eddy-current effects. *J Magn Reson*, 90:71–89, 1990.
- B. A. Carabello. Timing of valve replacement in aortic stenosis. Moving closer to perfection. *Circulation*, 95(9):2241–2243, May 1997.

- Ernesto Castillo, Nael F. Osman, Boaz D. Rosen, Iman El-Shehaby, Li Pan, Michael Jerosch-Herold, Shenghan Lai, David A. Bluemke, and Joao A C. Lima. Quantitative assessment of regional myocardial function with MR-tagging in a multi-center study: interobserver and intraobserver agreement of fast strain analysis with Harmonic Phase (HARP) MRI. *J Cardiovasc Magn Reson*, 7(5):783–791, 2005.
- Manuel D Cerqueira, Neil J Weissman, Vasken Dilsizian, Alice K Jacobs, Sanjiv Kaul, Warren K Laskey, Dudley J Pennell, John A Rumberger, Thomas Ryan, Mario S Verani, American Heart Association Writing Group on Myocardial Segmentation, and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*, 105(4):539–542, Jan 2002.
- Alexander Chernobelsky, Oleg Shubayev, Cindy R Comeau, and Steven D Wolff. Baseline correction of phase contrast images improves quantification of blood flow in the great vessels. *J Cardiovasc Magn Reson*, 9(4):681–685, 2007. doi: 10.1080/10976640601187588. URL <http://dx.doi.org/10.1080/10976640601187588>.
- J. M. Chia, S. E. Fischer, S. A. Wickline, and C. H. Lorenz. Performance of QRS detection for cardiac magnetic resonance imaging with a novel vectorcardiographic triggering method. *J Magn Reson Imaging*, 12(5):678–688, Nov 2000.
- M. L. Chuang, M. G. Hibberd, C. J. Salton, R. A. Beaudin, M. F. Riley, R. A. Parker, P. S. Douglas, and W. J. Manning. Importance of imaging method over imaging modality in noninvasive determination of left ventricular volumes and ejection fraction: assessment by two- and three-dimensional echocardiography and magnetic resonance imaging. *J Am Coll Cardiol*, 35(2):477–484, Feb 2000.

- Charles S. Chung, Mustafa Karamanoglu, and Sandor J. Kovacs. Duration of diastole and its phases as a function of heart rate during supine bicycle exercise. *Am J Physiol Heart Circ Physiol*, 287(5): H2003–H2008, Nov 2004. doi: 10.1152/ajpheart.00404.2004. URL <http://dx.doi.org/10.1152/ajpheart.00404.2004>.
- H. E. Cline, C. J. Hardy, and J. D. Pearlman. Fast MR cardiac profiling with two-dimensional selective pulses. *Magn Reson Med*, 17(2):390–401, Feb 1991.
- Ion Codreanu, Matthew D Robson, Stephen J Golding, Bernd A Jung, Kieran Clarke, and Cameron J Holloway. Longitudinally and circumferentially directed movements of the left ventricle studied by cardiovascular magnetic resonance phase contrast velocity mapping. *J Cardiovasc Magn Reson*, 12:48, 2010. doi: 10.1186/1532-429X-12-48. URL <http://dx.doi.org/10.1186/1532-429X-12-48>.
- Ion Codreanu, Tammy J. Pegg, Joseph B. Selvanayagam, Matthew D. Robson, Oliver J. Rider, Constantin A. Dasanu, Bernd A. Jung, David P. Taggart, Kieran Clarke, and Cameron J. Holloway. Details of left ventricular remodeling and the mechanism of paradoxical ventricular septal motion after coronary artery bypass graft surgery. *J Invasive Cardiol*, 23(7):276–282, Jul 2011a.
- Ion Codreanu, Matthew D. Robson, Oliver J. Rider, Tammy J. Pegg, Bernd A. Jung, Constantin A. Dasanu, Kieran Clarke, and Cameron J. Holloway. Chasing the reflected wave back into the heart: a new hypothesis while the jury is still out. *Vasc Health Risk Manag*, 7:365–373, 2011b. doi: 10.2147/VHRM.S20845. URL <http://dx.doi.org/10.2147/VHRM.S20845>.
- J. N. Cohn, G. R. Johnson, R. Shabetai, H. Loeb, F. Tristani, T. Rector, R. Smith, and R. Fletcher. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure. The V-HeFT VA Cooperative Studies Group. *Circulation*, 87(6 Suppl):VI5–V16, Jun 1993.

- J. De Backer, D. Matthys, T. C. Gillebert, A. De Paepe, and J. De Sutter. The use of Tissue Doppler Imaging for the assessment of changes in myocardial structure and function in inherited cardiomyopathies. *Eur J Echocardiogr*, 6(4):243–250, Aug 2005. doi: 10.1016/j.euje.2004.09.010. URL <http://dx.doi.org/10.1016/j.euje.2004.09.010>.
- Lioe-Fee de Geus-Oei, Annelies M C. Mavinkurve-Groothuis, Louise Bellersen, Martin Gotthardt, Wim J G. Oyen, Livia Kapusta, and Hanneke W M. van Laarhoven. Scintigraphic techniques for early detection of cancer treatment-induced cardiotoxicity. *J Nucl Med*, 52(4):560–571, Apr 2011. doi: 10.2967/jnumed.110.082784. URL <http://dx.doi.org/10.2967/jnumed.110.082784>.
- Benedicte M A Delattre, Robin M Heidemann, Lindsey A Crowe, Jean-Paul Vallee, and Jean-Noel Hyacinthe. Spiral demystified. *Magn Reson Imaging*, 28(6):862–881, Jul 2010. doi: 10.1016/j.mri.2010.03.036. URL <http://dx.doi.org/10.1016/j.mri.2010.03.036>.
- Jana G Delfino, Mohit Bhasin, Robert Cole, Robert L Eisner, John Merlino, Angel R Leon, and John N Oshinski. Comparison of myocardial velocities obtained with magnetic resonance phase velocity mapping and tissue Doppler imaging in normal subjects and patients with left ventricular dyssynchrony. *J Magn Reson Imaging*, 24(2):304–311, Aug 2006. doi: 10.1002/jmri.20641. URL <http://dx.doi.org/10.1002/jmri.20641>.
- Jana G Delfino, Brandon K Fornwalt, Robert L Eisner, Angel R Leon, and John N Oshinski. Determination of transmural, endocardial, and epicardial radial strain and strain rate from phase contrast MR velocity data. *J Magn Reson Imaging*, 27(3):522–528, Mar 2008a. doi: 10.1002/jmri.21211. URL <http://dx.doi.org/10.1002/jmri.21211>.
- Jana G Delfino, Kevin R Johnson, Robert L Eisner, Susan Eder, Angel R Leon, and John N Oshinski. Three-directional myocardial phase-contrast tissue ve-

- locity MR imaging with navigator-echo gating: in vivo and in vitro study. *Radiology*, 246(3):917–925, Mar 2008b. doi: 10.1148/radiol.2463062155. URL <http://dx.doi.org/10.1148/radiol.2463062155>.
- P. A. Dendale, P. R. Franken, G. J. Waldman, D. G. De Moor, D. A. Tombeur, P. F. Block, and A. De Roos. Low-dosage dobutamine magnetic resonance imaging as an alternative to echocardiography in the detection of viable myocardium after acute infarction. *Am Heart J*, 130(1):134–140, Jul 1995.
- Anagha Deshmane, Vikas Gulani, Mark A. Griswold, and Nicole Seiberlich. Parallel MR imaging. *J Magn Reson Imaging*, 36(1):55–72, Jul 2012. doi: 10.1002/jmri.23639. URL <http://dx.doi.org/10.1002/jmri.23639>.
- W. T. Dixon. Simple proton spectroscopic imaging. *Radiology*, 153(1):189–194, Oct 1984.
- Jennifer L. Dorosz, Dennis C. Lezotte, David A. Weitzenkamp, Larry A. Allen, and Ernesto E. Salcedo. Performance of 3-dimensional echocardiography in measuring left ventricular volumes and ejection fraction: a systematic review and meta-analysis. *J Am Coll Cardiol*, 59(20):1799–1808, May 2012. doi: 10.1016/j.jacc.2012.01.037. URL <http://dx.doi.org/10.1016/j.jacc.2012.01.037>.
- L. Dougherty, J. C. Asmuth, A. S. Blom, L. Axel, and R. Kumar. Validation of an optical flow method for tag displacement estimation. *IEEE Trans Med Imaging*, 18(4):359–363, Apr 1999. doi: 10.1109/42.768845. URL <http://dx.doi.org/10.1109/42.768845>.
- M. Drangova, Y. Zhu, and N. J. Pelc. Effect of artifacts due to flowing blood on the reproducibility of phase-contrast measurements of myocardial motion. *J Magn Reson Imaging*, 7(4):664–668, 1997.
- R. R. Edelman, B. Wallner, A. Singer, D. J. Atkinson, and S. Saini. Segmented

- turboFLASH: method for breath-hold MR imaging of the liver with flexible contrast. *Radiology*, 177(2):515–521, Nov 1990.
- R. R. Edelman, D. Chien, and D. Kim. Fast selective black blood MR imaging. *Radiology*, 181(3):655–660, Dec 1991.
- Thor Edvardsen, Robert Detrano, Boaz D. Rosen, J Jeffrey Carr, Kiang Liu, Shenghan Lai, Steven Shea, Li Pan, David A. Bluemke, and Joao A C. Lima. Coronary artery atherosclerosis is related to reduced regional left ventricular function in individuals without history of clinical cardiovascular disease: the Multiethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol*, 26(1):206–211, Jan 2006a. doi: 10.1161/01.ATV.0000194077.23234.ae. URL <http://dx.doi.org/10.1161/01.ATV.0000194077.23234.ae>.
- Thor Edvardsen, Boaz D Rosen, Li Pan, Michael Jerosch-Herold, Shenghan Lai, W. Gregory Hundley, Shantanu Sinha, Richard A Kronmal, David A Bluemke, and Joao A C Lima. Regional diastolic dysfunction in individuals with left ventricular hypertrophy measured by tagged magnetic resonance imaging—the Multi-Ethnic Study of Atherosclerosis (MESA). *Am Heart J*, 151(1):109–114, Jan 2006b. doi: 10.1016/j.ahj.2005.02.018. URL <http://dx.doi.org/10.1016/j.ahj.2005.02.018>.
- R. L. Ehman, M. T. McNamara, M. Pallack, H. Hricak, and C. B. Higgins. Magnetic resonance imaging with respiratory gating: techniques and advantages. *AJR Am J Roentgenol*, 143(6):1175–1182, Dec 1984. doi: 10.2214/ajr.143.6.1175. URL <http://dx.doi.org/10.2214/ajr.143.6.1175>.
- Richard L Ehman and JP Felmlee. Adaptive technique for high-definition MR imaging of moving structures. *Radiology*, 173(1):255–263, 1989. URL <http://radiology.rsna.org/content/173/1/255.short>.
- Daniel B. Ennis, Frederick H. Epstein, Peter Kellman, Lamah Fananapazir, Elliot R. McVeigh, and Andrew E. Arai. Assessment of regional systolic and

- diastolic dysfunction in familial hypertrophic cardiomyopathy using MR tagging. *Magn Reson Med*, 50(3):638–642, Sep 2003. doi: 10.1002/mrm.10543. URL <http://dx.doi.org/10.1002/mrm.10543>.
- Frederick H Epstein and Wesley D Gilson. Displacement-encoded cardiac MRI using cosine and sine modulation to eliminate (CANSEL) artifact-generating echoes. *Magn Reson Med*, 52(4):774–781, Oct 2004. doi: 10.1002/mrm.20232. URL <http://dx.doi.org/10.1002/mrm.20232>.
- D. A. Feinberg, J. C. Hoenninger, L. E. Crooks, L. Kaufman, J. C. Watts, and M. Arakawa. Inner volume MR imaging: technical concepts and their application. *Radiology*, 156(3):743–747, Sep 1985.
- J. P. Felmlee and R. L. Ehman. Spatial presaturation: a method for suppressing flow artifacts and improving depiction of vascular anatomy in MR imaging. *Radiology*, 164(2):559–564, Aug 1987.
- Li Feng, Robert Donnino, James Babb, Leon Axel, and Daniel Kim. Numerical and in vivo validation of fast cine displacement-encoded with stimulated echoes (DENSE) MRI for quantification of regional cardiac function. *Magn Reson Med*, 62(3):682–690, Sep 2009. doi: 10.1002/mrm.22045. URL <http://dx.doi.org/10.1002/mrm.22045>.
- Li Feng, Monvadi B. Srichai, Ruth P. Lim, Alexis Harrison, Wilson King, Ganesh Adluru, Edward V R. Dibella, Daniel K. Sodickson, Ricardo Otazo, and Daniel Kim. Highly accelerated real-time cardiac cine MRI using k-t SPARSE-SENSE. *Magn Reson Med*, Aug 2012. doi: 10.1002/mrm.24440. URL <http://dx.doi.org/10.1002/mrm.24440>.
- Veronica Rolim S. Fernandes, Joseph F. Polak, Susan Cheng, Boaz D. Rosen, Benilton Carvalho, Khurram Nasir, Robyn McClelland, Gregory Hundley, Greg Pearson, Daniel H. O’Leary, David A. Bluemke, and Joao A C. Lima. Arterial stiffness is associated with regional ventricular systolic and diastolic dys-

- function: the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol*, 28(1):194–201, Jan 2008. doi: 10.1161/ATVBAHA.107.156950. URL <http://dx.doi.org/10.1161/ATVBAHA.107.156950>.
- S. E. Fischer, G. C. McKinnon, S. E. Maier, and P. Boesiger. Improved myocardial tagging contrast. *Magn Reson Med*, 30(2):191–200, Aug 1993.
- S. E. Fischer, G. C. McKinnon, M. B. Scheidegger, W. Prins, D. Meier, and P. Boesiger. True myocardial motion tracking. *Magn Reson Med*, 31(4):401–413, Apr 1994.
- Daniela Föll, Bernd Jung, Felix Staehle, Elfriede Schilli, Christoph Bode, Jürgen Hennig, and Michael Markl. Visualization of multidirectional regional left ventricular dynamics by high-temporal-resolution tissue phase mapping. *J Magn Reson Imaging*, 29(5):1043–1052, May 2009. doi: 10.1002/jmri.21634. URL <http://dx.doi.org/10.1002/jmri.21634>.
- Daniela Föll, Bernd Jung, Elfriede Schilli, Felix Staehle, Annette Geibel, Jürgen Hennig, Christoph Bode, and Michael Markl. Magnetic resonance tissue phase mapping of myocardial motion: new insight in age and gender. *Circ Cardiovasc Imaging*, 3(1):54–64, Jan 2010. doi: 10.1161/CIRCIMAGING.108.813857. URL <http://dx.doi.org/10.1161/CIRCIMAGING.108.813857>.
- T. K. Foo, M. A. Bernstein, A. M. Aisen, R. J. Hernandez, B. D. Collick, and T. Bernstein. Improved ejection fraction and flow velocity estimates with use of view sharing and uniform repetition time excitation with fast cardiac techniques. *Radiology*, 195(2):471–478, May 1995.
- A. F. Frangi, W. J. Niessen, and M. A. Viergever. Three-dimensional modeling for functional analysis of cardiac images: a review. *IEEE Trans Med Imaging*, 20(1):2–25, Jan 2001. doi: 10.1109/42.906421. URL <http://dx.doi.org/10.1109/42.906421>.

- J. Garot, D. A. Bluemke, N. F. Osman, C. E. Rochitte, E. R. McVeigh, E. A. Zerhouni, J. L. Prince, and J. A. Lima. Fast determination of regional myocardial strain fields from tagged cardiac images using harmonic phase MRI. *Circulation*, 101(9):981–988, Mar 2000.
- Jerome Garot, Joao A C Lima, Bernhard L Gerber, Smita Sampath, Kathy C Wu, David A Bluemke, Jerry L Prince, and Nael F Osman. Spatially resolved imaging of myocardial function with strain-encoded MR: comparison with delayed contrast-enhanced MR imaging after myocardial infarction. *Radiology*, 233(2):596–602, Nov 2004. doi: 10.1148/radiol.2332031676. URL <http://dx.doi.org/10.1148/radiol.2332031676>.
- Peter D Gatehouse, Marijn P Rolf, Martin J Graves, Mark Bm Hofman, John Totman, Beat Werner, Rebecca A Quest, Yingmin Liu, Jochen von Spiczak, Matthias Dieringer, David N Firmin, Albert van Rossum, Massimo Lombardi, Juerg Schwitter, Jeanette Schulz-Menger, and Philip J Kilner. Flow measurement by cardiovascular magnetic resonance: a multi-centre multi-vendor study of background phase offset errors that can compromise the accuracy of derived regurgitant or shunt flow measurements. *J Cardiovasc Magn Reson*, 12:5, 2010. doi: 10.1186/1532-429X-12-5. URL <http://dx.doi.org/10.1186/1532-429X-12-5>.
- Peter D. Gatehouse, Marijn P. Rolf, Karin Markenroth Bloch, Martin J. Graves, Philip J. Kilner, David N. Firmin, and Mark B M. Hofman. A multi-center inter-manufacturer study of the temporal stability of phase-contrast velocity mapping background offset errors. *J Cardiovasc Magn Reson*, 14:72, 2012. doi: 10.1186/1532-429X-14-72. URL <http://dx.doi.org/10.1186/1532-429X-14-72>.
- Wesley D Gilson, Zequan Yang, Brent A French, and Frederick H Epstein. Complementary displacement-encoded MRI for contrast-enhanced infarct detection and quantification of myocardial function in mice. *Magn Re-*

- son Med*, 51(4):744–752, Apr 2004. doi: 10.1002/mrm.20003. URL <http://dx.doi.org/10.1002/mrm.20003>.
- Wesley D Gilson, Zequan Yang, Brent A French, and Frederick H Epstein. Measurement of myocardial mechanics in mice before and after infarction using multislice displacement-encoded MRI with 3D motion encoding. *Am J Physiol Heart Circ Physiol*, 288(3):H1491–H1497, Mar 2005. doi: 10.1152/ajpheart.00632.2004. URL <http://dx.doi.org/10.1152/ajpheart.00632.2004>.
- G. H. Glover. Multipoint Dixon technique for water and fat proton and susceptibility imaging. *J Magn Reson Imaging*, 1(5):521–530, 1991.
- G. H. Glover and J. M. Pauly. Projection reconstruction techniques for reduction of motion effects in MRI. *Magn Reson Med*, 28(2):275–289, Dec 1992.
- G. H. Glover and E. Schneider. Three-point Dixon technique for true water/fat decomposition with B0 inhomogeneity correction. *Magn Reson Med*, 18(2):371–383, Apr 1991.
- John Gorcsan, 3rd and Hidekazu Tanaka. Echocardiographic assessment of myocardial strain. *J Am Coll Cardiol*, 58(14):1401–1413, Sep 2011. doi: 10.1016/j.jacc.2011.06.038. URL <http://dx.doi.org/10.1016/j.jacc.2011.06.038>.
- Marco J W Götte, Tjeerd Germans, Iris K Rüssel, Jaco J M Zwanenburg, J. Tim Marcus, Albert C van Rossum, and Dirk J van Veldhuisen. Myocardial strain and torsion quantified by cardiovascular magnetic resonance tissue tagging: studies in normal and impaired left ventricular function. *J Am Coll Cardiol*, 48(10):2002–2011, Nov 2006. doi: 10.1016/j.jacc.2006.07.048. URL <http://dx.doi.org/10.1016/j.jacc.2006.07.048>.
- Mark A Griswold, Peter M Jakob, Robin M Heidemann, Mathias Nittka, Vladimir Jellus, Jianmin Wang, Berthold Kiefer, and Axel Haase. Gener-

- alized autocalibrating partially parallel acquisitions (GRAPPA). *Magn Reson Med*, 47(6):1202–1210, Jun 2002. doi: 10.1002/mrm.10171. URL <http://dx.doi.org/10.1002/mrm.10171>.
- Frank Grothues, Gillian C. Smith, James C C. Moon, Nicholas G. Bellenger, Peter Collins, Helmut U. Klein, and Dudley J. Pennell. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol*, 90(1):29–34, Jul 2002.
- Frank Grothues, James C. Moon, Nicholas G. Bellenger, Gillian S. Smith, Helmut U. Klein, and Dudley J. Pennell. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. *Am Heart J*, 147(2):218–223, Feb 2004. doi: 10.1016/j.ahj.2003.10.005. URL <http://dx.doi.org/10.1016/j.ahj.2003.10.005>.
- Matthias Gutberlet, Kerstin Schwinge, Patrick Freyhardt, Birgit Spors, Matthias Grothoff, Timm Denecke, Lutz Lidemann, Ralph Noeske, Thoralf Nienendorf, and Roland Felix. Influence of high magnetic field strengths and parallel acquisition strategies on image quality in cardiac 2D CINE magnetic resonance imaging: comparison of 1.5 T vs. 3.0 T. *Eur Radiol*, 15(8):1586–1597, Aug 2005. doi: 10.1007/s00330-005-2768-z. URL <http://dx.doi.org/10.1007/s00330-005-2768-z>.
- Juan Luis Gutierrez-Chico, Jose Luis Zamorano, Leopoldo Perez de Isla, Miguel Orejas, Carlos Almeria, Jose Luis Rodrigo, Joaquin Ferreiras, Viviana Serra, and Carlos Macaya. Comparison of left ventricular volumes and ejection fractions measured by three-dimensional echocardiography versus by two-dimensional echocardiography and cardiac magnetic resonance in patients with various cardiomyopathies. *Am J Cardiol*, 95(6):809–813, Mar 2005. doi: 10.1016/j.amjcard.2004.11.046. URL <http://dx.doi.org/10.1016/j.amjcard.2004.11.046>.

- M. A. Guttman, J. L. Prince, and E. R. McVeigh. Tag and contour detection in tagged MR images of the left ventricle. *IEEE Trans Med Imaging*, 13(1):74–88, 1994. doi: 10.1109/42.276146. URL <http://dx.doi.org/10.1109/42.276146>.
- A. Haase, J. Frahm, W. Hönicke, and D. Matthaei. ^1H NMR chemical shift selective (CHESS) imaging. *Phys Med Biol*, 30(4):341–344, Apr 1985.
- Ashraf Hamdan, Thomas Thouet, Sebastian Kelle, Kelle Sebastian, Ingo Paetsch, Rolf Gebker, Ernst Wellnhofer, Bernhard Schnackenburg, Ahmed S Fahmy, Nael F Osman, and Eckart Fleck. Regional right ventricular function and timing of contraction in healthy volunteers evaluated by strain-encoded MRI. *J Magn Reson Imaging*, 28(6):1379–1385, Dec 2008. doi: 10.1002/jmri.21526. URL <http://dx.doi.org/10.1002/jmri.21526>.
- Ashraf Hamdan, Thomas Thouet, Sebastian Kelle, Ernst Wellnhofer, Ingo Paetsch, Rolf Gebker, Bernhard Schnackenburg, Ahmed S Fahmy, Nael F Osman, Axel Bornstedt, and Eckart Fleck. Strain-encoded MRI to evaluate normal left ventricular function and timing of contraction at 3.0 Tesla. *J Magn Reson Imaging*, 29(4):799–808, Apr 2009. doi: 10.1002/jmri.21684. URL <http://dx.doi.org/10.1002/jmri.21684>.
- Michael S. Hansen, Thomas S. Sørensen, Andrew E. Arai, and Peter Kellman. Retrospective reconstruction of high temporal resolution cine images from real-time MRI using iterative motion correction. *Magn Reson Med*, 68(3):741–750, Sep 2012. doi: 10.1002/mrm.23284. URL <http://dx.doi.org/10.1002/mrm.23284>.
- Michael Schacht Hansen and Thomas Sangild Sørensen. Gadgetron: an open source framework for medical image reconstruction. *Magn Reson Med*, 69(6):1768–1776, Jun 2013. doi: 10.1002/mrm.24389. URL <http://dx.doi.org/10.1002/mrm.24389>.

- S. Hassan and P. Turner. Systolic time intervals: a review of the method in the non-invasive investigation of cardiac function in health, disease and clinical pharmacology. *Postgrad Med J*, 59(693):423–434, Jul 1983.
- Robin M. Heidemann, Mark A. Griswold, Nicole Seiberlich, Gunnar Krüger, Stephan A R. Kannengiesser, Berthold Kiefer, Graham Wiggins, Lawrence L. Wald, and Peter M. Jakob. Direct parallel image reconstructions for spiral trajectories using GRAPPA. *Magn Reson Med*, 56(2):317–326, Aug 2006. doi: 10.1002/mrm.20951. URL <http://dx.doi.org/10.1002/mrm.20951>.
- Thomas Helle-Valle, Jonas Crosby, Thor Edvardsen, Erik Lyseggen, Brage H. Amundsen, Hans-Jürgen Smith, Boaz D. Rosen, Joao A C. Lima, Hans Torp, Halfdan Ihlen, and Otto A. Smiseth. New noninvasive method for assessment of left ventricular rotation: speckle tracking echocardiography. *Circulation*, 112(20):3149–3156, Nov 2005. doi: 10.1161/CIRCULATIONAHA.104.531558. URL <http://dx.doi.org/10.1161/CIRCULATIONAHA.104.531558>.
- J. Hennig, B. Schneider, S. Peschl, M. Markl, T. Krause, and J. Laubenberger. Analysis of myocardial motion based on velocity measurements with a black blood prepared segmented gradient-echo sequence: methodology and applications to normal volunteers and patients. *J Magn Reson Imaging*, 8(4):868–877, 1998.
- Daniel A Herzka, Michael A Guttman, and Elliot R McVeigh. Myocardial tagging with SSFP. *Magn Reson Med*, 49(2):329–340, Feb 2003. doi: 10.1002/mrm.10361. URL <http://dx.doi.org/10.1002/mrm.10361>.
- Aaron T Hess, Xiaodong Zhong, Bruce S Spottiswoode, Frederick H Epstein, and Ernesta M Meintjes. Myocardial 3D strain calculation by combining cine displacement encoding with stimulated echoes (DENSE) and cine strain encoding (SENC) imaging. *Magn Reson Med*, 62(1):77–84, Jul 2009. doi: 10.1002/mrm.21984. URL <http://dx.doi.org/10.1002/mrm.21984>.

- Magnus Rudolph Hestenes and Eduard Stiefel. Methods of conjugate gradients for solving linear systems, 1952.
- Martin Heuschmid, Julia K. Rothfuss, Stephen Schroeder, Michael Fenchel, Norbert Stauder, Christof Burgstahler, Andreas Franow, Ronald S. Kuzo, Axel Kuettner, Stephan Miller, Claus D. Claussen, and Andreas F. Kopp. Assessment of left ventricular myocardial function using 16-slice multidetector-row computed tomography: comparison with magnetic resonance imaging and echocardiography. *Eur Radiol*, 16(3):551–559, Mar 2006. doi: 10.1007/s00330-005-0015-2. URL <http://dx.doi.org/10.1007/s00330-005-0015-2>.
- C. B. Higgins, BF Byrd, 2nd, M. T. McNamara, P. Lanzer, M. J. Lipton, E. Botvinick, N. B. Schiller, L. E. Crooks, and L. Kaufman. Magnetic resonance imaging of the heart: a review of the experience in 172 subjects. *Radiology*, 155(3):671–679, Jun 1985.
- Rainer Hoffmann, Ertunc Altıok, Bernd Nowak, Nicole Heussen, Harald Köhl, Hans Jürgen Kaiser, Udalrich Böll, and Peter Hanrath. Strain rate measurement by doppler echocardiography allows improved assessment of myocardial viability inpatients with depressed left ventricular function. *J Am Coll Cardiol*, 39(3):443–449, Feb 2002.
- A. E. Holland, J. W. Goldfarb, and R. R. Edelman. Diaphragmatic and cardiac motion during suspended breathing: preliminary experience and implications for breath-hold MR imaging. *Radiology*, 209(2):483–489, Nov 1998.
- Brian J Holland, Beth F Printz, and Wyman W Lai. Baseline correction of phase-contrast images in congenital cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*, 12:11, 2010. doi: 10.1186/1532-429X-12-11. URL <http://dx.doi.org/10.1186/1532-429X-12-11>.

- El-Sayed H Ibrahim, Matthias Stuber, Ahmed S Fahmy, Khaled Z Abd-Elmoniem, Tetsuo Sasano, M. Roselle Abraham, and Nael F Osman. Real-time MR imaging of myocardial regional function using strain-encoding (SENC) with tissue through-plane motion tracking. *J Magn Reson Imaging*, 26(6):1461–1470, Dec 2007a. doi: 10.1002/jmri.21125. URL <http://dx.doi.org/10.1002/jmri.21125>.
- El-Sayed H Ibrahim, Matthias Stuber, Dara L Kraitchman, Robert G Weiss, and Nael F Osman. Combined functional and viability cardiac MR imaging in a single breathhold. *Magn Reson Med*, 58(4):843–849, Oct 2007b. doi: 10.1002/mrm.21390. URL <http://dx.doi.org/10.1002/mrm.21390>.
- El-Sayed H Ibrahim, Robert G Weiss, Matthias Stuber, Amy E Spooner, and Nael F Osman. Identification of different heart tissues from MRI C-SENC images using an unsupervised multi-stage fuzzy clustering technique. *J Magn Reson Imaging*, 28(2):519–526, Aug 2008. doi: 10.1002/jmri.21452. URL <http://dx.doi.org/10.1002/jmri.21452>.
- A. E. Iskandrian, G. Germano, W. VanDecker, J. D. Ogilby, N. Wolf, R. Mintz, and D. S. Berman. Validation of left ventricular volume measurements by gated SPECT 99mTc-labeled sestamibi imaging. *J Nucl Cardiol*, 5(6):574–578, 1998.
- P. Jhooti, P. D. Gatehouse, J. Keegan, N. H. Bunce, A. M. Taylor, and D. N. Firmin. Phase ordering with automatic window selection (PAWS): a novel motion-resistant technique for 3D coronary imaging. *Magn Reson Med*, 43(3):470–480, Mar 2000.
- P. Jhooti, J. Keegan, and D. N. Firmin. A fully automatic and highly efficient navigator gating technique for high-resolution free-breathing acquisitions: Continuously adaptive windowing strategy. *Magn Reson Med*, 64(4):1015–1026, Oct 2010. doi: 10.1002/mrm.22491. URL <http://dx.doi.org/10.1002/mrm.22491>.

- P. Jhooti, T. Haas, N. Kawel, J. Bremerich, J. Keegan, and K. Scheffler. Use of respiratory biofeedback and CLAWS for increased navigator efficiency for imaging the thoracic aorta. *Magn Reson Med*, 66(6):1666–1673, Dec 2011. doi: 10.1002/mrm.22945. URL <http://dx.doi.org/10.1002/mrm.22945>.
- Bernd Jung, Britta Schneider, Michael Markl, Bernward Saurbier, Annette Geibel, and Juergen Hennig. Measurement of left ventricular velocities: phase contrast MRI velocity mapping versus tissue-doppler-ultrasound in healthy volunteers. *J Cardiovasc Magn Reson*, 6(4):777–783, 2004.
- Bernd Jung, Daniela Föll, Petra Böttler, Steffen Petersen, Jürgen Hennig, and Michael Markl. Detailed analysis of myocardial motion in volunteers and patients using high-temporal-resolution MR tissue phase mapping. *J Magn Reson Imaging*, 24(5):1033–1039, Nov 2006a. doi:10.1002/jmri.20703. URL <http://dx.doi.org/10.1002/jmri.20703>.
- Bernd Andre Jung, Björn W Kreher, Michael Markl, and Jürgen Hennig. Visualization of tissue velocity data from cardiac wall motion measurements with myocardial fiber tracking: principles and implications for cardiac fiber structures. *Eur J Cardiothorac Surg*, 29 Suppl 1:S158–S164, Apr 2006b. doi: 10.1016/j.ejcts.2006.02.060. URL <http://dx.doi.org/10.1016/j.ejcts.2006.02.060>.
- Hideaki Kanzaki, Satoshi Nakatani, Naoaki Yamada, Shin-Ichi Urayama, Kunio Miyatake, and Masafumi Kitakaze. Impaired systolic torsion in dilated cardiomyopathy: reversal of apical rotation at mid-systole characterized with magnetic resonance tagging method. *Basic Res Cardiol*, 101(6):465–470, Nov 2006. doi: 10.1007/s00395-006-0603-6. URL <http://dx.doi.org/10.1007/s00395-006-0603-6>.
- Athanasios Kapetanopoulos, Alan W. Ahlberg, Cynthia C. Taub, Deborah M. Katten, and Gary V. Heller. Regional wall-motion abnormalities on post-stress electrocardiographic-gated technetium-99m sestamibi single-photon

- emission computed tomography imaging predict cardiac events. *J Nucl Cardiol*, 14(6):810–817, 2007. doi: 10.1016/j.nuclcard.2007.07.014. URL <http://dx.doi.org/10.1016/j.nuclcard.2007.07.014>.
- S. P. Karwatowski, R. Mohiaddin, G. Z. Yang, D. N. Firmin, M. S. Sutton, S. R. Underwood, and D. B. Longmore. Assessment of regional left ventricular long-axis motion with MR velocity mapping in healthy subjects. *J Magn Reson Imaging*, 4(2):151–155, 1994a.
- S. P. Karwatowski, R. H. Mohiaddin, G. Z. Yang, D. N. Firmin, M. St John Sutton, and S. R. Underwood. Regional myocardial velocity imaged by magnetic resonance in patients with ischaemic heart disease. *Br Heart J*, 72(4):332–338, Oct 1994b.
- Tomoko S Kato, Akiko Noda, Hideo Izawa, Akira Yamada, Koji Obata, Kohzo Nagata, Mitsunori Iwase, Toyoaki Murohara, and Mitsuhiro Yokota. Discrimination of nonobstructive hypertrophic cardiomyopathy from hypertensive left ventricular hypertrophy on the basis of strain rate imaging by tissue Doppler ultrasonography. *Circulation*, 110(25):3808–3814, 2004. URL <http://circ.ahajournals.org/content/110/25/3808.short>.
- MD Katz, E William, MD Gulati, K Vijay, MS Mahler, M Christine, and John Gorcsan III. Quantitative Evaluation of the Segmental Left Ventricular Response to Dobutamine Stress by Tissue Doppler Echocardiography. *The American journal of cardiology*, 79(8):1036–1042, 1997. URL <http://www.sciencedirect.com/science/article/pii/S000291499700043X>.
- Daniel Kim and Peter Kellman. Improved cine displacement-encoded MRI using balanced steady-state free precession and time-adaptive sensitivity encoding parallel imaging at 3 T. *NMR Biomed*, 20(6):591–601, Oct 2007. doi: 10.1002/nbm.1126. URL <http://dx.doi.org/10.1002/nbm.1126>.
- Daniel Kim, Frederick H Epstein, Wesley D Gilson, and Leon Axel. Increasing

- the signal-to-noise ratio in DENSE MRI by combining displacement-encoded echoes. *Magn Reson Med*, 52(1):188–192, Jul 2004a. doi: 10.1002/mrm.20109. URL <http://dx.doi.org/10.1002/mrm.20109>.
- Daniel Kim, Wesley D Gilson, Christopher M Kramer, and Frederick H Epstein. Myocardial tissue tracking with two-dimensional cine displacement-encoded MR imaging: development and initial evaluation. *Radiology*, 230(3):862–871, Mar 2004b. doi: 10.1148/radiol.2303021213. URL <http://dx.doi.org/10.1148/radiol.2303021213>.
- Grigorios Korosoglou, Amr A Youssef, Kenneth C Bilchick, El-Sayed Ibrahim, Albert C Lardo, Shenghan Lai, and Nael F Osman. Real-time fast strain-encoded magnetic resonance imaging to evaluate regional myocardial function at 3.0 Tesla: comparison to conventional tagging. *J Magn Reson Imaging*, 27(5):1012–1018, May 2008. doi: 10.1002/jmri.21315. URL <http://dx.doi.org/10.1002/jmri.21315>.
- Grigorios Korosoglou, Dirk Lossnitzer, Dieter Schellberg, Antje Lewien, Angela Wochele, Tim Schaeufele, Mirja Neizel, Henning Steen, Evangelos Giannitsis, Hugo A Katus, and Nael F Osman. Strain-encoded cardiac MRI as an adjunct for dobutamine stress testing: incremental value to conventional wall motion analysis. *Circ Cardiovasc Imaging*, 2(2):132–140, Mar 2009. doi: 10.1161/CIRCIMAGING.108.790105. URL <http://dx.doi.org/10.1161/CIRCIMAGING.108.790105>.
- Grigorios Korosoglou, Stephanie Lehrke, Angela Wochele, Birgit Hoerig, Dirk Lossnitzer, Henning Steen, Evangelos Giannitsis, Nael F Osman, and Hugo A Katus. Strain-encoded CMR for the detection of inducible ischemia during intermediate stress. *JACC Cardiovasc Imaging*, 3(4):361–371, Apr 2010. doi: 10.1016/j.jcmg.2009.11.015. URL <http://dx.doi.org/10.1016/j.jcmg.2009.11.015>.

- M. Kouwenhoven, M. B. Hofman, and M. Sprenger. Motion induced phase shifts in MR: acceleration effects in quantitative flow measurements—a reconsideration. *Magn Reson Med*, 33(6):766–777, Jun 1995.
- D. L. Kraitchman, A. A. Young, C. N. Chang, and L. Axel. Semi-automatic tracking of myocardial motion in MR tagged images. *IEEE Trans Med Imaging*, 14(3):422–433, 1995. doi: 10.1109/42.414606. URL <http://dx.doi.org/10.1109/42.414606>.
- Dara L. Kraitchman, Smita Sampath, Ernesto Castillo, John A. Derbyshire, Raymond C. Boston, David A. Bluemke, Bernhard L. Gerber, Jerry L. Prince, and Nael F. Osman. Quantitative ischemia detection during cardiac magnetic resonance stress testing by use of FastHARP. *Circulation*, 107(15): 2025–2030, Apr 2003. doi: 10.1161/01.CIR.0000062684.47526.47. URL <http://dx.doi.org/10.1161/01.CIR.0000062684.47526.47>.
- C. M. Kramer, J. A. Lima, N. Reichek, V. A. Ferrari, M. R. Llaneras, L. C. Palmon, I. T. Yeh, B. Tallant, and L. Axel. Regional differences in function within noninfarcted myocardium during left ventricular remodeling. *Circulation*, 88(3):1279–1288, Sep 1993.
- U. Kramer, V. Deshpande, M. Fenchel, B. Klumpp, G. Laub, J. P. Finn, C. D. Claussen, and S. Miller. [Cardiac MR tagging: optimization of sequence parameters and comparison at 1.5 T and 3.0 T in a volunteer study]. *Rofo*, 178(5):515–524, May 2006. doi: 10.1055/s-2006-926473. URL <http://dx.doi.org/10.1055/s-2006-926473>.
- J. P. Kuijer, E. Jansen, J. T. Marcus, A. C. van Rossum, and R. M. Heethaar. Improved harmonic phase myocardial strain maps. *Magn Reson Med*, 46(5): 993–999, Nov 2001.
- Joost P A. Kuijer, J Tim Marcus, Marco J W. Götte, Albert C. van Rossum, and Robert M. Heethaar. Three-dimensional myocardial strains at end-systole

- and during diastole in the left ventricle of normal humans. *J Cardiovasc Magn Reson*, 4(3):341–351, 2002.
- Tomasz Kukulski, Jens Uwe Voigt, Ursula M Wilkenshoff, Jorg M Strotmann, Bengt Wranne, Liv Hatle, and George R Sutherland. A comparison of regional myocardial velocity information derived by pulsed and color Doppler techniques: an in vitro and in vivo study. *Echocardiography*, 17(7):639–651, 2000. URL <http://onlinelibrary.wiley.com/doi/10.1046/j.1540-8175.2000.00639.x/full>.
- John-Peder Escobar Kvitting, Tino Ebbers, Jan Engvall, George R Sutherland, Bengt Wranne, and Lars Wigström. Three-directional myocardial motion assessed using 3D phase contrast MRI. *J Cardiovasc Magn Reson*, 6(3):627–636, 2004.
- Roberto M. Lang, Michelle Bierig, Richard B. Devereux, Frank A. Flachskampf, Elyse Foster, Patricia A. Pellikka, Michael H. Picard, Mary J. Roman, James Seward, Jack S. Shanewise, Scott D. Solomon, Kirk T. Spencer, Martin St John Sutton, William J. Stewart, Chamber Quantification Writing Group, American Society of Echocardiography’s Guidelines, Standards Committee, and European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*, 18(12):1440–1463, Dec 2005.
- Jan-Willem Lankhaar, Mark B M Hofman, J. Tim Marcus, Jaco J M Zwanenburg, Theo J C Faes, and Anton Vonk-Noordegraaf. Correction of phase offset errors in main pulmonary artery flow quantification. *J Magn Reson Imaging*, 22(1):73–79, Jul 2005. doi: 10.1002/jmri.20361. URL <http://dx.doi.org/10.1002/jmri.20361>.

- P. C. Lauterbur. Image formation by induced local interactions. Examples employing nuclear magnetic resonance. 1973. *Clin Orthop Relat Res*, (244):3–6, Jul 1989.
- Eugene TY Lee. Choosing nodes in parametric curve interpolation. *Computer-Aided Design*, 21(6):363–370, 1989. URL <http://www.sciencedirect.com/science/article/pii/0010448589900031>.
- Marina Leitman, Peter Lysyansky, Stanislav Sidenko, Vladimir Shir, Eli Peleg, Michal Binenbaum, Edo Kaluski, Ricardo Krakover, and Zvi Vered. Two-dimensional strain-a novel software for real-time quantitative echocardiographic assessment of myocardial function. *J Am Soc Echocardiogr*, 17(10):1021–1029, Oct 2004. doi: 10.1016/j.echo.2004.06.019. URL <http://dx.doi.org/10.1016/j.echo.2004.06.019>.
- G. W. Lenz, E. M. Haacke, and R. D. White. Retrospective cardiac gating: a review of technical aspects and future directions. *Magn Reson Imaging*, 7(5):445–455, 1989.
- Darryl P. Leong, Carmine G. De Pasquale, and Joseph B. Selvanayagam. Heart failure with normal ejection fraction: the complementary roles of echocardiography and CMR imaging. *JACC Cardiovasc Imaging*, 3(4):409–420, Apr 2010. doi: 10.1016/j.jcmg.2009.12.011. URL <http://dx.doi.org/10.1016/j.jcmg.2009.12.011>.
- M H Levitt. Composite pulses. *Prog NMR Spectrosc*, 18:61–122, 1986.
- J. R. Liao, J. M. Pauly, T. J. Brosnan, and N. J. Pelc. Reduction of motion artifacts in cine MRI using variable-density spiral trajectories. *Magn Reson Med*, 37(4):569–575, Apr 1997.
- J. A. Lima, R. Jeremy, W. Guier, S. Bouton, E. A. Zerhouni, E. McVeigh, M. B. Buchalter, M. L. Weisfeldt, E. P. Shapiro, and J. L. Weiss. Accurate systolic

- wall thickening by nuclear magnetic resonance imaging with tissue tagging: correlation with sonomicrometers in normal and ischemic myocardium. *J Am Coll Cardiol*, 21(7):1741–1751, Jun 1993.
- A. Lingamneni, P. A. Hardy, K. A. Powell, N. J. Pelc, and R. D. White. Validation of cine phase-contrast MR imaging for motion analysis. *J Magn Reson Imaging*, 5(3):331–338, 1995.
- Y. L. Liu, S. J. Riederer, P. J. Rossman, R. C. Grimm, J. P. Debbins, and R. L. Ehman. A monitoring, feedback, and triggering system for reproducible breath-hold MR imaging. *Magn Reson Med*, 30(4):507–511, Oct 1993.
- D. B. Longmore, R. H. Klipstein, S. R. Underwood, D. N. Firmin, G. N. Hounsfield, M. Watanabe, C. Bland, K. Fox, P. A. Poole-Wilson, and R. S. Rees. Dimensional accuracy of magnetic resonance in studies of the heart. *Lancet*, 1(8442):1360–1362, Jun 1985.
- B. H. Lorell and B. A. Carabello. Left ventricular hypertrophy: pathogenesis, detection, and prognosis. *Circulation*, 102(4):470–479, Jul 2000.
- Hanzhang Lu, Chekesha Clingman, Xavier Golay, and Peter C M. van Zijl. Determining the longitudinal relaxation time (T1) of blood at 3.0 Tesla. *Magn Reson Med*, 52(3):679–682, Sep 2004. doi: 10.1002/mrm.20178. URL <http://dx.doi.org/10.1002/mrm.20178>.
- Anja Lutz, Axel Bornstedt, Robert Manzke, Patrick Etyngier, G Ulrich Nienhaus, and Volker Rasche. Acceleration of tissue phase mapping by k-t BLAST: a detailed analysis of the influence of k-t-BLAST for the quantification of myocardial motion at 3T. *J Cardiovasc Magn Reson*, 13:5, 2011. doi: 10.1186/1532-429X-13-5. URL <http://dx.doi.org/10.1186/1532-429X-13-5>.
- Anja Lutz, Jan Paul, Axel Bornstedt, G Ulrich Nienhaus, Patrick Etyngier, Peter Bernhardt, Wolfgang Rottbauer, and Volker Rasche. Volumet-

- ric motion quantification by 3D tissue phase mapped CMR. *J Cardiovasc Magn Reson*, 14:74, 2012. doi: 10.1186/1532-429X-14-74. URL <http://dx.doi.org/10.1186/1532-429X-14-74>.
- L. C. Man, J. M. Pauly, and A. Macovski. Improved automatic off-resonance correction without a field map in spiral imaging. *Magn Reson Med*, 37(6): 906–913, Jun 1997.
- W. J. Manning and D. J. Pennell. *Cardiovascular Magnetic Resonance*. Elsevier, 2010.
- J. T. Marcus, M. J. Götte, A. C. Van Rossum, J. P. Kuijer, R. M. Heethaar, L. Axel, and C. A. Visser. Myocardial function in infarcted and remote regions early after infarction in man: assessment by magnetic resonance tagging and strain analysis. *Magn Reson Med*, 38(5):803–810, Nov 1997.
- Eva Maret, Tim Todt, Lars Brudin, Eva Nylander, Eva Swahn, Jan L. Ohlsson, and Jan E. Engvall. Functional measurements based on feature tracking of cine magnetic resonance images identify left ventricular segments with myocardial scar. *Cardiovasc Ultrasound*, 7:53, 2009. doi: 10.1186/1476-7120-7-53. URL <http://dx.doi.org/10.1186/1476-7120-7-53>.
- M. Markl and J. Hennig. Phase contrast MRI with improved temporal resolution by view sharing: k-space related velocity mapping properties. *Magn Reson Imaging*, 19(5):669–676, Jun 2001.
- M. Markl, B. Schneider, J. Hennig, S. Peschl, J. Winterer, T. Krause, and J. Laubenberger. Cardiac phase contrast gradient echo MRI: measurement of myocardial wall motion in healthy volunteers and patients. *Int J Card Imaging*, 15(6):441–452, Dec 1999.
- Michael Markl, Scott B Reeder, Frandics P Chan, Marcus T Alley, Robert J Herfkens, and Norbert J Pelc. Steady-state free precession MR imaging: improved

- myocardial tag persistence and signal-to-noise ratio for analysis of myocardial motion. *Radiology*, 230(3):852–861, Mar 2004. doi: 10.1148/radiol.2303030181. URL <http://dx.doi.org/10.1148/radiol.2303030181>.
- J. R. Mayo, J. A. Culham, A. L. MacKay, and D. G. Aikins. Blood MR signal suppression by preexcitation with inverting pulses. *Radiology*, 173(1):269–271, Oct 1989.
- M. V. McConnell, V. C. Khasgiwala, B. J. Savord, M. H. Chen, M. L. Chuang, R. R. Edelman, and W. J. Manning. Comparison of respiratory suppression methods and navigator locations for MR coronary angiography. *AJR Am J Roentgenol*, 168(5):1369–1375, May 1997. doi: 10.2214/ajr.168.5.9129447. URL <http://dx.doi.org/10.2214/ajr.168.5.9129447>.
- E. R. McVeigh and BD Bolster, Jr. Improved sampling of myocardial motion with variable separation tagging. *Magn Reson Med*, 39(4):657–661, Apr 1998.
- E. R. McVeigh and E. A. Zerhouni. Noninvasive measurement of transmural gradients in myocardial strain with MR imaging. *Radiology*, 180(3):677–683, Sep 1991.
- C. H. Meyer, J. M. Pauly, A. Macovski, and D. G. Nishimura. Simultaneous spatial and spectral selective excitation. *Magn Reson Med*, 15(2):287–304, Aug 1990.
- C. C. Moore, S. B. Reeder, and E. R. McVeigh. Tagged MR imaging in a deforming phantom: photographic validation. *Radiology*, 190(3):765–769, Mar 1994.
- C. C. Moore, E. R. McVeigh, and E. A. Zerhouni. Quantitative tagged magnetic resonance imaging of the normal human left ventricle. *Top Magn Reson Imaging*, 11(6):359–371, Dec 2000.

- T. J. Mosher and M. B. Smith. A DANTE tagging sequence for the evaluation of translational sample motion. *Magn Reson Med*, 15(2):334–339, Aug 1990.
- E. Nagel, H. B. Lehmkuhl, W. Bocksch, C. Klein, U. Vogel, E. Frantz, A. Ellmer, S. Dreyse, and E. Fleck. Noninvasive diagnosis of ischemia-induced wall motion abnormalities with the use of high-dose dobutamine stress MRI: comparison with dobutamine stress echocardiography. *Circulation*, 99(6):763–770, Feb 1999.
- E. Nagel, M. Stuber, B. Burkhard, S. E. Fischer, M. B. Scheidegger, P. Boesiger, and O. M. Hess. Cardiac rotation and relaxation in patients with aortic valve stenosis. *Eur Heart J*, 21(7):582–589, Apr 2000a.
- E. Nagel, M. Stuber, M. Lakatos, M. B. Scheidegger, P. Boesiger, and O. M. Hess. Cardiac rotation and relaxation after anterolateral myocardial infarction. *Coron Artery Dis*, 11(3):261–267, May 2000b.
- S. F. Nagueh, L. L. Bachinski, D. Meyer, R. Hill, W. A. Zoghbi, J. W. Tam, M. A. Quicones, R. Roberts, and A. J. Marian. Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a novel means for an early diagnosis before and independently of hypertrophy. *Circulation*, 104(2):128–130, Jul 2001.
- Sherif F. Nagueh, Christopher P. Appleton, Thierry C. Gillebert, Paolo N. Marino, Jae K. Oh, Otto A. Smiseth, Alan D. Waggoner, Frank A. Flachskampf, Patricia A. Pellikka, and Arturo Evangelisa. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*, 10(2):165–193, Mar 2009. doi: 10.1093/ejechocard/jep007. URL <http://dx.doi.org/10.1093/ejechocard/jep007>.
- Abbas Nasiraei-Moghaddam and J Paul Finn. Tagging of cardiac magnetic resonance images in the polar coordinate system: Physical principles and prac-

- tical implementation. *Magn Reson Med*, Jun 2013. doi: 10.1002/mrm.24839. URL <http://dx.doi.org/10.1002/mrm.24839>.
- K. S. Nayak, C. M. Tsai, C. H. Meyer, and D. G. Nishimura. Efficient off-resonance correction for spiral imaging. *Magn Reson Med*, 45(3):521–524, Mar 2001.
- G. L. Nayler, D. N. Firmin, and D. B. Longmore. Blood flow imaging by cine magnetic resonance. *J Comput Assist Tomogr*, 10(5):715–722, 1986.
- Mirja Neizel, Dirk Lossnitzer, Grigorios Korosoglou, Tim Schäufole, Antje Lewien, Henning Steen, Hugo A Katus, Nael F Osman, and Evangelos Giannitsis. Strain-encoded (SENC) magnetic resonance imaging to evaluate regional heterogeneity of myocardial strain in healthy volunteers: Comparison with conventional tagging. *J Magn Reson Imaging*, 29(1):99–105, Jan 2009. doi: 10.1002/jmri.21612. URL <http://dx.doi.org/10.1002/jmri.21612>.
- Mirja Neizel, Grigorios Korosoglou, Dirk Lossnitzer, Harald Köhl, Rainer Hoffmann, Christina Ocklenburg, Evangelos Giannitsis, Nael F Osman, Hugo A Katus, and Henning Steen. Impact of systolic and diastolic deformation indexes assessed by strain-encoded imaging to predict persistent severe myocardial dysfunction in patients after acute myocardial infarction at follow-up. *J Am Coll Cardiol*, 56(13):1056–1062, Sep 2010. doi: 10.1016/j.jacc.2010.02.070. URL <http://dx.doi.org/10.1016/j.jacc.2010.02.070>.
- G. S. Nelson, C. W. Curry, B. T. Wyman, A. Kramer, J. Declerck, M. Talbot, M. R. Douglas, R. D. Berger, E. R. McVeigh, and D. A. Kass. Predictors of systolic augmentation from left ventricular preexcitation in patients with dilated cardiomyopathy and intraventricular conduction delay. *Circulation*, 101(23):2703–2709, Jun 2000.
- Tomoko Nishikage, Hiromi Nakai, Victor Mor-Avi, Roberto M. Lang, Ivan S. Salgo, Scott H. Settlemier, Stephane Husson, and Masaaki Takeuchi. Quan-

- titative assessment of left ventricular volume and ejection fraction using two-dimensional speckle tracking echocardiography. *Eur J Echocardiogr*, 10(1):82–88, Jan 2009. doi: 10.1093/ejechocard/jen166. URL <http://dx.doi.org/10.1093/ejechocard/jen166>.
- D. G. Norris and J. M. Hutchison. Concomitant magnetic field gradients and their effects on imaging at low magnetic field strengths. *Magn Reson Imaging*, 8(1):33–37, 1990.
- Sarwar H. Orakzai, Raza H. Orakzai, Khurram Nasir, and Matthew J. Budoff. Assessment of cardiac function using multidetector row computed tomography. *J Comput Assist Tomogr*, 30(4):555–563, 2006.
- J. N. Oshinski, L. Hofland, S Mukundan, Jr, W. T. Dixon, W. J. Parks, and R. I. Pettigrew. Two-dimensional coronary MR angiography without breath holding. *Radiology*, 201(3):737–743, Dec 1996.
- N. F. Osman and J. L. Prince. Visualizing myocardial function using HARP MRI. *Phys Med Biol*, 45(6):1665–1682, Jun 2000.
- N. F. Osman, W. S. Kerwin, E. R. McVeigh, and J. L. Prince. Cardiac motion tracking using CINE harmonic phase (HARP) magnetic resonance imaging. *Magn Reson Med*, 42(6):1048–1060, Dec 1999.
- N. F. Osman, E. R. McVeigh, and J. L. Prince. Imaging heart motion using harmonic phase MRI. *IEEE Trans Med Imaging*, 19(3):186–202, Mar 2000. doi: 10.1109/42.845177. URL <http://dx.doi.org/10.1109/42.845177>.
- N. F. Osman, S. Sampath, E. Atalar, and J. L. Prince. Imaging longitudinal cardiac strain on short-axis images using strain-encoded MRI. *Magn Reson Med*, 46(2):324–334, Aug 2001.
- Nael F. Osman and Jerry L. Prince. Regenerating MR tagged images using harmonic phase (HARP) methods. *IEEE Trans Biomed Eng*, 51

- (8):1428–1433, Aug 2004. doi: 10.1109/TBME.2004.827932. URL <http://dx.doi.org/10.1109/TBME.2004.827932>.
- Helen C. Oxenham, Alistair A. Young, Brett R. Cowan, Thomas L. Gentles, Christopher J. Occleshaw, Carissa G. Fonseca, Robert N. Doughty, and Norman Sharpe. Age-related changes in myocardial relaxation using three-dimensional tagged magnetic resonance imaging. *J Cardiovasc Magn Reson*, 5(3):421–430, Jul 2003.
- Noriko Oyama-Manabe, Naoki Ishimori, Hiroyuki Sugimori, Marc Van Cauteren, Kohsuke Kudo, Osamu Manabe, Tomoyuki Okuaki, Tamotsu Kamishima, Yoichi M. Ito, Hiroyuki Tsutsui, Khin Khin Tha, Satoshi Terae, and Hiroki Shirato. Identification and further differentiation of subendocardial and transmural myocardial infarction by fast strain-encoded (SENC) magnetic resonance imaging at 3.0 Tesla. *Eur Radiol*, 21(11):2362–2368, Nov 2011. doi: 10.1007/s00330-011-2177-4. URL <http://dx.doi.org/10.1007/s00330-011-2177-4>.
- Bernard P Paelinck, Albert de Roos, Jeroen J Bax, Johan M Bosmans, Rob J van Der Geest, Dominique Dhondt, Paul M Parizel, Christiaan J Vrints, and Hildo J Lamb. Feasibility of tissue magnetic resonance imaging: a pilot study in comparison with tissue Doppler imaging and invasive measurement. *J Am Coll Cardiol*, 45(7):1109–1116, Apr 2005. doi: 10.1016/j.jacc.2004.12.051. URL <http://dx.doi.org/10.1016/j.jacc.2004.12.051>.
- Vinay M Pai and Leon Axel. Advances in MRI tagging techniques for determining regional myocardial strain. *Curr Cardiol Rep*, 8(1):53–58, Feb 2006.
- Li Pan, Jerry L Prince, Joao A C Lima, and Nael F Osman. Fast tracking of cardiac motion using 3D-HARP. *IEEE Trans Biomed Eng*, 52(8):1425–1435, Aug 2005. doi: 10.1109/TBME.2005.851490. URL <http://dx.doi.org/10.1109/TBME.2005.851490>.

- Li Pan, Matthias Stuber, Dara L Kraitichman, Danielle L Fritzges, Wesley D Gilson, and Nael F Osman. Real-time imaging of regional myocardial function using fast-SENC. *Magn Reson Med*, 55(2):386–395, Feb 2006. doi: 10.1002/mrm.20770. URL <http://dx.doi.org/10.1002/mrm.20770>.
- J. Park, D. Metaxas, and L. Axel. Analysis of left ventricular wall motion based on volumetric deformable models and MRI-SPAMM. *Med Image Anal*, 1(1): 53–71, Mar 1996.
- J. Pauly, D. Spielman, and A. Macovski. Echo-planar spin-echo and inversion pulses. *Magn Reson Med*, 29(6):776–782, Jun 1993.
- L. R. Pelc, J. Sayre, K. Yun, L. J. Castro, R. J. Herfkens, D. C. Miller, and N. J. Pelc. Evaluation of myocardial motion tracking with cine-phase contrast magnetic resonance imaging. *Invest Radiol*, 29(12):1038–1042, Dec 1994.
- Hsu-Hsia Peng, Simon Bauer, Teng-Yi Huang, Hsiao-Wen Chung, Jürgen Hennig, Bernd Jung, and Michael Markl. Optimized parallel imaging for dynamic PC-MRI with multidirectional velocity encoding. *Magn Reson Med*, 64(2):472–480, Aug 2010. doi: 10.1002/mrm.22432. URL <http://dx.doi.org/10.1002/mrm.22432>.
- D. C. Peters, F. H. Epstein, and E. R. McVeigh. Myocardial wall tagging with undersampled projection reconstruction. *Magn Reson Med*, 45(4):562–567, Apr 2001.
- Steffen E Petersen, Bernd A Jung, Frank Wiesmann, Joseph B Selvanayagam, Jane M Francis, Juergen Hennig, Stefan Neubauer, and Matthew D Robson. Myocardial tissue phase mapping with cine phase-contrast mr imaging: regional wall motion analysis in healthy volunteers. *Radiology*, 238(3):816–826, Mar 2006. doi: 10.1148/radiol.2383041992. URL <http://dx.doi.org/10.1148/radiol.2383041992>.

- Caroline Petitjean, Nicolas Rougon, and Philippe Cluzel. Assessment of myocardial function: a review of quantification methods and results using tagged MRI. *J Cardiovasc Magn Reson*, 7(2):501–516, 2005.
- James Bell Pettigrew. On the Arrangement of the Muscular Fibres in the Ventricles of the Vertebrate Heart, with Physiological Remarks. *Philosophical Transactions of the Royal Society of London*, 154:445–500, 1864.
- M. A. Pfeffer, E. Braunwald, L. A. Moya, L. Basta, EJ Brown, Jr, T. E. Cuddy, B. R. Davis, E. M. Geltman, S. Goldman, and G. C. Flaker. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med*, 327(10):669–677, Sep 1992. doi: 10.1056/NEJM199209033271001. URL <http://dx.doi.org/10.1056/NEJM199209033271001>.
- J. L. Prince and E. R. McVeigh. Motion estimation from tagged MR image sequences. *IEEE Trans Med Imaging*, 11(2):238–249, 1992. doi: 10.1109/42.141648. URL <http://dx.doi.org/10.1109/42.141648>.
- K. P. Pruessmann, M. Weiger, M. B. Scheidegger, and P. Boesiger. SENSE: sensitivity encoding for fast MRI. *Magn Reson Med*, 42(5):952–962, Nov 1999.
- K. P. Pruessmann, M. Weiger, P. Börnert, and P. Boesiger. Advances in sensitivity encoding with arbitrary k-space trajectories. *Magn Reson Med*, 46(4):638–651, Oct 2001.
- R. B. Rehr, C. R. Malloy, N. G. Filipchuk, and R. M. Peshock. Left ventricular volumes measured by MR imaging. *Radiology*, 156(3):717–719, Sep 1985.
- Meral Reyhan, Yutaka Natsuaki, and Daniel B. Ennis. Fourier analysis of STimulated echoes (FAST) for the quantitative analysis of left ventricular twist. *J Magn Reson Imaging*, 35(3):587–593, Mar 2012. doi: 10.1002/jmri.22863. URL <http://dx.doi.org/10.1002/jmri.22863>.

- Meral Reyhan, Hyun J. Kim, Matthew S. Brown, and Daniel B. Ennis. Intra- and interscan reproducibility using fourier analysis of stimulated echoes (FAST) for the rapid and robust quantification of left ventricular twist. *J Magn Reson Imaging*, Apr 2013. doi: 10.1002/jmri.24162. URL <http://dx.doi.org/10.1002/jmri.24162>.
- M. D. Robson and R. T. Constable. Three-dimensional strain-rate imaging. *Magn Reson Med*, 36(4):537–546, Oct 1996.
- WJ Rogers, Jr, E. P. Shapiro, J. L. Weiss, M. B. Buchalter, F. E. Rademakers, M. L. Weisfeldt, and E. A. Zerhouni. Quantification of and correction for left ventricular systolic long-axis shortening by magnetic resonance tissue tagging and slice isolation. *Circulation*, 84(2):721–731, Aug 1991.
- Boaz D. Rosen, Joao A C. Lima, Khurram Nasir, Thor Edvardsen, Aaron R. Folsom, Shenghan Lai, David A. Bluemke, and Michael Jerosch-Herold. Lower myocardial perfusion reserve is associated with decreased regional left ventricular function in asymptomatic participants of the multi-ethnic study of atherosclerosis. *Circulation*, 114(4):289–297, Jul 2006a. doi: 10.1161/CIRCULATIONAHA.105.588525. URL <http://dx.doi.org/10.1161/CIRCULATIONAHA.105.588525>.
- Boaz D. Rosen, Mohammed F. Saad, Steven Shea, Khurram Nasir, Thor Edvardsen, Gregory Burke, Michael Jerosch-Herold, Donna K. Arnett, Shenghan Lai, David A. Bluemke, and Joao A C. Lima. Hypertension and smoking are associated with reduced regional left ventricular function in asymptomatic individuals the Multi-Ethnic Study of Atherosclerosis. *J Am Coll Cardiol*, 47(6):1150–1158, Mar 2006b. doi: 10.1016/j.jacc.2005.08.078. URL <http://dx.doi.org/10.1016/j.jacc.2005.08.078>.
- Iris K. Rüssel, Wessel P. Brouwer, Tjeerd Germans, Paul Knaapen, J Tim Marcus, Jolanda van der Velden, Marco J W. Götte, and Albert C.

- van Rossum. Increased left ventricular torsion in hypertrophic cardiomyopathy mutation carriers with normal wall thickness. *J Cardiovasc Magn Reson*, 13:3, 2011. doi: 10.1186/1532-429X-13-3. URL <http://dx.doi.org/10.1186/1532-429X-13-3>.
- Salome Ryf, Marcus A. Spiegel, Michael Gerber, and Peter Boesiger. Myocardial tagging with 3D-CSPAMM. *J Magn Reson Imaging*, 16(3):320–325, Sep 2002. doi: 10.1002/jmri.10145. URL <http://dx.doi.org/10.1002/jmri.10145>.
- Salome Ryf, Kraig V Kissinger, Marcus A Spiegel, Peter Börnert, Warren J Manning, Peter Boesiger, and Matthias Stuber. Spiral MR myocardial tagging. *Magn Reson Med*, 51(2):237–242, Feb 2004a. doi: 10.1002/mrm.10688. URL <http://dx.doi.org/10.1002/mrm.10688>.
- Salome Ryf, Jeffrey Tsao, Juerg Schwitter, Anja Stuessi, and Peter Boesiger. Peak-combination HARP: A method to correct for phase errors in HARP. *Journal of Magnetic Resonance Imaging*, 20(5):874–880, 2004b. URL <http://onlinelibrary.wiley.com/doi/10.1002/jmri.20186/full>.
- T. S. Sachs, C. H. Meyer, B. S. Hu, J. Kohli, D. G. Nishimura, and A. Macovski. Real-time motion detection in spiral MRI using navigators. *Magn Reson Med*, 32(5):639–645, Nov 1994.
- H. Sakuma, N. Fujita, T. K. Foo, G. R. Caputo, S. J. Nelson, J. Hartiala, A. Shimakawa, and C. B. Higgins. Evaluation of left ventricular volume and mass with breath-hold cine MR imaging. *Radiology*, 188(2):377–380, Aug 1993.
- Smita Sampath, J. Andrew Derbyshire, Ergin Atalar, Nael F Osman, and Jerry L Prince. Real-time imaging of two-dimensional cardiac strain using a harmonic phase magnetic resonance imaging (HARP-MRI) pulse sequence. *Magn Reson Med*, 50(1):154–163, Jul 2003. doi: 10.1002/mrm.10509. URL <http://dx.doi.org/10.1002/mrm.10509>.

- Gregory B. Sands, Bruce H. Smaill, and Ian J. LeGrice. Virtual sectioning of cardiac tissue relative to fiber orientation. *Conf Proc IEEE Eng Med Biol Soc*, 2008:226–229, 2008. doi: 10.1109/IEMBS.2008.4649131. URL <http://dx.doi.org/10.1109/IEMBS.2008.4649131>.
- Scarborough, Bhatnagar, Wickramasinghe, Smolina, Mitchell, and Rayner. Coronary heart disease statistics - 2010 edition. Website, 2010. URL <http://www.bhf.org.uk/research/statistics/economic-costs.aspx>.
- K. Scheffler and J. Hennig. Reduced circular field-of-view imaging. *Magn Reson Med*, 40(3):474–480, Sep 1998.
- F. Schick. Simultaneous highly selective MR water and fat imaging using a simple new type of spectral-spatial excitation. *Magn Reson Med*, 40(2):194–202, Aug 1998.
- F. Schick, J. Forster, J. Machann, R. Kuntz, and C. D. Claussen. Improved clinical echo-planar MRI using spatial-spectral excitation. *J Magn Reson Imaging*, 8(4):960–967, 1998.
- B. Schneider, M. Markl, C. Geiges, J. T. Winterer, C. Thuerl, J. Laubenberger, J. Hennig, and M. Langer. Cardiac phase contrast gradient echo MRI: characterization of abnormal left ventricular wall motion in patients with ischemic heart disease. *J Comput Assist Tomogr*, 25(4):550–557, 2001.
- Joanne D. Schuijf, Jeroen J. Bax, Liesbeth P. Salm, J Wouter Jukema, Hildo J. Lamb, Ernst E. van der Wall, and Albert de Roos. Noninvasive coronary imaging and assessment of left ventricular function using 16-slice computed tomography. *Am J Cardiol*, 95(5):571–574, Mar 2005. doi: 10.1016/j.amjcard.2004.11.002. URL <http://dx.doi.org/10.1016/j.amjcard.2004.11.002>.
- Andrew D Scott, Jennifer Keegan, and David N Firmin. Motion in cardiovascular MR imaging. *Radiology*, 250(2):331–351, Feb 2009. doi: 10.1148/radiol.2502071998. URL <http://dx.doi.org/10.1148/radiol.2502071998>.

- Nicole Seiberlich, Gregory Lee, Philipp Ehse, Jeffrey L Duerk, Robert Gilkeson, and Mark Griswold. Improved temporal resolution in cardiac imaging using through-time spiral GRAPPA. *Magnetic Resonance in Medicine*, 66(6):1682–1688, 2011. URL <http://onlinelibrary.wiley.com/doi/10.1002/mrm.22952/full>.
- Pernilla Selskog, Einar Heiberg, Tino Ebbers, Lars Wigström, and Matts Karlsson. Kinematics of the heart: strain-rate imaging from time-resolved three-dimensional phase contrast MRI. *IEEE Trans Med Imaging*, 21(9):1105–1109, Sep 2002. doi: 10.1109/TMI.2002.804431. URL <http://dx.doi.org/10.1109/TMI.2002.804431>.
- Randolph M. Setser, Richard D. White, Bernhard Sturm, Patrick M. McCarthy, Randall C. Starling, James B. Young, Jane Kasper, Tiffany Buda, Nancy Obuchowski, and Michael L. Lieber. Noninvasive assessment of cardiac mechanics and clinical outcome after partial left ventriculectomy. *Ann Thorac Surg*, 76(5):1576–85; discussion 1585–6, Nov 2003.
- Monda L Shehata, Susan Cheng, Nael F Osman, David A Bluemke, and Joao A C Lima. Myocardial tissue tagging with cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*, 11:55, 2009. doi: 10.1186/1532-429X-11-55. URL <http://dx.doi.org/10.1186/1532-429X-11-55>.
- Monda L Shehata, Tamer A Basha, Wahid H Tantawy, Joao A Lima, Jens Vogel-Claussen, David A Bluemke, Paul M Hassoun, and Nael F Osman. Real-time single-heartbeat fast strain-encoded imaging of right ventricular regional function: normal versus chronic pulmonary hypertension. *Magn Reson Med*, 64(1):98–106, Jul 2010. doi: 10.1002/mrm.22408. URL <http://dx.doi.org/10.1002/mrm.22408>.
- Rosa Sicari, Petros Nihoyannopoulos, Arturo Evangelista, Jaroslav Kasprzak, Patrizio Lancellotti, Don Poldermans, Jen-Uwe Voigt, Jose Luis Zamorano,

- and European Association of Echocardiography . Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur J Echocardiogr*, 9(4):415–437, Jul 2008.
- Robin Simpson, Jennifer Keegan, and David Firmin. Efficient and reproducible high resolution spiral myocardial phase velocity mapping of the entire cardiac cycle. *J Cardiovasc Magn Reson*, 15(1):34, Apr 2013a. doi: 10.1186/1532-429X-15-34. URL <http://dx.doi.org/10.1186/1532-429X-15-34>.
- Robin M. Simpson, Jennifer Keegan, and David N. Firmin. MR assessment of regional myocardial mechanics. *J Magn Reson Imaging*, 37(3):576–599, Mar 2013b. doi: 10.1002/jmri.23756. URL <http://dx.doi.org/10.1002/jmri.23756>.
- R. Sinkus and P. Börnert. Motion pattern adapted real-time respiratory gating. *Magn Reson Med*, 41(1):148–155, Jan 1999.
- D. K. Sodickson and W. J. Manning. Simultaneous acquisition of spatial harmonics (SMASH): fast imaging with radiofrequency coil arrays. *Magn Reson Med*, 38(4):591–603, Oct 1997.
- Sahar Soleimanifard, Khaled Z. Abd-Elmoniem, Tetsuo Sasano, Harsh K. Agarwal, M Roselle Abraham, Theodore P. Abraham, and Jerry L. Prince. Three-dimensional regional strain analysis in porcine myocardial infarction: a 3T magnetic resonance tagging study. *J Cardiovasc Magn Reson*, 14:85, 2012. doi: 10.1186/1532-429X-14-85. URL <http://dx.doi.org/10.1186/1532-429X-14-85>.
- Thomas Sangild Sørensen, David Atkinson, Tobias Schaeffter, and Michael Schacht Hansen. Real-time reconstruction of sensitivity encoded radial magnetic resonance imaging using a graphics processing unit. *IEEE Trans*

- Med Imaging*, 28(12):1974–1985, Dec 2009. doi: 10.1109/TMI.2009.2027118. URL <http://dx.doi.org/10.1109/TMI.2009.2027118>.
- B. Spottiswoode. Measuring LV-RV interventricular dyssynchrony using cine DENSE-MRI. In *Proceedings of the 14th ISMRM Conference*, 2006.
- B. Spottiswoode, J. B. Russell, S. Moosa, E. M. Meintjes, F. H. Epstein, and B. M. Mayosi. Abnormal diastolic and systolic septal motion following pericardiectomy demonstrated by cine DENSE MRI. *Cardiovasc J Afr*, 19(4):208–209, 2008.
- Elmar Spuentrup, Warren J. Manning, Rene M. Botnar, Kraig V. Kissinger, and Matthias Stuber. Impact of navigator timing on free-breathing submillimeter 3D coronary magnetic resonance angiography. *Magn Reson Med*, 47(1):196–201, Jan 2002.
- Jennifer A. Steeden, Daniel S. Knight, Shreya Bali, David Atkinson, Andrew M. Taylor, and Vivek Muthurangu. Self-navigated tissue phase mapping using a golden-angle spiral acquisition—proof of concept in patients with pulmonary hypertension. *Magn Reson Med*, Feb 2013. doi: 10.1002/mrm.24646. URL <http://dx.doi.org/10.1002/mrm.24646>.
- R. E. Steiner, G. M. Bydder, A. Selwyn, J. Deanfield, D. B. Longmore, R. H. Klipsten, and D. Firmin. Nuclear magnetic resonance imaging of the heart. Current status and future prospects. *Br Heart J*, 50(3):202–208, Sep 1983.
- Asbjorn Stoylen, Andreas Heimdal, Knut Bjornstad, Hans G. Torp, and Terje Skjaerpe. Strain Rate Imaging by Ultrasound in the Diagnosis of Regional Dysfunction of the Left Ventricle. *Echocardiography*, 16(4):321–329, May 1999.
- Hiroyuki Sugimori, Noriko Oyama-Manabe, Kinya Ishizaka, Hiroyuki Hamaguchi, and Motomichi Sakata. Comparison of SPAMM and SENC methods for evaluating peak circumferential strain at 3T. *Magn Reson Med Sci*, 12(1):69–75, Mar 2013.

- GR Sutherland, MJ Stewart, KW Groundstroem, CM Moran, A Fleming, FJ Guell-Peris, RA Riemersma, LN Fenn, KA Fox, and WN McDicken. Color Doppler myocardial imaging: a new technique for the assessment of myocardial function. *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography*, 7(5):441–458, 1993. URL <http://europepmc.org/abstract/MED/7986541>.
- Masaaki Takeuchi, Tomoko Nishikage, Victor Mor-Avi, Lissa Sugeng, Lynn Weinert, Hironi Nakai, Ivan S. Salgo, Olivier Gerard, and Roberto M. Lang. Measurement of left ventricular mass by real-time three-dimensional echocardiography: validation against magnetic resonance and comparison with two-dimensional and m-mode measurements. *J Am Soc Echocardiogr*, 21(9):1001–1005, Sep 2008. doi: 10.1016/j.echo.2008.07.008. URL <http://dx.doi.org/10.1016/j.echo.2008.07.008>.
- Andrew M Taylor, Permi Jhooti, David N Firmin, and Dudley J Pennell. Automated monitoring of diaphragm end-expiratory position for real-time navigator echo MR coronary angiography. *Journal of Magnetic Resonance Imaging*, 9(3):395–401, 1999.
- C. M. Tsai and D. G. Nishimura. Reduced aliasing artifacts using variable-density k-space sampling trajectories. *Magn Reson Med*, 43(3):452–458, Mar 2000.
- S. Urheim, T. Edvardsen, H. Torp, B. Angelsen, and O. A. Smiseth. Myocardial strain by Doppler echocardiography. Validation of a new method to quantify regional myocardial function. *Circulation*, 102(10):1158–1164, Sep 2000.
- N. R. Van de Veire, J. De Sutter, J. J. Bax, and J R T C. Roelandt. Technological advances in tissue Doppler imaging echocardiography. *Heart*, 94(8):1065–1074, Aug 2008. doi: 10.1136/hrt.2007.120758. URL <http://dx.doi.org/10.1136/hrt.2007.120758>.

- P. van Dijk. Direct cardiac NMR imaging of heart wall and blood flow velocity. *J Comput Assist Tomogr*, 8(3):429–436, Jun 1984.
- Jens-Uwe Voigt, Uwe Nixdorff, Ruxandra Bogdan, Bert Exner, Kristin Schmiedehausen, Günther Platsch, Torsten Kuwert, Werner G. Daniel, and Frank A. Flachskampf. Comparison of deformation imaging and velocity imaging for detecting regional inducible ischaemia during dobutamine stress echocardiography. *Eur Heart J*, 25(17):1517–1525, Sep 2004. doi: 10.1016/j.ehj.2004.05.014. URL <http://dx.doi.org/10.1016/j.ehj.2004.05.014>.
- P. G. Walker, G. B. Cranney, M. B. Scheidegger, G. Waseleski, G. M. Pohost, and A. P. Yoganathan. Semiautomated method for noise reduction and background phase error correction in MR phase velocity data. *J Magn Reson Imaging*, 3(3):521–530, 1993.
- Y. Wang, P. S. Christy, F. R. Korosec, M. T. Alley, T. M. Grist, J. A. Polzin, and C. A. Mistretta. Coronary MRI with a respiratory feedback monitor: the 2D imaging case. *Magn Reson Med*, 33(1):116–121, Jan 1995.
- Y. Wang, R. C. Grimm, J. P. Felmlee, S. J. Riederer, and R. L. Ehman. Algorithms for extracting motion information from navigator echoes. *Magn Reson Med*, 36(1):117–123, Jul 1996a.
- Y. Wang, P. J. Rossman, R. C. Grimm, S. J. Riederer, and R. L. Ehman. Navigator-echo-based real-time respiratory gating and triggering for reduction of respiration effects in three-dimensional coronary MR angiography. *Radiology*, 198(1):55–60, Jan 1996b.
- V. J. Wedeen. Magnetic resonance imaging of myocardial kinematics. Technique to detect, localize, and quantify the strain rates of the active human myocardium. *Magn Reson Med*, 27(1):52–67, Sep 1992.
- A. M. Weissler, W. S. Harris, and C. D. Schoenfeld. Systolic time intervals in heart failure in man. *Circulation*, 37(2):149–159, Feb 1968.

- Han Wen, Keith A Marsolo, Eric E Bennett, Kwame S Kutten, Ryan P Lewis, David B Lipps, Neal D Epstein, Jonathan F Plehn, and Pierre Croisille. Adaptive postprocessing techniques for myocardial tissue tracking with displacement-encoded MR imaging. *Radiology*, 246(1):229–240, Jan 2008. doi: 10.1148/radiol.2461070053. URL <http://dx.doi.org/10.1148/radiol.2461070053>.
- J. Wikstrand, G. Berglund, L. Wilhelmsen, and I. Wallentin. Value of systolic and diastolic time intervals. Studies in normotensive and hypertensive 50-year-old men and in patients after myocardial infarction. *Br Heart J*, 40(3): 256–267, Mar 1978.
- Stefanie Winkelmann, Tobias Schaeffter, Thomas Koehler, Holger Eggers, and Olaf Doessel. An optimal radial profile order based on the Golden Ratio for time-resolved MRI. *IEEE Trans Med Imaging*, 26(1):68–76, Jan 2007. doi: 10.1109/TMI.2006.885337. URL <http://dx.doi.org/10.1109/TMI.2006.885337>.
- M. Wong, G. Johnson, R. Shabetai, V. Hughes, G. Bhat, B. Lopez, and J. N. Cohn. Echocardiographic variables as prognostic indicators and therapeutic monitors in chronic congestive heart failure. Veterans Affairs cooperative studies V-HeFT I and II. V-HeFT VA Cooperative Studies Group. *Circulation*, 87(6 Suppl):VI65–VI70, Jun 1993.
- Chun Xu, James J Pilla, Gamaliel Isaac, Joseph H Gorman, Aaron S Blom, Robert C Gorman, Zhou Ling, and Lawrence Dougherty. Deformation analysis of 3D tagged cardiac images using an optical flow method. *J Cardiovasc Magn Reson*, 12:19, 2010. doi: 10.1186/1532-429X-12-19. URL <http://dx.doi.org/10.1186/1532-429X-12-19>.
- Masaki Yamamuro, Eiji Tadamura, Shigeto Kubo, Hiroshi Toyoda, Takeshi Nishina, Muneo Ohba, Ryohei Hosokawa, Takeshi Kimura, Nagara Tamaki,

- Masashi Komeda, Toru Kita, and Junji Konishi. Cardiac functional analysis with multi-detector row CT and segmental reconstruction algorithm: comparison with echocardiography, SPECT, and MR imaging. *Radiology*, 234(2):381–390, Feb 2005. doi: 10.1148/radiol.2342031271. URL <http://dx.doi.org/10.1148/radiol.2342031271>.
- G. Z. Yang, P. Burger, P. J. Kilner, S. P. Karwatowski, and D. N. Firmin. Dynamic range extension of cine velocity measurements using motion-registered spatiotemporal phase unwrapping. *J Magn Reson Imaging*, 6(3):495–502, 1996.
- S. B. Yeon, N. Reichek, B. A. Tallant, J. A. Lima, L. P. Calhoun, N. R. Clark, E. A. Hoffman, K. K. Ho, and L. Axel. Validation of in vivo myocardial strain measurement by magnetic resonance tagging with sonomicrometry. *J Am Coll Cardiol*, 38(2):555–561, Aug 2001.
- A. A. Young, L. Axel, L. Dougherty, D. K. Bogen, and C. S. Parenteau. Validation of tagging with MR imaging to estimate material deformation. *Radiology*, 188(1):101–108, Jul 1993.
- A. A. Young, C. M. Kramer, V. A. Ferrari, L. Axel, and N. Reichek. Three-dimensional left ventricular deformation in hypertrophic cardiomyopathy. *Circulation*, 90(2):854–867, Aug 1994.
- A. A. Young, D. L. Kraitchman, L. Dougherty, and L. Axel. Tracking and finite element analysis of stripe deformation in magnetic resonance tagging. *IEEE Trans Med Imaging*, 14(3):413–421, 1995. doi: 10.1109/42.414605. URL <http://dx.doi.org/10.1109/42.414605>.
- A. A. Young, S. Dokos, K. A. Powell, B. Sturm, A. D. McCulloch, R. C. Starling, P. M. McCarthy, and R. D. White. Regional heterogeneity of function in non-ischemic dilated cardiomyopathy. *Cardiovasc Res*, 49(2):308–318, Feb 2001.
- Alistair A. Young and Brett R. Cowan. Evaluation of left ventricular torsion by cardiovascular magnetic resonance. *J Cardiovasc*

- Magn Reson*, 14:49, 2012. doi: 10.1186/1532-429X-14-49. URL <http://dx.doi.org/10.1186/1532-429X-14-49>.
- Amr Youssef, El-Sayed H Ibrahim, Grigorios Korosoglou, M. Roselle Abraham, Robert G Weiss, and Nael F Osman. Strain-encoding cardiovascular magnetic resonance for assessment of right-ventricular regional function. *J Cardiovasc Magn Reson*, 10:33, 2008. doi: 10.1186/1532-429X-10-33. URL <http://dx.doi.org/10.1186/1532-429X-10-33>.
- E. A. Zerhouni, D. M. Parish, W. J. Rogers, A. Yang, and E. P. Shapiro. Human heart: tagging with MR imaging—a method for noninvasive assessment of myocardial motion. *Radiology*, 169(1):59–63, Oct 1988.
- Jia Zhong and Xin Yu. Strain and torsion quantification in mouse hearts under dobutamine stimulation using 2D multiphase MR DENSE. *Magn Reson Med*, Aug 2010. doi: 10.1002/mrm.22530. URL <http://dx.doi.org/10.1002/mrm.22530>.
- X. Zhong. Two-dimensional spiral cine DENSE. In *Proceedings of the 15th ISMRM Conference*, 2007.
- Xiaodong Zhong, Bruce S Spottiswoode, Elizabeth A Cowart, Wesley D Gilson, and Frederick H Epstein. Selective suppression of artifact-generating echoes in cine DENSE using through-plane dephasing. *Magn Reson Med*, 56(5):1126–1131, Nov 2006. doi: 10.1002/mrm.21058. URL <http://dx.doi.org/10.1002/mrm.21058>.
- Xiaodong Zhong, Patrick A Helm, and Frederick H Epstein. Balanced multipoint displacement encoding for DENSE MRI. *Magn Reson Med*, 61(4):981–988, Apr 2009. doi: 10.1002/mrm.21851. URL <http://dx.doi.org/10.1002/mrm.21851>.
- Xiaodong Zhong, Bruce S Spottiswoode, Craig H Meyer, Christopher M Kramer, and Frederick H Epstein. Imaging three-dimensional myocardial mechan-

- ics using navigator-gated volumetric spiral cine DENSE MRI. *Magn Reson Med*, 64(4):1089–1097, Oct 2010. doi: 10.1002/mrm.22503. URL <http://dx.doi.org/10.1002/mrm.22503>.
- Y. Zhu, M. Drangova, and N. J. Pelc. Estimation of deformation gradient and strain from cine-PC velocity data. *IEEE Trans Med Imaging*, 16(6):840–851, Dec 1997. doi: 10.1109/42.650880. URL <http://dx.doi.org/10.1109/42.650880>.
- Jaco J M Zwanenburg, Joost P A Kuijer, J. Tim Marcus, and Robert M Heethaar. Steady-state free precession with myocardial tagging: CSPAMM in a single breathhold. *Magn Reson Med*, 49(4):722–730, Apr 2003. doi: 10.1002/mrm.10422. URL <http://dx.doi.org/10.1002/mrm.10422>.

Glossary of terms

Ca^{2+} Calcium

K^{+} Potassium

Na^{+} Sodium

AHA American Heart Association

bSSFP Balanced Steady State Free Precession

BB Black Blood

CAD Coronary Artery Disease

CNR Contrast-to-Noise Ratio

DENSE Displacement Encoding with Stimulated Echoes

DCM dilated cardiomyopathy

ECG Electrocardiogram

EF Ejection Fraction

EPI Echo-Planar Imaging

FOV Field of View

FFT Fast Fourier Transform

FT Fourier Transform

GPU Graphics Processing Unit

HARP Harmonic Phase

HCM Hypertrophic Cardiomyopathy

LV Left Ventricle

MR Magnetic Resonance

MRI Magnetic Resonance Imaging

PVM Phase Velocity Mapping

PSF Point Spread Function

RCL Radial-Circumferential-Longitudinal

RF Radio Frequency

RV Right Ventricle

SENC Strain-Encoded Imaging

SENSE Sensitivity Encoding

SNR Signal-to-Noise Ratio

SPAMM Spatial Modulation of Magnetisation

SPECT Single Photon Emission Computed Tomography

STAE Stimulated Anti-Echo

SD Standard Deviation

STE Stimulated Echo

STEAM Stimulated Echo Acquisition Mode

TDI Tissue Doppler Imaging

TTP Time-To-Peak

Appendix A

Water excitation proof

A water excitation works by using a series of RF pulses with flip angles which add up to the required total flip angle ϕ but which have delays between them which allow fat to nutate by π radians between each pulse (in the rotating co-ordinate system water does not nutate). At the end of the excitation water has been excited by

$$\alpha \sum_{j=0}^n \binom{n}{j} \quad (\text{A.1})$$

where α is a normalisation factor

$$\alpha = \frac{\phi}{\sum_{j=0}^n \binom{n}{j}} \quad (\text{A.2})$$

whereas fat is excited by

$$\alpha \sum_{j=0}^n (-1)^j \binom{n}{j}. \quad (\text{A.3})$$

where the extra $(-1)^j$ is due to the nutation of π radians between each pulse. This should be equal to zero so that fat is not excited. This can be proved by using induction and the identity:

$$\binom{n}{k} + \binom{n}{k+1} = \binom{n+1}{k+1} \quad (\text{A.4})$$

in the following way.

For $n=1$:

$$(-1)^0 \binom{1}{0} + (-1)^1 \binom{1}{1} = 0 \quad (\text{A.5})$$

Assuming the equality is true for $n-1$, ie

$$\sum_{j=0}^{n-1} (-1)^j \binom{n-1}{j} = 0 \quad (\text{A.6})$$

we can show that the equality is true for n :

$$\sum_{j=0}^n (-1)^j \binom{n}{j} = \sum_{j=0}^n (-1)^j \left\{ \binom{n-1}{j-1} + \binom{n-1}{j} \right\} \quad (\text{A.7})$$

where Equation A.4 has been used. We know that the $j=0$ term is 1 and the $j=n$ term is $(-1)^n$ so we can write

$$= 1 + \sum_{j=1}^{n-1} (-1)^j \left\{ \binom{n-1}{j-1} + \binom{n-1}{j} \right\} + (-1)^n \quad (\text{A.8})$$

Using Equation A.6 and again using the fact that the $j=0$ term equals 1, we can rewrite the $\binom{n-1}{j}$ term:

$$= 1 + \sum_{j=1}^{n-1} (-1)^j \binom{n-1}{j-1} - 1 + (-1)^n \quad (\text{A.9})$$

Now rewriting with a new variable $q = j - 1$

$$= \sum_{q=0}^{n-2} (-1)^{q+1} \binom{n-1}{q} + (-1)^n \quad (\text{A.10})$$

$$= - \sum_{q=0}^{n-2} (-1)^q \binom{n-1}{q} + (-1)^n \quad (\text{A.11})$$

Again using Equation A.4

$$= -(-1)^{n-2} + (-1)^n = 0 \quad (\text{A.12})$$

So for any binomial series, fat is not excited at all while water is excited by ϕ which is the desired result.

Appendix B

Publications

Simpson R., Keegan J., Gatehouse P, Hansen M., Firmin D. *Spiral tissue phase velocity mapping in a breath-hold with non-Cartesian SENSE* Accepted for publication in MRM.

Simpson, R., Keegan, J. and Firmin, D. *Efficient and reproducible high resolution spiral myocardial phase velocity mapping of the entire cardiac cycle* JCMR; 15(1):34

Simpson, R., Keegan, J. and Firmin, D. *MR assessment of regional myocardial mechanics* (Review article). J Magn Reson Imaging 2013; 37(3):576-599 (DOI: 10.1002/jmri.23756).

Appendix C

Conference abstracts

C.1 Oral presentations

Simpson, R., Keegan, J. and Firmin, D. *High resolution spiral myocardial phase velocity mapping (PVM) of the entire cardiac cycle* **Early Career Award - Basic Science** session in SCMR scientific sessions 2013.

Simpson, R., Keegan, J. and Firmin, D. *Characterising global and regional myocardial motion patterns for the whole cardiac cycle using retrogated spiral phase velocity mapping* ISMRM Annual meeting 2013 - awarded a *magna cum laude* merit award.

Simpson, R., Keegan, J. and Firmin, D. *High resolution spiral myocardial MRI phase velocity mapping of the entire cardiac cycle* NHLI Postgraduate Symposium 2013

C.2 E-posters

Simpson, R., Keegan, J., Gatehouse, P. and Firmin, D. *Right ventricular velocities over the entire cardiac cycle measured with high resolution spiral phase velocity mapping: results, reproducibility and comparison with the left ventricle* In ISMRM annual meeting 2013.

Simpson, R., Keegan, J. and Firmin, D. *Reproducibility of peak and time to peak velocity measurements with a high resolution spiral phase velocity mapping (PVM) sequence* In SCMR scientific sessions 2013.

Simpson, R., Keegan, J., and Firmin, D. *Regional analysis of 3-directional myocardial velocities acquired in a breath-hold with efficient retro-gated spiral phase velocity mapping* In: ISMRM Annual meeting 2012.

C.3 Traditional posters

Simpson, R., Keegan, J. and Firmin, D. *Measuring myocardial velocities with high resolution using retrogated spiral phase velocity mapping* BC-ISMARM 2013 Post-graduate symposium

Simpson, R., Keegan, J. and Firmin, D. *Right ventricular (RV) velocity measurements using high resolution spiral myocardial phase velocity mapping (PVM)* In SCMR scientific sessions 2013.

Simpson, R., Keegan, J., Gatehouse, P. and Firmin, D. *Retrogated spiral 3-directional myocardial phase velocity mapping in a single breath-hold* In: SCMR/ISMARM jointly sponsored CV flow and motion workshop 2012 and SCMR scientific sessions 2012.

Simpson, R., Keegan, J. and Firmin, D. *Spiral myocardial MRI phase velocity map-*

ping Mayneord Phillips Summer School 2012.

Appendix D

Copyright Permissions

Figure	Source	Copyright holder and year	Permission to re-use
1.5	Pettigrew (1864)	©The Royal Society 1864	Does not require permission
1.11	Orakzai et al. (2006)	©Wolters Kluwer Health 2006	Licence No. 3224790560861
1.10	Nagueh et al. (2009)	©Elsevier 2009	Licence No. 3224790460626
1.13	Simpson et al. (2013b)	©John Wiley and Sons 2012	Licence No. 3238770989115
1.14	Van de Veire et al. (2008)	©BMJ Publishing Group Ltd. 2008	Licence No. 3224790689409
1.15	Leitman et al. (2004)	©Elsevier 2004	Licence No. 3224790773932
2.1	Simpson et al. (2013b)	©John Wiley and Sons	Licence No. 3238770989115
2.2A	Sampath et al. (2003)	©John Wiley and Sons 2003	Licence No. 3224780310325
2.2B	Osman and Prince (2000)	©IEEE 2000	Does not require permission
2.3	Rosen et al. (2006a)	©Elsevier 2006	Licence No. 3224800067685
2.4	Simpson et al. (2013b)	©John Wiley and Sons 2012	Licence No. 3238770989115
2.5	Jung et al. (2006a)	©John Wiley and Sons 2006	Licence No. 3230700182969
2.6	Simpson et al. (2013b)	©John Wiley and Sons 2012	Licence No. 3238770989115
2.6	Aletras et al. (1999a)	©Elsevier 1999	Licence No. 3224800156223
2.7	Kim et al. (2004b)	©RSNA 2004	See below
2.8	Zhong and Yu (2010)	©John Wiley and Sons 2010	License No. 3224780821810
2.9	Simpson et al. (2013b)	©John Wiley and Sons 2012	Licence No. 3238770989115
2.9	Osman et al. (2001)	©John Wiley and Sons 2001	Licence No. 3224781084925
2.10	Osman et al. (2001)	©John Wiley and Sons 2001	Licence No. 3224781084925
2.11	Korosoglou et al. (2010)	©Elsevier 2010	Licence No. 3224800421752
2.12 (left)	Osman et al. (1999)	©John Wiley and Sons 1999	Licence No. 3224781170071
2.12 (right)	Kim et al. (2004a)	©John Wiley and Sons 1999	Licence No. 3224781252744
3.8	Drangova et al. (1997)	©John Wiley and Sons 1997	Licence No. 3224790281421
3.20	Deshmane et al. (2012)	©John Wiley and Sons 2012	Licence No. 3224790176988
3.21	Delattre et al. (2010)	©Elsevier 2010	Licence No. 3224800494056



620 Jorie Blvd
Oak Brook, IL 60521
TEL 1-630-571-2670
FAX 1-630-571-7837
RSNA.org

September 9, 2013

Robin Simpson
Royal Brompton Hospital, Sydney Street
London SW3 6NP
Great Britain

Dear Robin Simpson:

The Radiological Society of North America (RSNA®) is pleased to grant you permission to reproduce the following figure in print and electronic formats for educational use in your dissertation/thesis, provided you give full credit to the authors of the original publication.

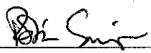
Figure A1

Kim D, Gilson WD, Kramer CM, et al. Myocardial tissue tracking with two-dimensional cine displacement-encoded MR imaging: development and initial evaluation. *Radiology* 2004;230:862-871.

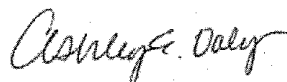
This permission is a one-time, non-exclusive grant for English-language use and is exclusively limited to the usage stated and underlined above. The requestor guarantees to reproduce the material as originally published. Permission is granted under the condition that a full credit line is prominently placed (i.e. author name(s), journal name, copyright year, volume #, inclusive pages and copyright holder).

This permission becomes effective upon receipt of this signed contract. Please sign a copy of this agreement, return a signed copy to me and retain a copy for your files. Thank you for your interest in our publication.

[Print Name]: ROBIN SIMPSON

SIGNATURE:  Date: 11th Sept 2013

Sincerely,



Ashley E. Daly
Senior Manager, Journal Rights & Communications
Publications

Phone: 630-590-7771

Fax: 630-590-7724

E-mail: permissions@rsna.org