

Magnetic resonance coronary vessel wall imaging with highly efficient respiratory motion correction

Andrew David Scott

Cardiovascular Magnetic Resonance Unit,

The Royal Brompton Hospital and National Heart and Lung Institute,

Imperial College London.

Supervised by Dr Jennifer Keegan and Professor David Firmin.

Submitted for the degree of Doctor of Philosophy at Imperial College London.

This thesis and the work it describes is original work performed by the author except where referenced. The copyright of this thesis rests with the author and no quotation from it or information derived from it may be published without the prior written consent of the author.

Abstract

There is a need for a noninvasive imaging technique for use in longitudinal studies of sub-clinical coronary artery disease. Magnetic resonance (MR) can be used to selectively and non-invasively image the coronary wall without the use of ionising radiation. However, high-resolution 3D studies are often time consuming and unreliable, as data acquisition is generally gated to a small window of diaphragm positions around end-expiration which results in inherently poor and variable respiratory efficiency. This thesis describes the development and application of a novel technique (beat-to-beat respiratory motion correction (B2B-RMC)) for correcting respiratory motion in 3D spiral MR coronary imaging. This technique uses motion of the epicardial fat surrounding the artery as a surrogate for the motion of the artery itself and enables retrospective motion correction with respiratory efficiency close to 100%.

This thesis first describes an assessment of the performance of B2B-RMC using a purpose built respiratory motion phantom with realistic coronary artery test objects. Subsequently, MR coronary angiography studies in healthy volunteers show that the respiratory efficiency of B2B-RMC far exceeds that of conventional navigator gating, yet the respiratory motion correction is equally effective. The performance and reproducibility of 3D spiral imaging with B2B-RMC for assessment of the coronary artery vessel wall is subsequently compared to that of commonly used 2D navigator gated techniques. The results demonstrate the high performance, reproducibility and reliability of 3D spiral imaging with B2B-RMC when data acquisition is gated to alternate cardiac cycles. Using this technique, a further *in-vivo* study demonstrates thickening of the coronary vessel wall with age in healthy subjects and these results are shown to be consistent with outward remodelling of the vessel wall. Finally, the performance of B2B-RMC in a variety of coronary vessel wall applications, including in a small cohort of patients with confirmed coronary artery disease, is presented.

Acknowledgements

This work would not have been possible without the help, support and coronary arteries of the staff of the Cardiovascular Magnetic Resonance Unit at The Royal Brompton Hospital. In particular, the hard work, experience, attention to detail, patience and inspiration of both Dr Jennifer Keegan and Professor David Firmin were imperative. Further thanks must go to the physics group, the research nurses, the IT support, the administrative staff and the hospital workshop. Finally, my wife Gemma deserves a medal for her patience and support, and the recent addition to our family – Malachy Joseph Andrew – was a definite motivation to finish.

Table of Contents

Abstract	3
Acknowledgements	5
Table of Contents.....	7
List of Figures	15
List of Tables.....	23
Supplementary Material	25
Thesis	25
Selected figures.....	25
Movies.....	26
Publications.....	28
List of Abbreviations.....	29
1. Introduction	33
1.a The heart.....	34
1.a.i Anatomy	34
1.a.ii. Contraction of the heart.....	37
1.a.iii The coronary arteries: a macroscopic view.....	39
1.a.iv Microscopic coronary artery anatomy and physiology	43
1.b Coronary heart disease: from fatty streaks to myocardial infarction	45
1.b.i The development of an atherosclerotic lesion	45
1.b.ii Consequences and treatment of coronary artery disease	47
1.b.ii.1 Treatment of coronary artery disease in the acute setting	47
1.b.ii.2 Treatment of risk factors and CAD in the chronic setting.....	48
1.b.iii Classification of coronary atherosclerotic plaque	49
1.c Motion of the heart and coronary arteries.....	53
1.c.i Cardiac motion	53

1.c.ii	Respiratory induced motion.....	58
1.d	Non-MR based coronary artery imaging.....	61
1.d.i	X-ray contrast angiography.....	62
1.d.ii	Transthoracic and transesophageal ultrasound imaging.....	63
1.d.iii	Intravascular ultrasound imaging.....	64
1.d.iv	Intravascular optical methods.....	65
1.d.v	X-ray computed tomography.....	66
1.d.vi	Molecular imaging.....	71
1.e	MR coronary artery imaging.....	76
1.e.i	MR coronary angiography.....	76
1.e.i.1	Imaging sequences.....	76
1.e.i.2	Contrast mechanisms.....	79
1.e.i.3	Whole heart vs. targeted imaging.....	79
1.e.i.4	Comparison with CT coronary angiography.....	80
1.e.i.5	Future outlook.....	81
1.e.ii	MR coronary vessel wall imaging.....	83
1.e.ii.1	Blood signal suppression.....	83
1.e.ii.2	Imaging sequences.....	84
1.e.ii.3	Respiratory motion compensation and improving efficiency.....	86
1.e.ii.4	Accuracy and reproducibility.....	87
1.e.ii.5	Application in patient cohorts.....	90
1.e.ii.6	T1-weighted contrast- and non-contrast-enhanced imaging.....	92
1.e.ii.7	Future outlook.....	94
1.f	Summary and conclusions.....	95
2.	Motion in MR imaging.....	97
2.a	Motion from the cardiac cycle.....	97
2.a.i	Cardiac gating.....	97
2.a.ii	Selection of the acquisition window.....	98
2.b	Respiratory motion.....	99
2.b.i	Simple breath-holding.....	99
2.b.ii	Monitoring respiration.....	100

2.b.iii	Using displacement information to guide and gate acquisitions	101
2.b.iv	Methods of improving respiratory efficiency in prospectively gated free-breathing acquisitions	102
2.b.v	Slice tracking and motion correction.....	104
2.b.vi	Image based corrections and self-gating.....	107
2.b.vi.1	Self-gated and related techniques.....	108
2.b.vi.2	Techniques using sub-images	109
2.b.vi.3	Techniques acquiring additional low resolution images	110
2.b.vi.4	Techniques using co-registration of multiple full images.....	112
2.b.vii	Conclusions.....	112
2.c	Beat-to-beat respiratory motion correction	113
3.	Development of the B2B-RMC technique.....	117
3.a	Aim.....	117
3.b	Implementation.....	117
3.b.i	Basic sequence implementation.....	118
3.b.ii	Reconstruction, processing and analysis tools.....	120
3.b.ii.1	Reconstruction	120
3.b.ii.2	Processing.....	121
3.b.ii.3	Analysis.....	124
3.c	Improving motion detection and correction	125
3.c.i	Developments to the low resolution acquisitions.....	125
3.c.ii	Selection and evaluation of the search and reference ROIs used in the normalised sub-pixel cross-correlation.....	128
3.c.iii	Gating data acquired at extreme respiratory displacements	131
3.c.iv	Respiratory motion of the chest wall relative to the heart.....	134
3.d	Developments to the high resolution acquisition.....	137
3.d.i	Introduction	137
3.d.ii	Parameter comparison.....	137
3.d.iii	Discussion.....	147
3.e	Development of an optimal coronary artery vessel wall imaging protocol	150
3.f	The modified B2B-RMC sequence.....	153

4.	An accurate and reproducible respiratory motion phantom for coronary artery imaging	155
4.a	Motivation	155
4.b	Design and construction.....	155
4.c	Software development.....	157
4.d	Construction of realistic test objects	158
4.d.i	Introduction	158
4.d.ii	Construction materials.....	158
4.d.iii	The coronary artery test object.....	159
4.d.iv	The coronary vessel wall test object.....	159
4.d.v	Additional complications.....	161
4.e	Validation tests	162
4.e.i	Introduction	162
4.e.ii	Validating motion of the phantom.....	163
4.e.ii.1	Methods	163
4.e.ii.2	Results.....	163
4.e.ii.3	Discussion	164
4.e.iii	Accuracy of NSPCC.....	165
4.e.iii.1	Methods	165
4.e.iii.2	Results.....	165
4.e.iii.3	Discussion	166
4.e.iv	The performance of B2B-RMC for MR coronary angiography	168
4.e.iv.1	Methods	168
4.e.iv.2	Results.....	170
4.e.iv.3	Discussion	170
4.e.v	The performance of B2B-RMC for coronary artery vessel wall imaging.....	173
4.e.v.1	Methods	173
4.e.v.2	Results.....	174
4.e.v.3	Discussion	182
4.e.vi	The dependence of high resolution image quality on the spatial resolution of the low resolution images used in B2B-RMC for coronary artery vessel wall imaging	184

4.e.vi.1	Methods	184
4.e.vi.2	Results	184
4.e.vi.3	Discussion	185
4.e.vii	The dependence of high resolution image quality on the SNR of the low resolution images used in B2B-RMC for coronary artery vessel wall imaging	190
4.e.vii.1	Methods	190
4.e.vii.2	Results	191
4.e.vii.3	Discussion	192
4.f	Discussion.....	197
5.	A direct <i>in-vivo</i> comparison between B2B-RMC and navigator gating applied to targeted MR coronary angiography	201
5.a	Introduction.....	201
5.b	Methods.....	201
5.b.i	B2B-RMC 3D spiral	202
5.b.ii	Navigator gated balanced-steady state free precession.....	205
5.b.iii	Image processing and analysis	205
5.c	Results	208
5.d	Discussion.....	214
6.	3D spiral coronary artery wall imaging with beat to beat respiratory motion correction: Reproducibility and comparison with standard methods.....	217
6.a	Introduction.....	217
6.b	Methods.....	218
6.b.i	Preparatory imaging	218
6.b.ii	Right coronary artery vessel wall imaging	218
6.b.iii	B2B-RMC 3D spiral acquisitions.....	219
6.b.iv	Navigator gated 2D spiral.....	220
6.b.v	Navigator gated 2D Turbo-Spin Echo	221
6.b.vi	Repeat Studies.....	221
6.b.vii	Data Analysis.....	222
6.c	Results	223
6.c.i	Acquisition Duration and Respiratory Efficiency	226
6.c.ii	Vessel Wall Thickness.....	227

6.c.iii	Reproducibility.....	229
6.d	Discussion.....	230
7.	Non-invasive detection of coronary artery wall thickening with age in healthy subjects using 3D spiral imaging with B2B-RMC	237
7.a	Introduction.....	237
7.b	Methods.....	238
7.b.i	Subjects	238
7.b.ii	Imaging	238
7.b.iii	Analysis.....	238
7.b.iv	Statistics.....	239
7.c	Results	239
7.d	Discussion.....	243
8.	Further applications of B2B-RMC to coronary vessel wall imaging	245
8.a	In-plane RCA vessel wall imaging.....	245
8.b	Left coronary vessel wall imaging.....	249
8.c	Simultaneous left and right coronary vessel wall imaging.....	252
8.c.i	Introduction	252
8.c.ii	Methods	252
8.c.iii	Results.....	254
8.c.iv	Discussion.....	257
8.d	Preliminary experience using 3D spiral imaging with B2B-RMC for coronary vessel wall imaging in patients.....	258
8.d.i	Introduction	258
8.d.ii	Methods	258
8.d.ii.1	Recruitment.....	258
8.d.ii.2	MR imaging.....	259
8.d.iii	Results.....	259
8.d.iv	Discussion.....	265
9.	Discussion.....	267
9.a	Summary of findings.....	267
9.b	Limitations	269

9.c Further work.....	271
9.c.i Processing.....	271
9.c.ii Improved left coronary artery and in-plane vessel wall imaging.....	271
9.c.iii Parallel imaging and compressed sensing.....	271
9.c.iv Clinical studies.....	271
9.d Conclusion.....	272
References	273
Appendix A: Publications arising	299
Appendix B: Conference presentations and posters arising.....	300
Presentations.....	300
Posters	301

List of Figures

Figure 1.1: The circulatory system.....	35
Figure 1.2: A schematic of anatomy and flow within the heart	36
Figure 1.3: An ex-vivo heart.....	37
Figure 1.4: A Wiggers diagram	39
Figure 1.5: The coronary arteries	41
Figure 1.6: Blood flow to the myocardium from the major coronary arteries using a 16- segment model.....	42
Figure 1.7: Blood flow velocity in the coronary arteries.....	43
Figure 1.8: Anatomy of an arterial wall	44
Figure 1.9: Histology slides of coronary arteries.....	44
Figure 1.10: Possible developmental stages of a fibrous cap atheroma in the coronary arteries.....	46
Figure 1.11: Progression of plaque types within the modified AHA scheme	50
Figure 1.12: Motion of the left ventricular free wall assessed using MR phase velocity mapping.....	55
Figure 1.13: Motion of the RCA origin with the cardiac cycle in 4 patients.....	57
Figure 1.14: Right coronary rest period duration as a function of heart rate	57
Figure 1.15: Motion of the heart with respiration demonstrating the subject specific and hysteretic nature of the relationship	59
Figure 1.16: Respiratory motion of the origin of the RCA	61
Figure 1.17: A comparison of intracoronary imaging techniques	66
Figure 1.18: CAC scoring images.....	68
Figure 1.19: Reformatted images from CT coronary angiography	69
Figure 1.20: Luminography images of a 90% stenosis in the LAD	70
Figure 1.21: Coronary vessel wall thickening in the LAD assessed by CT	71

Figure 1.22: PET/CT imaging of the LAD with ^{18}F -FDG tracer.....	73
Figure 1.23: In-stent thrombus imaged with a thrombin targeting contrast agent (EP-2104R) using MR.....	74
Figure 1.24: A comparison of Cartesian GRE and spiral MR coronary angiography techniques.....	78
Figure 1.25: Whole heart MR coronary angiography images.....	80
Figure 1.26: Coronary vessel wall imaging and x-ray contrast angiography.....	85
Figure 1.27: In-plane images of diseased RCAs.....	87
Figure 1.28: Vessel wall remodelling using MR coronary artery vessel wall imaging.....	91
Figure 1.29: Hyperintense plaque on non-contrast enhanced T1 weighted black-blood MR imaging.....	94
Figure 2.1: Accept/reject navigator gating.....	102
Figure 2.2: A comparison of navigator based respiratory motion correction techniques	107
Figure 2.3: Example of PROPELLER based respiratory motion correction	110
Figure 2.4: Comparison of B2B-RMC with no correction and navigator based correction in coronary artery vessel wall imaging.....	111
Figure 2.5: Motion correction of multiple images acquired during free-breathing.....	112
Figure 2.6: The original B2B-RMC sequence for dark blood coronary artery vessel wall imaging	114
Figure 2.7: Example low resolution images obtained in six consecutive cardiac cycles demonstrating beat-to-beat respiratory translations of the epicardial fat	115
Figure 3.1: The sequence diagram for the original B2B-RMC implementation	119
Figure 3.2: Cross-sectional anatomy imaged in the B2B-RMC technique	122
Figure 3.3: An ex-vivo human heart showing the RCA within the right AV groove	123
Figure 3.4: Coloured overlay of the low resolution fat data onto the high resolution water data.....	123
Figure 3.5: Schematic representation of the 3D sub-pixel cross correlation shown in 2D.	124
Figure 3.6: A schematic of the low resolution acquisition with partial Fourier acquisition.....	127
Figure 3.7: A comparison of low resolution phantom images acquired with varying spiral length and in-plane resolution.....	127
Figure 3.8: Visualising the NSPCC results	129
Figure 3.9: Respiratory displacements obtained using NSPCC plotted against the diaphragmatic navigator displacement in a typical subject	130

Figure 3.10: Respiratory displacements obtained from NSPCC plotted against diaphragmatic navigator displacement in a case of an insufficient search ROI	131
Figure 3.11: The diaphragmatic navigator displacement corresponding to the images shown in figure 3.12.....	133
Figure 3.12: The effect of extreme respiratory displacements on B2B-RMC correction	133
Figure 3.13: The effect of non-rigid motion between the chest wall and coronary arteries in B2B-RMC	134
Figure 3.14: A numerical representation of the chest wall and right AV groove containing the RCA	135
Figure 3.15: The results of the chest wall motion – numerical simulations.....	135
Figure 3.16: Ghosting artefact caused by dark blood preparation and navigator echoes in coronary vessel wall imaging with B2B-RMC.....	136
Figure 3.17: Example images from comparison 1	141
Figure 3.18: Example images from comparison 2	142
Figure 3.19: Example images from comparison 3	144
Figure 3.20: Example images from comparison 4	145
Figure 3.21: Example images from comparison 5	146
Figure 3.22: Example images from comparison 6	147
Figure 3.23: The effect of an insufficient sampling rate in the spiral readouts.....	150
Figure 3.24: The optimised protocol for RCA vessel wall imaging with B2B-RMC.....	152
Figure 3.25: The modified B2B-RMC imaging sequence (imaging section only).....	153
Figure 4.1: A schematic of the basic phantom design	156
Figure 4.2: The completed respiratory motion phantom	157
Figure 4.3: A schematic of the coronary artery test object	159
Figure 4.4: The effect of air-tissue boundaries in spiral images.....	160
Figure 4.5: The susceptibility artefact caused by air vs. wax	160
Figure 4.6: The design of the coronary artery wall test object	161
Figure 4.7: Spiral images of a coronary artery vessel wall test object in three orientations.....	162
Figure 4.8: The frequency offset of lard and of oil	162
Figure 4.9: Validation of phantom motion using a navigator	164
Figure 4.10: A preliminary phantom used in the tests of NSPCC performance	165
Figure 4.11: The performance of the NSPCC for in-plane motion.....	166

Figure 4.12: The performance of the NSPCC for through-plane motion	167
Figure 4.13: The physiological respiratory traces used in the respiratory motion phantom tests with the coronary artery and coronary artery vessel wall test objects.....	169
Figure 4.14: Results of the phantom tests comparing navigator gating and B2B-RMC in a coronary artery test object.....	172
Figure 4.15: The phantom setup used in the coronary artery wall imaging tests.....	174
Figure 4.16: Images from the tests using a coronary vessel wall test object	176
Figure 4.17: B2B-RMC displacements plotted with navigator displacements for the phantom tests using the coronary artery wall test object (sinusoidal input, $A_{pp}=15\text{mm}$, $T=5\text{s}$)	177
Figure 4.18: B2B-RMC displacements plotted with navigator displacements for the phantom tests using the coronary artery wall test object (sinusoidal input, $A_{pp}=25\text{mm}$, $T=5\text{s}$)	178
Figure 4.19: B2B-RMC displacements plotted with navigator displacements for the phantom tests using the coronary artery wall test object (sinusoidal input, $A_{pp}=15\text{mm}$, $T=3\text{s}$)	179
Figure 4.20: The performance of B2B-RMC in correcting sinusoidal motion in images of a coronary artery wall test object.....	180
Figure 4.21: Example uncorrected, B2B-RMC and gated images acquired with a coronary artery test object following physiological respiratory traces 1-3.....	181
Figure 4.22: Example uncorrected, B2B-RMC and gated images acquired with a coronary artery test object following respiratory traces 4-6.....	182
Figure 4.23: The effect of in-plane resolution on the performance of B2B-RMC in correcting sinusoidal motion of a coronary artery wall test object.....	186
Figure 4.24: B2B-RMC displacements plotted with navigator displacements for the sinusoid with $A_{pp}=25\text{mm}$ and $T=5\text{s}$ after degrading the low resolution images to $21.6\times 21.6\text{mm}$ in-plane resolution	187
Figure 4.25: The effect of in-plane resolution on the performance of B2B-RMC in correcting respiratory motion of a coronary artery wall test object (traces 1-3).....	188
Figure 4.26: The effect of in-plane resolution on the performance of B2B-RMC in correcting respiratory motion of a coronary artery wall test object (traces 4-6).....	189
Figure 4.27: The variation of the FWHM of the intensity profiles with noise in the low resolution images.....	190

Figure 4.28: The effect of noise on the performance of B2B-RMC in correcting sinusoidal motion of a coronary artery wall test object.....	193
Figure 4.29: B2B-RMC displacements plotted with navigator displacements for the sinusoid with $A_{pp}=15\text{mm}$ and $T=5\text{s}$ after increasing the noise in the low resolution images by a factor of 25	194
Figure 4.30: The effect of noise on the performance of B2B-RMC in correcting respiratory motion of a coronary artery wall test object (traces 1-3)	195
Figure 4.31: The effect of noise on the performance of B2B-RMC in correcting respiratory motion of a coronary artery wall test object (traces 4-6)	196
Figure 4.32: The variation of the FWHM of the intensity profiles with noise in the low resolution images.....	197
Figure 5.1: The B2B-RMC 3D spiral sequence used for the MR coronary angiography study	203
Figure 5.2: Transparent overlay of end-expiratory low resolution fat images onto the uncorrected high resolution image to aid ROI positioning	204
Figure 5.3: Schematic diagram of the nav-bSSFP acquisition	205
Figure 5.4: Calculation of the vessel diameter and sharpness from the MIP images	207
Figure 5.5: Comparison MIP images with and without motion correction	208
Figure 5.6: Example images from one subject comparing B2B-RMC 3D spiral to nav-bSSFP	209
Figure 5.7: Example images from one subject comparing B2B-RMC 3D spiral to nav-bSSFP	210
Figure 5.8: Example images from one subject comparing B2B-RMC 3D spiral to nav-bSSFP	210
Figure 5.9: Example imaging from one subject comparing B2B-RMC 3D spiral to nav-bSSFP	211
Figure 5.10: Comparison of B2B-RMC 3D spiral images corrected for proximal and distal RCA motion compared to the equivalent images acquired with nav-bSSFP	212
Figure 5.11: B2B-RMC respiratory displacements plotted against navigator displacements in the proximal and distal RCA.....	213
Figure 5.12: Curved planar reformat of combined datasets corrected for proximal and distal RCA motion acquired using the B2B-RMC 3D spiral technique.....	213
Figure 6.1: Cross-sectional 2D MR coronary angiography planning studies	218
Figure 6.2: The sequence diagram for the 3D spiral with B2B-RMC acquisition.....	219

Figure 6.3: A schematic of the 2D spiral navigator gated sequence.....	221
Figure 6.4: A schematic of the 2D TSE navigator gated sequence	221
Figure 6.5: Circular ROIs drawn around the coronary vessel wall for wall thickness measurements.....	222
Figure 6.6: Example images obtained using all techniques in one healthy subject	224
Figure 6.7: Example images obtained using all techniques in one healthy subject	225
Figure 6.8: Example images obtained using all techniques in one healthy subject	225
Figure 6.9: Intra- and inter-observer reproducibility of the vessel wall thickness measurement technique	228
Figure 6.10: Example initial and repeat image acquired in one subject.....	229
Figure 6.11: Inter-study reproducibility	230
Figure 6.12: Over-estimation of the RCA rest period by visual analysis	232
Figure 6.13: Under-estimation of the RCA rest period by visual analysis.....	232
Figure 6.14: Example images from the initial and repeat studies of subject 8.....	233
Figure 6.15: Example images from the initial and repeat studies of subject 9	234
Figure 7.1: Example coronary vessel wall images from three healthy subjects	241
Figure 7.2: The change in coronary vessel wall thickness and W/OW with age	242
Figure 7.3: The change in coronary outer wall area and lumen area with vessel wall thickness.....	242
Figure 8.1: Example of cross-sectional and in-plane right coronary vessel wall imaging using B2B-RMC 3D spiral imaging.....	247
Figure 8.2: Example of cross-sectional and in-plane right coronary vessel wall imaging using B2B-RMC 3D spiral imaging.....	247
Figure 8.3: Example of cross-sectional and in-plane right coronary vessel wall imaging using B2B-RMC 3D spiral imaging.....	248
Figure 8.4: Example of cross-sectional and in-plane right coronary vessel wall imaging using B2B-RMC 3D spiral imaging.....	249
Figure 8.5: Cross-sectional and in-plane images of the LAD vessel wall acquired in a healthy subject using B2B-RMC 3D spiral imaging.....	251
Figure 8.6: A schematic diagram of the modified B2B-RMC 3D spiral sequence used for simultaneous left and right coronary vessel wall imaging.....	253
Figure 8.7: Location of the imaging volumes and the dark blood reinversion slabs used for simultaneous left and right coronary artery imaging	254

Figure 8.8: Example images from a simultaneous left and right 3D coronary vessel wall acquisition with B2B-RMC	255
Figure 8.9: Example images from a simultaneous left and right 3D coronary vessel wall acquisition with B2B-RMC	256
Figure 8.10: Example images from a simultaneous left and right 3D coronary vessel wall acquisition with B2B-RMC compared to a standard acquisition.....	256
Figure 8.11: Cross-sectional B2B-RMC 3D spiral images acquired in patient 1	261
Figure 8.12: MR coronary angiography planning study for patient 2 showing the location of the coronary vessel wall imaging volume.....	262
Figure 8.13: Cross-sectional B2B-RMC 3D spiral images acquired in patient 2	262
Figure 8.14: MR coronary angiography planning study for patient 3 showing the location of the coronary vessel wall imaging volume.....	263
Figure 8.15: Cross-sectional B2B-RMC 3D spiral images acquired in patient 3	263
Figure 8.16: In-plane MR coronary angiography and coronary vessel wall images acquired in patient 5	264
Figure 8.17: In-plane B2B-RMC 3D spiral images acquired in patient 5	265
Figure 8.18: Cross-sectional B2B-RMC 3D spiral images acquired in patient 5	265

List of Tables

Table 1.1: Diameters of normal coronary arteries in right dominant men and women assessed by x-ray coronary angiography.....	40
Table 1.2: Vessel wall thicknesses obtained at autopsy in male subjects who died of non- coronary related causes.....	41
Table 1.3: Atherosclerotic plaque classification according to Virmani et al. (2000).....	51
Table 1.4: Criteria for defining vulnerable plaques.....	52
Table 1.5: Motion of the ventricles in healthy volunteers throughout the cardiac cycle.....	54
Table 1.6: Maximum displacements of the coronary arteries within the cardiac cycle during breath-holding in 8 healthy volunteers.....	56
Table 1.7: Whole heart rigid transformation parameters and selected point displacements between end expiration and end inspiration for a fixed point in the cardiac cycle.....	60
Table 1.8: Maximum displacement of coronary landmarks through the respiratory cycle.....	60
Table 1.9: Velocity of various points in the coronary artery system during free breathing.....	60
Table 1.10: Coronary vessel wall thickness obtained using MR and other measurement techniques in normal subjects.....	89
Table 2.1: Slice tracking factors relating the SI, AP and LR motion of different regions of the heart to the SI motion of the diaphragm.....	106
Table 3.1: A comparison of low resolution imaging parameters used in the original work and those chosen here.....	128
Table 3.2: Imaging parameters used for the basic high resolution acquisition.....	138
Table 3.3: Results of the imaging parameter comparisons.....	140
Table 3.4: Imaging parameters used for the basic high resolution acquisition.....	149
Table 4.1: Results of the phantom tests using the coronary artery test object.....	171
Table 5.1: Comparison of B2B-RMC 3D spiral and nav-bSSFP sequence parameters.....	204
Table 5.2: Comparison of the respiratory efficiency, vessel sharpness and vessel diameter between sequences.....	212

Table 6.1: High resolution coronary artery wall imaging parameter comparison	220
Table 6.2: Image quality scores from the high resolution coronary artery vessel wall acquisitions.....	226
Table 6.3: Overview of respiratory efficiency, duration and related parameters in the initial study by imaging technique.....	227
Table 6.4: Vessel wall thicknesses obtained in the initial and repeat studies	228
Table 6.5: Inter-study reproducibility.....	229
Table 7.1: Summary of subject characteristics.....	240
Table 7.2: Summary of results by sex.....	241
Table 8.1: Patient characteristics and the corresponding B2B-RMC 3D spiral acquisition parameters.....	259

Supplementary Material

Thesis

Electronic copy of this thesis

Selected figures

Figure 3.24

Figure 4.14

Figure 4.16

Figure 4.20

Figure 4.21

Figure 4.22

Figure 4.23

Figure 4.25

Figure 4.26

Figure 4.28

Figure 4.30

Figure 4.31

Movies

- S.1 The fat around the right coronary artery in 9 of the 16 slices imaged every cardiac cycle. Each frame corresponds to one RR-interval. The movie, therefore, shows the fat moving with respiration. This example was acquired in one healthy subject.
- S.2 Clicking through the slices of a 3D coronary vessel wall imaging volume using the image viewer, adding an overlay of the low resolution fat data, zooming in and adjusting the contrast and brightness.
- S.3 Selecting and modifying the search (blue) and reference (red) ROIs for the NSPCC in 3D.
- S.4 Rotating a 3D targeted MR coronary angiography data set in the image viewer before selecting the slices and nulling overlying anatomy for a parallel maximum intensity projection (MIP).
- S.5 Selecting the points in a 3D targeted MR coronary angiography study for creating a curved planar reformat image in the image viewer.
- S.6 Measuring the FWHM and 20-80% intensity distance (the inverse of the sharpness) on a MIP from a 3D targeted MR coronary angiography study in the image viewer. The image is first interpolated and zoomed to show the right coronary artery. The user traces the centre of the vessel lumen (the proximal section in this case). Intensity profiles perpendicular to the line along the centre of the vessel lumen are generated (the magenta lines show every 5th profile). From the intensity profiles the full width half maximum (green points) and 20% and 80% (red and blue points respectively) are found. The user is able to remove any points which are clearly incorrect, before the FWHM and 20%-80% intensity distance is plotted with the displacement along the vessel.
- S.7 Measuring vessel wall thickness on a coronary vessel wall image using the image viewer. The inner and outer edge of the coronary vessel wall are selected with circular ROIs. The average vessel wall thickness is then calculated.
- S.8 Using the measurement viewer. The original reference (blue) and search (red) ROIs are shown superimposed on any slice or volume the user selects. The central slice and in-plane (x and y) displacement of the reference ROI for the current NSPCC result is shown (yellow number and cyan text) with the displaced reference ROI.
- S.9 A method of visualising the NSPCC output, shown for data acquired in one example subject. Three perpendicular slices of the r -values obtained using NSPCC containing the peak r -value (circle), are shown on the left hand side with the scale of each shown in mm. The slice of the search ROI nearest to the peak r -value is shown on the right with the scale shown in mm. The position of the slice shown in the through-plane (z) direction is plotted

below. The slice shown on the right should demonstrate a similar shaped piece of fat moving in-plane.

- S.10 The fat around the right coronary artery in one slice after correction for respiratory motion using B2B-RMC. Each frame corresponds to the data acquired in one RR-interval in one example healthy subject. The size of the image in mm is indicated.
- S.11 One slice of the low resolution fat volume, acquired in every simulated RR-interval, of a basic test object, moving sinusoidally on a respiratory motion phantom. See section 4.e.iii for a full description of these tests.
- S.12 One slice of the low resolution volume acquired in every simulated RR-interval of a basic test object on the respiratory motion phantom (as also shown in S.11). This image has been corrected for motion using B2B-RMC. The size of the image in mm is indicated.
- S.13 A method of visualising the NSPCC output, shown for data acquired in a basic test object (also shown in S.11 and S.12) moving with sinusoidal motion on a respiratory motion phantom.

Publications

- Scott AD, Keegan J, Firmin D. Motion in cardiovascular MRI. *Radiology* 2009. 250; 331-351.
- Scott AD, Keegan J, Firmin D. Cardiac and respiratory motion in MRI of the heart. *Rad Magazine* March 2010.
- Scott AD, Keegan J, Firmin D. High resolution 3D magnetic resonance coronary vessel wall imaging with near 100% respiratory efficiency using epicardial fat tracking: reproducibility and comparison with standard methods. *Journal of Magnetic Resonance Imaging* 2011. 33; 77-86.
- Scott AD, Keegan J, Firmin D. Beat-to-beat respiratory motion correction with near 100% efficiency: A quantitative assessment using high resolution coronary artery imaging. *Magnetic Resonance Imaging* 2011. 29; 568-578.

List of Abbreviations

$\langle A_{pp} \rangle$ – mean peak to peak amplitude

$\langle T \rangle$ – mean period

1RR gating – data acquired every cardiac cycle

2RR gating – data acquired every other cardiac cycle

3D – three dimensional

AP – anterior-posterior

A_{pp} – peak to peak amplitude

ARA – acceptance/rejection algorithm

AV – atrioventricular

B_0 – the main magnetic field

B2B-RMC – beat-to-beat respiratory motion correction

BMI – body mass index

BPM – beats per minute

bSSFP – balanced steady state free precession

CABG – coronary artery bypass grafting

CAC – coronary artery calcium

CAD – coronary artery disease

CBF - coronary blood flow

CFR - coronary flow reserve

CLAWS – continuously adaptive windowing strategy

CNR – contrast to noise ratio

COPE – centrally ordered phase encoding

CT – x-ray computed tomography

DENSE - displacement encoding with stimulated echoes

DVA – diminishing variance algorithm

EBCT – electron beam CT

ECG – electrocardiogram

EPI – echo planar imaging

FDG – flourodeoxyglucose

FFR – fractional flow reserve

FLASH – fast low angle shot

FOV – field of view

FWHM – full width half maximum

GRE – gradient recalled echo

GRICS – generalised reconstruction by inversion of coupled systems

GUI – graphical user interface

HARP - harmonic phase

HDL - high density lipoprotein

HOPE – hybrid ordered phase encoding

HR – heart rate

IVUS – intravascular ultrasound

LAD – left anterior descending coronary artery

LCX – left circumflex coronary artery

LDL – low density lipoprotein

LM – left main coronary artery

LR – left-right

LV – left ventricle

MAG – motion adapted gating

MDCT – multi-detector CT

MI – myocardial infarction

MIP – maximum intensity projection

MMP – matrix metalloproteinases

MR – magnetic resonance

nav-bSSFP – navigator gated balanced steady state free precession

NO - nitrous oxide

NSF – nephrogenic systemic fibrosis

NSPCC – normalised sub-pixel cross-correlation

OCT – optical coherence tomography

PAWS – phase ordering with automatic window selection

PCI – percutaneous coronary intervention

PDA – posterior descending artery

PET – positron emission tomography

QCA – quantitative coronary angiography

RA - right atrium

RCA – right coronary artery

RHD – right hemi-diaphragm

RMS – root mean square

ROI – region of interest

ROPE – respiratory ordered phase encode

RRG – retrospective respiratory gating

RV – right ventricle

SA – sinoatrial

SI – superior-inferior

SMC – smooth muscle cell

SNR – signal to noise ratio

SPAMM - spatial modulation of magnetisation

SPECT – single photon emission computed tomography

T – period

T1 – the time constant of longitudinal recovery of magnetisation

T2 – the time constant of transverse dephasing of magnetisation

T2-prep – T2-weighting preparatory pulse

TI – inversion time

TIMI – thrombosis in myocardial infarction

TSE – turbo spin echo

W/OW – wall/outer wall area ratio

1. Introduction

Atherosclerotic coronary artery disease (CAD) is a degradation of the wall of the arteries supplying the heart muscle with blood, eventually leading to narrowing or complete blockage of the lumen. Cardiovascular disease is the most common cause of death in the UK, and CAD accounts for the majority of these fatalities (Scarborough et al., 2010). Current diagnostic techniques (see section 1.d and 1.e for a full description) predominantly diagnose the extent of already severe disease and are often invasive and/or require the use of ionising radiation and nephrotoxic contrast agents. There is a pressing clinical need for a non-invasive technique which may be used to assess the atherosclerotic burden in the coronary arteries in both early and late disease in a reproducible manner, in order to assess disease progression, regression and response to therapy and/or lifestyle changes. This thesis describes the implementation, development and evaluation of the efficacy of a three dimensional (3D) magnetic resonance (MR) coronary vessel wall imaging technique with a novel efficient respiratory motion correction scheme. The small size and mobile nature of the coronary arteries means that MR coronary vessel wall imaging is extremely challenging and as a result, it has so far had very limited impact on clinical practice. The work described here results in a reproducible, reliable and flexible technique with potentially wide ranging implications.

The thesis is structured as follows. This initial chapter describes the need for a new 3D MR coronary vessel wall imaging technique, starting with anatomy, physiology and motion of the heart; CAD and techniques used in imaging the coronary arteries, including currently available MR methods. This is followed by a review of available strategies used to combat motion in cardiovascular MR imaging (chapter 2). The efficacy of the respiratory motion correction scheme developed (see chapter 3 for a description of the developments) is demonstrated in controlled conditions using a purpose built respiratory motion phantom (chapter 4). Subsequently, *in-vivo* studies demonstrate the performance of the technique for imaging of the coronary arteries (chapter 5) and coronary vessel walls (chapter 6) including a comparison of vessel wall thickness and reproducibility measured using four MR techniques. In later sections, a study demonstrating the first non-invasive demonstration of coronary vessel wall thickening with age in healthy subjects (chapter 7) is described; initial results with a new and novel technique for further improving overall imaging efficiency in MR coronary vessel wall are presented (chapter 8); and the technique is demonstrated in MR coronary vessel wall imaging of patients (also chapter 8).

This first chapter briefly reviews the anatomy and physiology of the heart and coronary artery system before describing the formation and development of an atherosclerotic plaque, its classification and potential treatments available. However a full description can be found in any comprehensive modern cardiology text (Fuster et al. (2008) for example). A review of the motion of the heart and coronary arteries with the cardiac and respiratory cycles is then presented. Finally in this chapter, existing imaging techniques available for assessment of coronary artery disease are discussed with a particular focus on MR based methods.

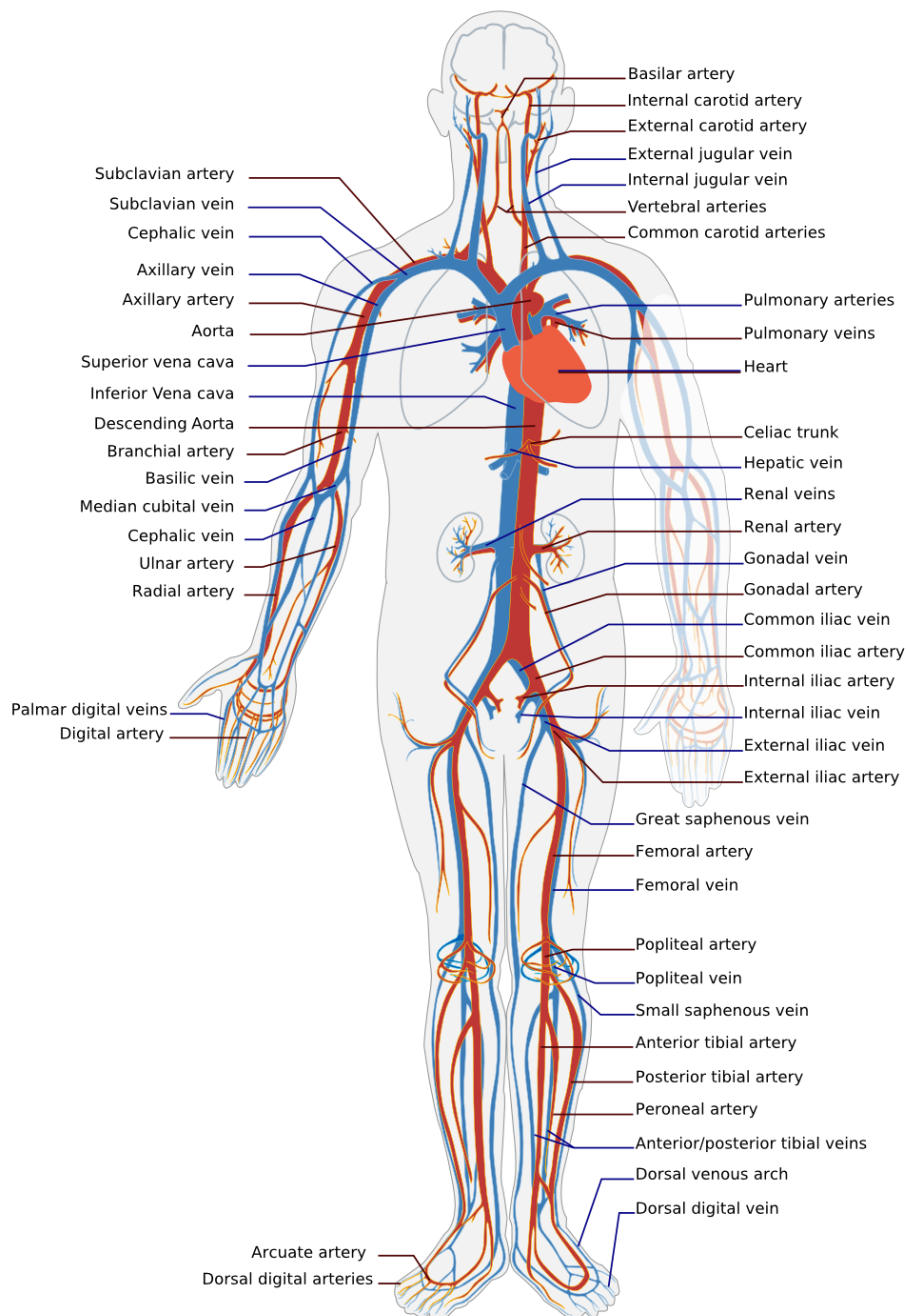
1.a The heart

The circulation of blood serves to distribute oxygen, nutrients and heat throughout the body (see figure 1.1). Blood flow is primarily driven by the heart (see figure 1.2a.) which is a four chamber muscular pump located between the lungs, anatomically slightly left of centre underneath the rib cage. Deoxygenated blood enters the heart from the venous system, primarily through the venae cavae into the right heart which pumps blood towards the lungs via the pulmonary artery. Blood is oxygenated in the lungs and returned to the left heart via the pulmonary veins. Oxygenated blood exits the left heart via the aorta at a rate of approximately 5L/min (Barrett and Ganong, 2010) to supply all organs of the body.

1.a.i Anatomy

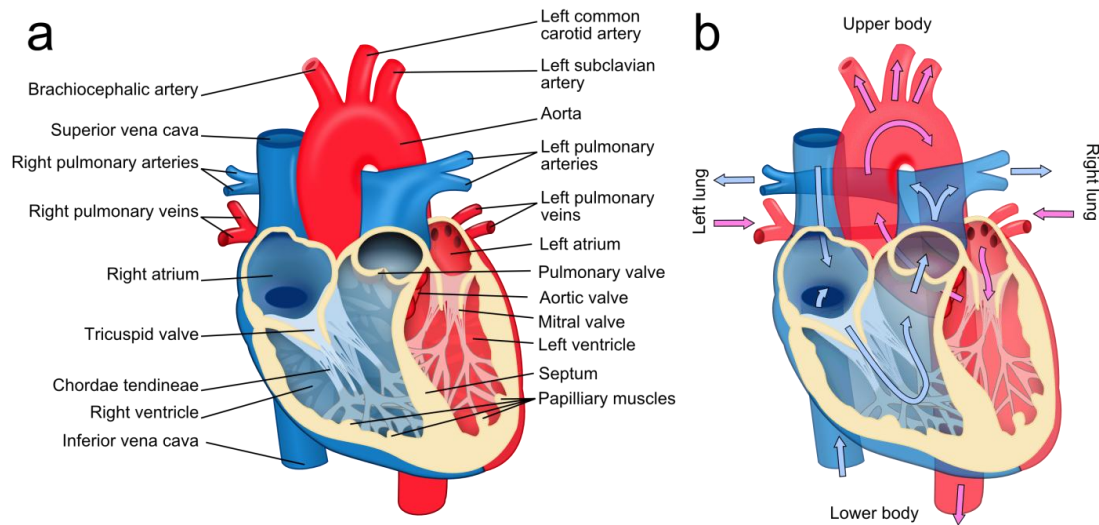
The heart is located within the fluid filled double-walled sac of the pericardium enabling movement relative to the surrounding organs with little friction. The large fist sized muscular structure is 250-350g in mass (Kumar et al., 2005), when empty and is orientated such that the narrow end (the apex) points inferiorly and towards the subject's left.

Figure 1.1: The circulatory system



The heart pumps blood around the human circulation. Vessels carrying oxygenated blood (arteries, excluding the pulmonary arteries) are coloured red, whereas vessels carrying deoxygenated blood (veins, excluding the pulmonary veins) are coloured blue. Reproduced from Wikipedia (http://en.wikipedia.org/wiki/Circulatory_system, last accessed 23rd December 2010).

Figure 1.2: A schematic of anatomy and flow within the heart



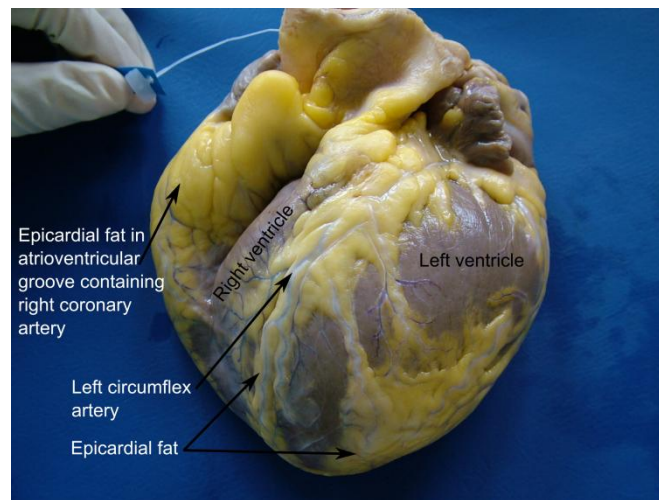
The structure of the heart (a) and the flow of oxygenated (red) and deoxygenated blood (blue) through the heart (b). Reproduced from Wikimedia Commons (http://commons.wikimedia.org/wiki/File:Heart_diagram-en.svg and http://commons.wikimedia.org/wiki/File:Heart_diagram_blood_flow-en.svg) under the Creative Commons Attribution-Share Alike 3.0 Unported license. Last accessed 3rd January 2011.

Both the left and right heart consist of two chambers (see figure 1.2.a), the upper atria and the lower ventricles. The thicker walled ventricles provide the strength for the ejection of blood whereas the thinner atria serve to fill the ventricles with blood. The walls of each of the 4 cardiac chambers consist of compacted heart muscle with an inner lining of trabeculations which are an irregular mesh of muscular strands, not present on the in and outflow tracts. The heart wall consists of 3 layers: an inner endocardium, the muscular myocardium (which makes up the majority of the thickness) and the outer epicardium. The one way flow of blood is ensured by valves (see figure 1.2.b). The mitral and tricuspid valves prevent back flow from the ventricles to the atria in the left and right heart respectively. The pulmonary and aortic valves prevent back flow from the pulmonary artery and aorta respectively. Each of the valves consists of three moving leaflets, except the mitral valve which consists of two, which meet near the free edge when closed. The outer edge of each of the valves is a supportive ring of fibrous tissue. Leaflets of the mitral and tricuspid valve are attached to the ventricular myocardium via tendons (chordae tendineae) connected to the papillary muscles which exert a degree of control over the leaf motion. The outflow aortic and pulmonary valves have no such muscular control or tendon attachments.

Within the pericardial sac, around 80% of the heart's surface is covered in a layer of fat. Epicardial fat deposits are situated in the atrioventricular (AV) and interventricular grooves surrounding the major coronary artery branches (Iacobellis et al., 2005, Rabkin, 2007), as shown in figure 1.3. At body temperature this fat is liquid and in normal subjects constitutes around 20% of ventricular mass (Corradi et al., 2004), but the deposits increase with age to a maximum somewhere between age 20 and 40 years. The functions of these fat deposits are thought to include buffering the forces

on the coronary arteries during cardiac contraction and allowing them to expand in response to arterial pressure and to Glagov remodelling (see section 1.b)(Rabkin, 2007).

Figure 1.3: An ex-vivo heart



An ex-vivo normal human heart. Heart muscle tissue is purple and fat is a yellow colour. The epicardial coronary arteries are visible within the epicardial fat. Image courtesy of Dr Mary Sheppard, Director of the CRY Unit for Cardiac Pathology, Imperial College London.

1.a.ii. Contraction of the heart

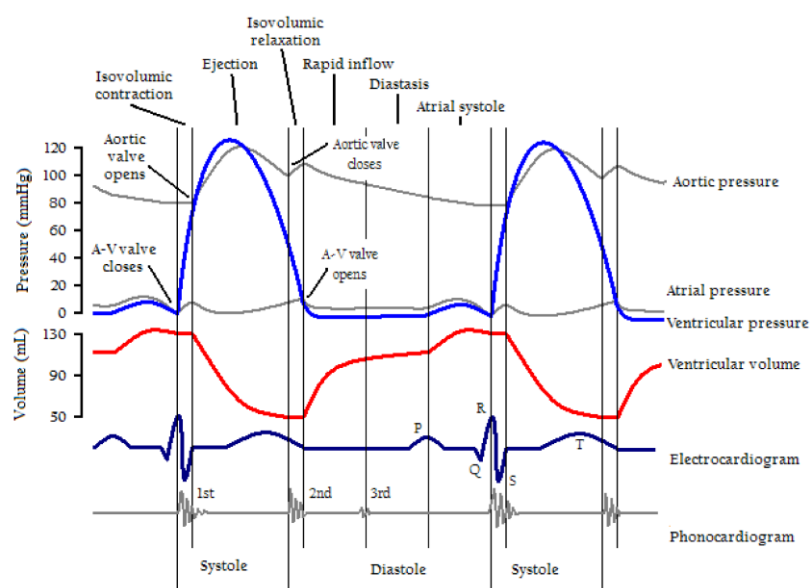
The cells of the myocardium, known as myocytes, are maintained at a resting potential of -80 to -90mV with respect to the extracellular space via an influx and efflux of K^+ , Cl^- , Ca^{2+} and Na^+ ions using ion pumps and active membrane channels. When the cell reaches a threshold voltage (around -40mV to -50mV), voltage sensitive channels in the membrane open, allowing an influx of Ca^{2+} ions and therefore, depolarisation of the cell. It is the increased cellular Ca^{2+} concentration which results in contraction of the myocyte. During depolarisation the membrane potential reaches a peak of around +10mV and then repolarises after some time due to further changes in the selective permeability of the cell. In most myocytes, the threshold potential is only reached when the cell is stimulated by the depolarisation of neighbouring myocytes, but in some (non-contracting) cells, the resting potential of the myocytes naturally drifts towards 0V and reaches the depolarising potential without stimulation. These self-stimulating cells act as the pacemaker of the heart and are located within several regions of the heart. The primary pacemaker is the sinoatrial node (SA node), located in the right atrium (RA) near the opening of the superior vena cava. Without external stimulation, the SA node depolarises around 100 times per minute. In healthy subjects, however, the depolarisation frequency (heart rate) is controlled by a central nervous system connection to the SA node and by the release of adrenaline and noradrenaline from the adrenal medulla, generally resulting in a resting heart rate of 50-80 beats per minute (BPM). Depolarisation of the SA node results in a depolarisation wave (positive potential) travelling across the right atrium. The positive potential also travels down internodal pathways (the Bachman, Wenckebach and Thorel tracts) to the atrioventricular (AV) node which is located in the septum at the level of the AV valve attachments. The AV node acts as a secondary pace maker, firing at 40-60

BPM in the absence of stimulation from the SA node. Importantly, the AV node also delays the spread of the depolarization by around 0.12s, allowing time for the blood to move from the atria into the ventricles. From here the depolarisation travels down the bundle of His to the left and right bundle branches, then on to the Purkinje fibres which distribute the action potential to the ventricles. These conduction fibres may also act as tertiary pace makers firing at between 30 and 60BPM.

The increased cellular concentration of Ca^{2+} ions as a result of the cell depolarisation causes the myofilaments (comprising 45-60% of myocardial volume) within the cell, and hence the cell itself, to contract. Contraction of the myofilaments is a complex, incompletely resolved process that is thought to be the result of the generation and destruction of links between myosin and actin fibres, which constitute the myofilaments. The orientation of the myocytes is dependent on their depth within the myocardium (Villarreal et al., 2005). Between the endo and epicardium, fibre orientation can rotate up to 180° which has important consequences for the motion of the chambers, discussed in section 1.c.i.

The electrical action of the heart may be recorded at the exterior of the chest in an electrocardiogram (ECG) and the action of the valves closing is audible in the heart sounds. The ECG is commonly related to the intracardiac pressure using a Wiggers diagram, as shown in figure 1.4. Beginning in diastole (the phase in which the heart is relaxing and relaxed), blood flows into the ventricles via the atria because the venous blood pressure is greater than that in the heart. Atrial depolarization is observed as the P-wave of the ECG. The corresponding atrial contraction causes an increase in atrial pressure and, therefore, further filling of the ventricles. Ventricular depolarization, observed as the QRS complex (duration: ~80ms, starting ~180ms after the beginning of the P-wave (Barrett and Ganong, 2010)) in the ECG denotes the beginning of the systolic phase. During ventricular contraction, the ventricular free walls move inwards towards the septum, which remains relatively stationary in the centre. This contraction causes an increase in the ventricular pressure, resulting in closure of the atrioventricular valves, which is audible as the first heart sound. All valves are now closed and the contraction of the ventricles results in an isovolumetric increase in ventricular pressure until it exceeds the aortic (or pulmonary artery) pressure whereupon the pulmonary and mitral valves open. Rapid ejection of blood occurs in this phase with an associated reduction in ventricular volume. Towards the end of this ejection phase, ventricular repolarisation occurs which is observed as the T-wave (starting ~320ms after the S-wave) in the ECG (atrial repolarisation is masked by the QRS complex). Once aortic (or pulmonary) pressure exceeds the ventricular pressure, the pulmonary and mitral valves close, audible as the second heart sound and indicating the beginning of diastole (the filling stage). All valves are again closed resulting in an isovolumetric reduction in ventricular pressure. Once ventricular pressure falls below that of the atria, the atrioventricular valves open and ventricular filling begins once again.

Figure 1.4: A Wiggers diagram



A Wiggers diagram describes the pressure and volume in the left heart and their relationship to the ECG signal and heart sounds. Reproduced from Wikimedia Commons (http://commons.wikimedia.org/wiki/File:Cardiac_Cycle_Left_Ventricle.PNG) under the Creative Commons Attribution-Share Alike 2.5 Generic license. Last accessed 7th January 2011.

1.a.iii The coronary arteries: a macroscopic view

The heart requires more oxygen per unit mass than any other organ in the body ($8\text{mL min}^{-1} 100\text{g}^{-1}$ at rest) which is provided by the coronary artery system. Approximately 4-5% of the total cardiac output is diverted into the coronary circulation (225mL min^{-1}) at rest, which increases by up to a factor of 5 during exercise (Sircar, 2008). The arteries are relatively narrow (typically 2-5mm inner diameter, see table 1.1 for examples) and are generally narrower in women than in men (Dodge et al., 1992). Measurements of the thickness of the coronary artery wall in healthy subjects are difficult to obtain due to the early initiation of disease in the population (see section 1.b.i) and the invasive nature of the measurements (see section 1.d). Table 1.2 gives proximal vessel wall thicknesses obtained from previously healthy male subjects at autopsy, which vary from 0.16mm in the right coronary artery of new born babies to 0.83mm in the left coronary artery of subjects older than 60 years (Ozolanta et al., 1998).

Table 1.1: Diameters of normal coronary arteries in right dominant men and women assessed by x-ray coronary angiography

Segment	Diameter in men (mm)	Diameter in women (mm)
Left main	4.5±0.5	3.9±0.4
Left anterior descending (proximal)	3.6±0.5	3.2±0.5
Left anterior descending (mid)	2.5±0.5	2.4±0.4
Left anterior descending (distal)	1.7±0.5	1.6±0.4
Left circumflex (proximal)	3.4±0.5	2.9±0.6
Left circumflex (mid)	2.8±0.6	3.1±0.4
Left circumflex (distal)	1.6±0.6	1.4±0.6
Right coronary (proximal)	3.9±0.6	3.3±0.6
Right coronary (mid)	3.4±0.5	3.0±0.5
Right coronary (distal)	3.1±0.5	2.8±0.5

Values given are for the mid sub-segment measurement in each case. Proximal, mid and distal segments here correspond to main artery segments 1 to 3 respectively in the original work. Data from (Dodge et al., 1992).

The exact anatomical configuration of the coronary system is subject-specific and there are too many common variants to fully describe here (for a detailed discussion, see (McAlpine, 1975)). In the large majority of subjects, the right and left coronary arteries branch from the ascending aorta at the right and left coronary sinuses respectively. The right coronary artery (RCA) is initially orientated almost perpendicular to the aorta (see figure 1.5) before turning approximately 90° towards the apex and coursing within the fat of the right AV groove. The left main artery (LM) forms a more acute angle at the point at which it branches from the aorta and, in the majority of subjects, bifurcates after a short distance into the left anterior descending artery (LAD) and the left circumflex artery (LCX). The LAD is located within the fat of the anterior interventricular groove and reaches around the apex and some way back up the posterior interventricular groove. The LCX courses within the fat of the left AV groove. In the majority of subjects the posterior descending artery (PDA) branches from the distal right coronary artery and reaches along the posterior interventricular groove. This is known as right dominant circulation. Subjects may also be left dominant (where the PDA branches from the left coronary circulation) or co-dominant. Typically, the diameter of the dominant artery is larger than that the non-dominant artery (Dodge et al., 1992). Each of these major coronary arteries sub-divides further into numerous, smaller diameter vessels to provide the whole myocardium, cardiac nervous system and papillary muscles with blood. Likewise, deoxygenated blood from the coronary circulation is drained via the coronary venous system directly into the right ventricle, primarily via the coronary sinus. Figure 1.6 demonstrates the common territories supplied by blood originating from the RCA, LAD and LCX. The RCA supplies the right ventricular free wall and the basal posterior, basal posteroseptal, mid inferior and mid inferior septal regions of the left ventricle. The LCX artery supplies the basal posterolateral and mid inferolateral regions of the left ventricle. The LAD provides blood for the

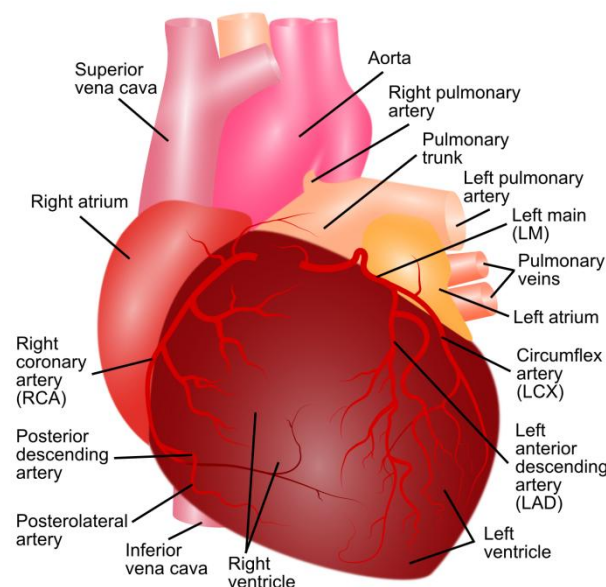
rest of the ventricular muscle including, the entire apical left ventricle and septum and the anterior half of the left ventricle and septum in the mid and basal regions. The blood supply to the posterior papillary muscle is usually provided by the RCA, while the anterior papillary muscle is most commonly supplied by both the LAD and LCX (Voci et al., 1995). An occlusion of the coronaries supplying the papillary muscles can result in a failure of the atrioventricular valves. Adequate blood supply to the nervous system of the heart is also critical in order to maintain correct cardiac rhythm.

Table 1.2: Vessel wall thicknesses obtained at autopsy in male subjects who died of non-coronary related causes

Age group	Left coronary wall thickness (mm)	Right coronary wall thickness (mm)
0-1 years	0.20±0.03	0.16±0.02
1-7 years	0.40±0.10	0.39±0.11
8-19 years	0.43±0.12	0.40±0.13
20-39 years	0.75±0.24	0.68±0.20
40-59 years	0.69±0.21	0.67±0.26
60-80 years	0.83±0.31	0.78±0.20

Data from from (Ozolanta et al., 1998) (121 subjects).

Figure 1.5: The coronary arteries

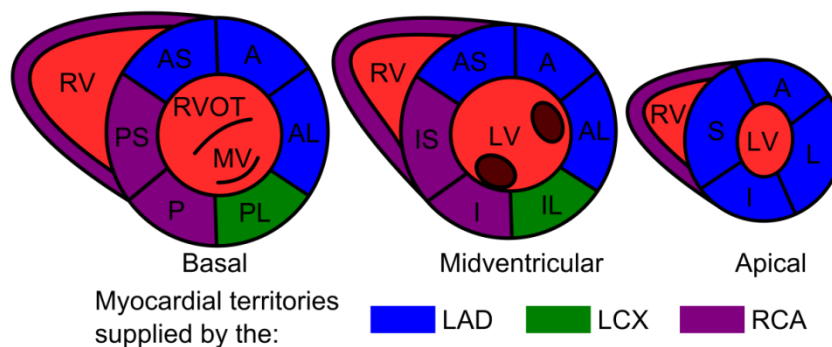


A schematic diagram of the major coronary artery paths across the myocardial surface. Although not apparent, for reasons of clarity, the left and right coronary artery systems both originate from the aorta.

When measured in a cross-section of the vessel (using an intravascular Doppler ultrasound probe), coronary blood flow (CBF) has been shown to exhibit a parabolic, skewed or M shaped velocity

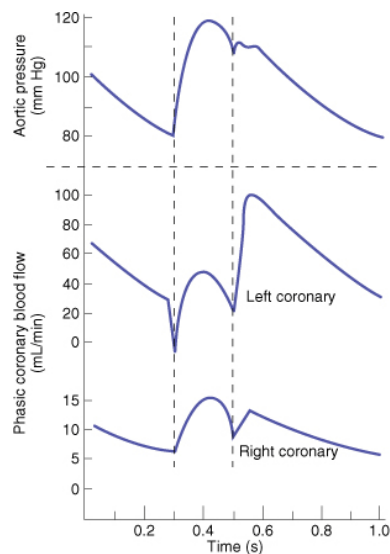
profile (Kajiya et al., 1993). Near to the vessel wall, frictional forces result in a blood velocity close to stationary and the velocity typically reaches a peak near the centre of the vessel. However, around bifurcations and narrow sections (near a stenosis for example) of the vessel, flow is often turbulent. As demonstrated in figure 1.7 average coronary blood flow over the vessel cross-section as a function of time is biphasic, with the majority of blood flow occurring during diastole, despite the increased aortic pressure during systole. During systole, ventricular contraction results in a high pressure within the subendocardial coronary arteries, arterioles and capillaries, preventing any substantial inflow of blood. During ventricular diastole, the pressure within these sub-endocardial vessels is reduced and blood flows in. This biphasic pattern is more evident in the left coronary arteries which supply large amounts of the left ventricle where the myocardial contraction is more forceful. Regulators of coronary blood flow include adjustments in coronary vascular resistance in response to changes in aortic pressure. This ensures that a drop in aortic pressure does not result in an equivalent drop in myocardial perfusion. Other controls of CBF include the autonomic nervous system which influences smooth muscle tone and nitrous oxide (NO), which is a powerful vasodilator released by the cells lining the coronary arteries (endothelial cells) in response to stress.

Figure 1.6: Blood flow to the myocardium from the major coronary arteries using a 16-segment model



Schematic diagram of three levels in the heart, demonstrating the 16-segment model used for wall motion and perfusion analysis. A, anterior; AL, anterolateral; AS, anterior ventricular septum; I, inferior; IL, inferolateral; IS, inferior ventricular septum; L, lateral; LV, left ventricle; LVOT, left ventricular outflow tract; P, posterior; PL, posterolateral; PS, posterior ventricular septum; RV, right ventricle; S, septum. The colour coding indicates the common coronary artery supplying the region: blue, left anterior descending (LAD); green, left circumflex (LCX); and purple, right coronary artery (RCA).

Figure 1.7: Blood flow velocity in the coronary arteries



Blood pressure in the aorta (top) and blood flow in the right (middle) and left (bottom) coronary arteries throughout the cardiac cycle. Systole occurs between the two dashed lines. Reproduced from Berne and Levy (1988) with permission, copyright Elsevier.

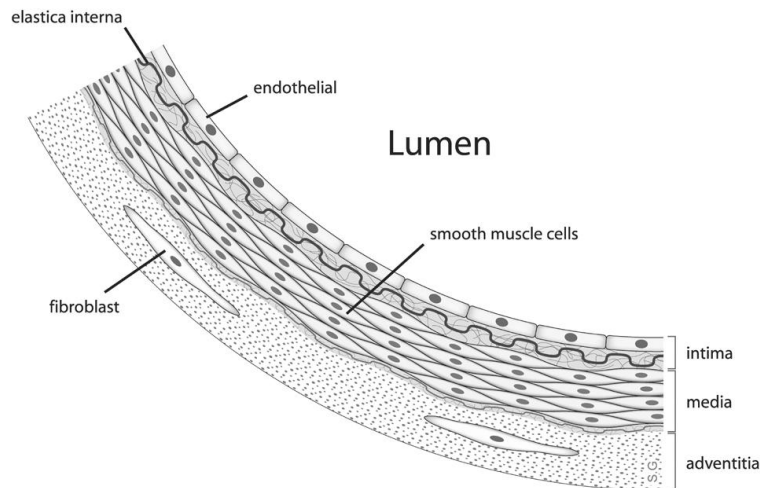
As the myocardium is highly efficient in extracting oxygen from the blood (75-90%) an increase in oxygen demand must be primarily met by an increase in coronary blood flow. Hypoxia of the myocardium stimulates the generation of adenosine by myocytes. Adenosine causes the smooth muscle of the coronary arteries to relax, resulting in vasodilation and increased myocardial blood supply. The ratio of CBF at rest to that following administration of adenosine is known as coronary flow reserve (CFR) and indicates the ability of the coronary arteries to respond to changes in myocardial demand.

1.a.iv Microscopic coronary artery anatomy and physiology

The coronary artery walls, although only 0.5-1mm thick, are a complex organ in their own right. As with other arteries, there are three distinct layers (see figure 1.8 and 1.9.a). The outer layer (the adventitia) consists of fibrous tissue attaching the artery to the surrounding organs. The middle layer (the media) consists of smooth muscle cells and elastic tissue, which enables the vasoconstriction and -dilation required to maintain myocardial blood flow. The innermost layer (the intima) plays a crucial role in the release and absorption of cytokines (cell signalling proteins). This inner layer actually consists of 3 sub-layers: an elastic membrane (the fenestrated layer or elastica interna in figure 1.8) consisting of elastic tissue; a thin central layer known as the subendothelial layer (not always present and not shown in figure 1.8) which consists of a small number of cells; and a little connective tissue and the inner layer known as the endothelium. The endothelium is in direct contact with the blood flow, it is sensitive to the local environment and plays a large role in atherosclerotic disease. The endothelial cells provide a low friction surface

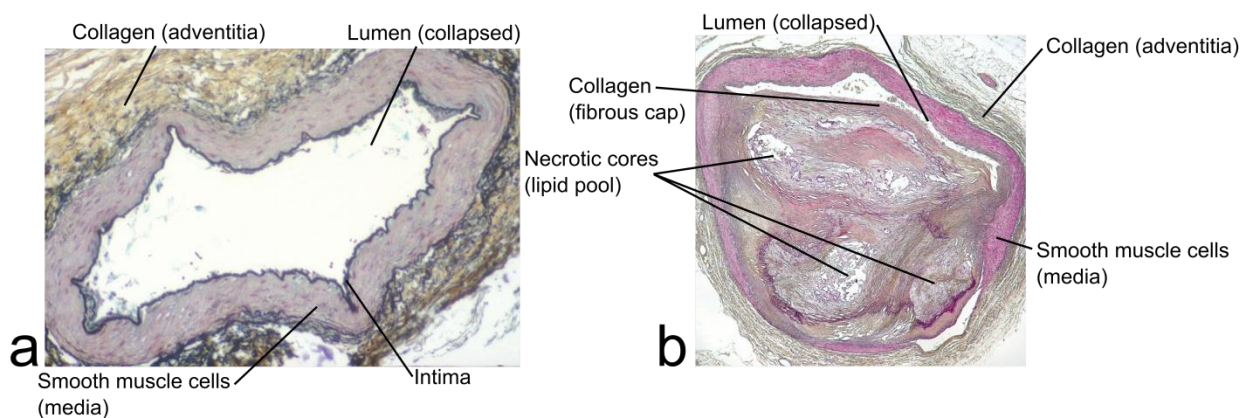
thereby reducing the arterial resistance experienced by the blood and under normal circumstances, inhibiting the formation of thrombus.

Figure 1.8: Anatomy of an arterial wall



The anatomy of an arterial vessel wall consists of 3 layers, the outer adventitia, a central media consisting of smooth muscle cells and the inner intimal layer. The intimal layer consists of sub-layers: the elastic membrane (elastica interna or fenestrated layer), possibly a central sub-endothelial layer (not present in this example) and the inner endothelial layer. Reproduced from Wikipedia (<http://en.wikipedia.org/wiki/Artery>, last accessed 23rd December 2010) under the Creative Commons Attribution-Share Alike 2.5 Generic license (<http://creativecommons.org/licenses/by-sa/2.5/deed.en>).

Figure 1.9: Histology slides of coronary arteries



Cross-sectional histology slides from a normal coronary artery (a) and from a transplanted heart (b) with an advanced plaque showing multiple lipid pools. The normally circular vessel is collapsed without the outward pressure of the arterial blood within the lumen (a). The lumen in (b) is also collapsed, but even with the vessel under pressure, the plaque presents a substantial obstruction to normal blood flow. Images courtesy of the Biobank, University of British Columbia James Hogg Research Laboratory, Providence Heart and Lung Institute, St Paul's Hospital, Vancouver.

1.b Coronary heart disease: from fatty streaks to myocardial infarction

1.b.i The development of an atherosclerotic lesion

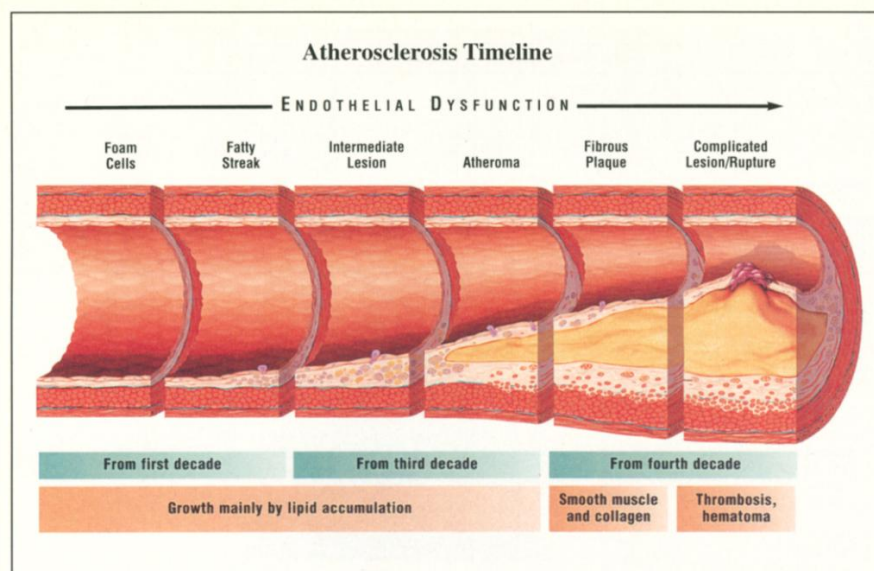
Formation of an atheromatous plaque is a complex process that is still under research. The description given here describes only one possibly pathway leading to the formation of one particular type of plaque (Libby, 2002) and is illustrated in figure 1.10.

Low density lipoprotein (LDL) particles perform the vital task of transporting cholesterol between organs in the blood. At normal concentrations, the LDL particles are able to move relatively freely between the blood stream and the intimal layer of the vessel wall. However, under certain circumstances, the LDL particles can become stuck within the extracellular matrix underneath the endothelial layer within the intima. The retention of LDL may be the result of an increased blood concentration of LDL, a dysfunctional endothelium or inflammation of the vessel wall, possibly due to a local or distal infection. Regions where the wall shear stress due to blood flow is reduced, reversed or highly oscillatory are more susceptible to this process, due to changes in gene expression with shear. Therefore, plaque formation is more common at branches, bifurcations and on curved vessel sections (Caro et al., 1969, Segers et al., 2008, Caro, 2009). High density lipoprotein (HDL) facilitates the transport of LDL out of the vessel wall and a low blood concentration of HDL can assist the injury. Following injury the endothelium no longer functions as it should. The lipid within the LDL particles can become oxidised and the protein within the LDL may be oxidised and glycated. The modified LDL particles stimulate the smooth muscle and endothelial cells to release cytokines which first attract monocyte cells and then convert them into macrophage cells. The endothelial cells also undergo changes which result in monocytes attaching to the usually “slippery” vessel wall surface. The macrophages consume the LDL particles, each consuming multiple fatty particles and becoming “foam cells”. T-cells are also attracted to this injured region of intima where they release further cytokines and amplify the arterial wall inflammation. This early stage plaque is often known as a fatty streak and may be observed in many people from their teenage years.

The next stages of development typically involve the cells of the inflamed intima in the fatty streak secreting factors which cause some of the smooth muscle of the media to migrate to the top of the intima, where they replicate and generate new extracellular matrix. This new tissue on the lumen side of the early stage plaque forms a fibrous cap, separating the plaque from the blood. Some of the foam cells below the fibrous cap then die, releasing their contents to form a lipid pool in the centre of the plaque. Typically these plaques result in an increase in the vessel wall thickness which is compensated by a corresponding increase in the vessel wall size, thereby maintaining the vessel lumen. This process is known as Glagov remodelling (Glagov et al., 1987) and is demonstrated in figure 1.10, although, in reality the scale of the compensatory enlargement is probably under-estimated in this figure.

Plaques may grow further in size as the lipid pool attracts further macrophages and LDL particles. Once the vessel is maximally distended outward by the plaque a reduction of the vessel lumen area, known as a stenosis occurs (see figure 1.9b). The logical conclusion of such growth is an occluded artery resulting in insufficient blood supply to an area of myocardium (an ischemic region). However, the majority of such events are due to erosion of or formation of a fissure in the fibrous cap of much smaller plaques, often before the stage at which they result in a flow limiting stenosis. The most vulnerable plaques are thought to be those with large lipid pools but thin fibrous caps. These thin caps may become inflamed causing the internal macrophages to release collagen degrading enzymes, resulting in fissure of the cap. Blood flows into the plaque and meets with the highly thrombogenic contents. Platelets rush to the site of the injury and combine with fibrous material manufactured as a result of the interaction of plaque contents and blood. The result is a thrombus attached to the vessel wall at the plaque site. The cells of the plaque also release inhibitors that prevent the body's natural internal thrombolytic processes. Alternatively a thrombus may form in response to an injured endothelial layer, potentially in plaques with little lipid content. Either way it is generated, the resulting thrombus may result in total vessel occlusion and potentially death, or it may be broken up and dispersed. After thrombolysis the plaque then heals, but its size increases as a result of new scar tissue. The thrombus remnants also provide a pro-thrombotic substrate, increasing the risk of future events at this site. Over time such plaques may become complex structures, with calcified material distal to the lumen, multiple lipid pools and irregular surfaces. Large plaques often develop their own blood supply, increasing the supply of inflammatory cells to the plaque contents and providing additional cholesterol from red blood cell casings subsequent to haemorrhage of these new vessels.

Figure 1.10: Possible developmental stages of a fibrous cap atheroma in the coronary arteries



A schematic diagram of one route for atherosclerotic plaque development, with lesion descriptors, typical timescales and growth mechanisms also noted. This diagram probably under-estimates the degree of compensatory vessel wall (Glagov) remodelling in response to the growth of the plaque. Other types of plaque are also thought to result in thrombotic acute coronary events. Reproduced from Pepine (1998) with permission, copyright Elsevier.

1.b.ii Consequences and treatment of coronary artery disease

A stenosed coronary artery with an associated reduction in luminal cross-section of 75% (or a 50% reduction in diameter) will lead to a reduction in CFR (see section 1.a.iii). As a result, these flow limiting stenoses can result in insufficient myocardial blood supply (ischemia). This ischemia, typically results in breathlessness and a chest pain, known as angina. Such symptoms, observed in a reproducible fashion during exercise are known as stable angina, whereas angina at rest or sporadically occurring is labelled unstable angina and is more suggestive of repetitive thrombotic coronary events. A short period of myocardial ischemia can result in myocardial stunning, whereby the stunned myocardium is akinetic after the injury but gradually recovers over a period of hours to days. A longer period of ischemia or repeated small ischemic events may lead to areas of dysfunctional hibernating myocardium, requiring a period of days to months to recover following the return of an adequate blood supply. Alternatively, cell death within a region of ischemic myocardium may result in infarcted (dead) tissue. Myocardial infarction has many possible consequences including ventricular remodelling, reduced ejection fraction (as a result of dysfunctional myocardium), myocardial rupture, valve dysfunction, aneurysms, arrhythmia and death. While large stenotic plaques result in more thrombotic events per plaque, the majority of such events arise from smaller plaques due to their considerably greater prevalence. The culprit lesion is most commonly located in the LAD (50%), followed by the RCA (30-45%) and the LCX (15-20%). In some patients (<5%) no culprit lesion is identified (Fuster, 2008). In a study of 241 sudden death CAD patients, Virmani et al. (2000) found that ~50% of such fatalities were caused by acute thrombotic events.

1.b.ii.1 Treatment of coronary artery disease in the acute setting

Patients presenting with a suspected myocardial infarction (MI) are initially tested to confirm the diagnosis using a combination of symptoms, ECG changes (particularly in the ST segment) and biochemical markers. Patients with confirmed acute MI must be treated as early as possible in order to minimise the time that the myocardium is left without blood supply. Early revascularization is associated with smaller infarct sizes (Francone et al., 2009) and a lower mortality rate (Hochman et al., 1999, Hochman et al., 2006, Dalby et al., 2009). Patients typically receive supplementary oxygen, morphine based pain relief, a coronary vasodilator (nitroglycerin), beta blockers to reduce myocardial oxygen consumption and anti thrombus drugs (clopidogrel and aspirin).

Revascularisation may be achieved with one of two strategies: thrombolysis or primary percutaneous coronary intervention (PCI). Thrombolysis is generally less effective (Dalby et al., 2003) but can be administered early (even in the ambulance) when there is no local access to primary PCI facilities or when patients are not suitable for PCI. This procedure involves administering anti platelet (aspirin and clopidogrel), anti coagulation (Heparin) and fibrinolytic (streptokinase or reteplase) drugs in order to break up the thrombus at the site of the coronary

occlusion. The primary PCI procedure involves inserting a catheter into the coronary arteries under x-ray fluoroscopic guidance (see section 1.d.i), using radio-opaque iodine contrast agent to visualise the coronary lumen. A thin guide wire is passed through the occlusion in the coronary artery and a balloon catheter is inserted over the guide wire. Inflating the balloon pushes the plaque and thrombus towards the vessel wall. Typically an expandable wire mesh (a stent) is placed at the occlusion site to prevent re-occlusion. Although the use of a stent does improve results, smooth muscle cells proliferate at the stent site, often resulting in a future restenosis and requiring further intervention. Recently drug eluting stents have been used to inhibit the proliferation of the smooth muscle cells and, in one pooled-analysis, were shown to reduce reintervention rates in the target vessel from 27.5% using bare metal stents to 12.1% using Sirolimus-eluting stents (Stone et al., 2007). However, the long-term safety with regard to in-stent thrombosis remains controversial (Stone et al., 2007, Garg and Serruys, 2010).

1.b.ii.2 Treatment of risk factors and CAD in the chronic setting

The probability of an individual developing CAD can be predicted using a number of risk factors (Fuster, 2008, Dawber et al., 1951, Wilson et al., 1998, Batsis and Lopez-Jimenez, 2010). Risk factors which may be modified include high levels of LDL in the blood stream (Goldstein et al., 1983), a diet high in saturated and hydrogenated fats, smoking, high blood pressure (hypertension), diabetes (Haffner et al., 1998), physical inactivity and obesity. Rates of CAD rise sharply with age, which cannot be modified, as is also the case for the menopause, which removes a degree of cardioprotection afforded to younger women. There are also links between the incidence of CAD with both family history of early heart disease and socio-economic status (Hopkins and Williams, 1989, Kaplan and Keil, 1993).

Patients with chronic CAD or subjects at high risk of developing CAD are advised to make lifestyle changes in order to reduce the risk. Such changes may involve dietary changes, smoking cessation, a program of physical activity and weight loss. A number of drugs may be prescribed in order to lower blood pressure, reduce platelet activity (aspirin) and reduce blood LDL concentrations (statins, which also have an additional anti-inflammatory benefit).

Chronic CAD with angina may be treated in two invasive ways: PCI or coronary artery bypass grafting (CABG). PCI is essentially performed in the same manner as in the acute setting and is amalgamated into the diagnostic angiogram procedure in many centres. The CABG procedure is usually substantially more invasive than PCI and is used mainly in cases of more complex or more prevalent disease. CABG typically involves a sternotomy followed by a cardiopulmonary bypass for “on-pump” procedures where the heart is arrested. Alternatively the procedure may be performed “off-pump” while the heart is still beating using mechanical stabilizers to reduce the motion of the target vessel. LAD stenoses are bypassed by detaching the distal end (an in-situ graft) of the left internal mammary artery from the chest wall and using fine sutures to attach it to the LAD downstream of the stenosis. RCA or LCX stenoses are typically bypassed using a section of the

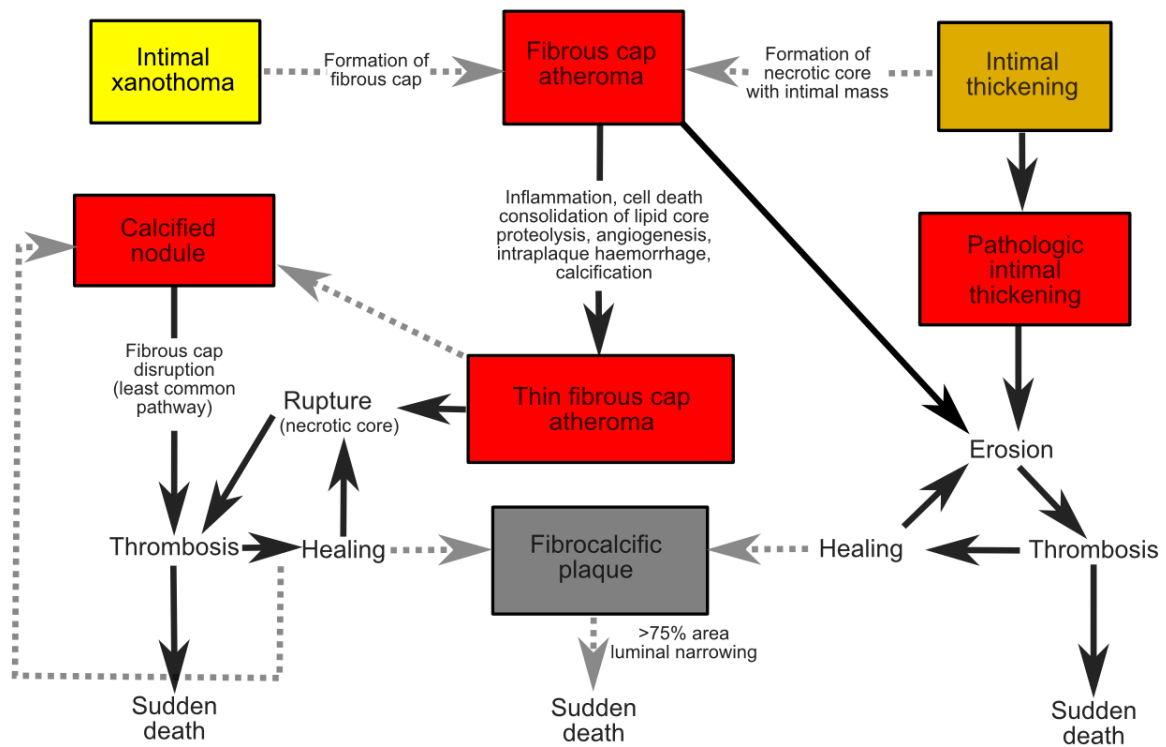
saphenous vein (from the leg). Venous grafts require correct orientation or valve removal to ensure that blood flow is not prevented by the valves. The donor vessel is used to connect the proximal aorta to the diseased coronary artery downstream of the stenosis. The use of a vein as an arterial vessel, however, renders the bypass particularly susceptible to developing new, dangerous, atherosclerotic disease. CABG is also used as an emergency backup procedure in failed PCI procedures.

1.b.iii Classification of coronary atherosclerotic plaque

Atherosclerotic plaques have been classified according to several different schemes for the purpose of labelling the developmental stage of, risk of future acute coronary events from or ability to treat a lesion (Wilson et al., 1986, Ryan et al., 1988, Stary et al., 1994, Stary, 2000, Virmani et al., 2000, Naghavi et al., 2003a, Naghavi et al., 2003b, Schaar et al., 2004, Fuster et al., 2005). Early classifications concentrated on the likelihood that PCI (without stent placement) would be successful in a particular lesion and are based on geometry, location, age and calcification (Ryan et al., 1988) or the shape of the lesion. However, such classifications only applied to flow limiting stenoses (>50% diameter reduction) and, therefore do not consider early stage disease and have little consideration for plaque composition. Subsequent classifications defined lesions primarily in terms of plaque composition (Stary et al., 1994). Virmani et al. (2000) classified plaques from early intimal thickenings or xanthomas (fatty streaks) through to ruptured and calcified plaques, as described in table 1.3. The possible progression between these stages is demonstrated in figure 1.11, particularly highlighting the potential degeneration of a thick fibrous cap, resulting in a rupture prone thin capped plaque. However, acute coronary events are not solely caused by thin fibrous cap atheroma type lesions and Naghavi et al. (2003b) have proposed the concept of a vulnerable plaque using a 2 tier system of major and minor criteria, as described in table 1.4.

The ability to accurately determine the structure and shape of disease potentially allows identification of vulnerable plaques and those that are likely to transform into vulnerable plaques without intervention. This would permit accurate targeting of the correct treatment and monitoring of the efficacy of such interventions, particularly early non-invasive treatments.

Figure 1.11: Progression of plaque types within the modified AHA scheme



More likely progression pathways are highlighted with solid black arrows, whereas less likely pathways are indicated by the grey dotted arrows. Reproduced from Virmani et al. (2000) with permission.

Table 1.3: Atherosclerotic plaque classification according to Virmani et al. (2000)

Classification	Description	Thrombosis
Nonatherosclerotic intimal lesions		
Intimal thickening	The normal accumulation of smooth muscle cells (SMCs) in the intima in the absence of lipid or macrophage foam cells.	Absent
Intimal xanthoma or “fatty streak”	Luminal accumulation of foam cells without a necrotic core or fibrous cap. Based on animal and human data, such lesions usually regress.	Absent
Progressive atherosclerotic lesions		
Pathological intimal thickening	SMCs in a proteoglycan-rich matrix with areas of extracellular lipid accumulation without necrosis.	Absent
Erosion	Luminal thrombosis; plaque same as above.	Thrombus mostly mural and infrequently occlusive.
Fibrous cap atheroma	Well-formed necrotic core with an overlying fibrous cap.	Absent
Erosion	Luminal thrombosis; plaque same as above; no communication of thrombus with necrotic core.	Thrombus mostly mural and infrequently occlusive.
Thin cap atheroma	A thin fibrous cap infiltrated by macrophages and lymphocytes with rare SMCs and an underlying necrotic core.	Absent; may contain intraplaque haemorrhage/fibrin.
Plaque rupture	Fibroatheroma with cap disruption; luminal thrombus communicates with the underlying necrotic core.	Thrombus usually occlusive.
Calcified nodule	Eruptive nodular calcification with underlying fibrocalcific plaque.	Thrombus usually nonocclusive.
Fibrocalcific plaque	Collagen-rich plaque with significant stenosis usually contains large areas of calcification with few inflammatory cells; a necrotic core may be present.	Absent

Reproduced from Virmani et al. (2000). SMC – smooth muscle cell.

Table 1.4: Criteria for defining vulnerable plaques

Criteria	Description
Major criteria	
Active inflammation	Extensive macrophage infiltration of the plaque.
Thin cap with large lipid core	A cap thickness of <100µm and a lipid core of >40% of the total plaque volume.
Endothelial denudation with superficial platelet aggregation	Erosion of the endothelium and a build up of platelets and thrombin (precursors to thrombus) on the plaque.
Fissured plaque	Plaques which have previously fissured without resulting in a fully occlusive thrombus are more likely to generate another thrombus.
Stenosis >90%	The shear stress over a highly stenotic plaque is greater leading to a higher probability of thrombus. The presence of highly stenotic plaques also suggests the presence of other vulnerable lesions.
Minor criteria	
Superficial calcified nodule	A calcified nodule close to or through the plaque surface, which may cause plaque rupture.
Glistening yellow appearance	A glistening yellow plaque observed on angioscopy may indicate the plaque contains a large lipid pool with a thin cap. Although this criterion may lack specificity.
Intraplaque haemorrhage	The presence of red blood cells or iron deposits within the plaque may indicate plaque instability.
Endothelial dysfunction	There is evidence linking endothelial dysfunction to CAD. The active inflammation and oxidation in vulnerable plaques are likely to link with endothelial dysfunction.
Outward remodelling	Compensatory enlargement of the vessel wall before the plaque significantly impinges on the vessel lumen (Glagov remodelling) may be a potential marker of plaque vulnerability.

Reproduced from Naghavi et al. (2003b).

1.c. Motion of the heart and coronary arteries

This section is a modified version of the first 2 parts of the paper: Scott et al. (2009).

Motion of the heart is the vector sum of three components: that caused by the pumping action of the 4 chambers, that caused by respiration and any resulting from voluntary or involuntary subject movement. This review will not discuss the contribution of bulk motion or the motion of blood within the heart, which is an important consideration in many MR techniques and other imaging modalities, but not the primary concern of this thesis. Here, the motion of the heart with the cardiac and respiratory cycles is described in healthy subjects, primarily from MR data. In particular, close attention is paid to the motion of the coronary arteries and key differences between breath-holding and free-breathing are highlighted.

1.c.i Cardiac motion

Many imaging techniques build up images over a number of cardiac cycles, assuming that cardiac motion is identical between heart beats. This is, however, an over simplification as heart motion and heart rate vary naturally on a beat-to-beat basis, with time of day, respiration (Hirsch and Bishop, 1981, Innes et al., 1993, Thompson and McVeigh, 2006), breath-holding (Raper et al., 1967) and other factors.

As described in section 1.a.ii contraction of the heart typically occurs at 50 – 80 BPM in healthy subjects. The contractile systolic phase begins at the R-wave of the ECG and its duration is relatively heart rate invariant, lasting around 400msec (Weissler et al., 1968). The diastolic phase fills the remainder of the R-R interval and is, therefore more dependent on heart rate.

Motion of the left ventricle (LV) in humans has been extensively examined using tagged MR techniques (Zerhouni et al., 1988, Axel and Dougherty, 1989a, Axel et al., 1992, Petitjean et al., 2005). Tagging has been performed using spatial modulation of magnetisation (SPAMM) (Axel and Dougherty, 1989a, Axel and Dougherty, 1989b) with the displacement information and other motion parameters, such as strain (Azhari et al., 1993), initially being obtained by semi-automatic tracking of the tag lines (Guttman et al., 1994, Kraitchman et al., 1995, Kumar and Goldgof, 1994, Prince and McVeigh, 1992). More recently, harmonic phase (HARP) (Osman et al., 1999) post-processing has been used to extract the motion information by applying a band-pass filter around the tagging peak in k-space and by detecting the phase of the tag modulation. Alternatively, the motion information may be obtained by using displacement encoding with stimulated echoes (DENSE) (Aletras et al., 1999) where the displacement encoding is obtained using bipolar gradients to produce motion related signal phase shifts in the appropriate directions. The contractile movement of the LV may be divided into 3 major components during systole: longitudinal shortening, radial contraction and opposite hand rotation of the apex of the chamber relative to the base due to fibre orientation within the myocardium (table 1.5). The reduction in base-apex length is a result of the base moving whilst the apex remains relatively stationary (Hoffman and Ritman,

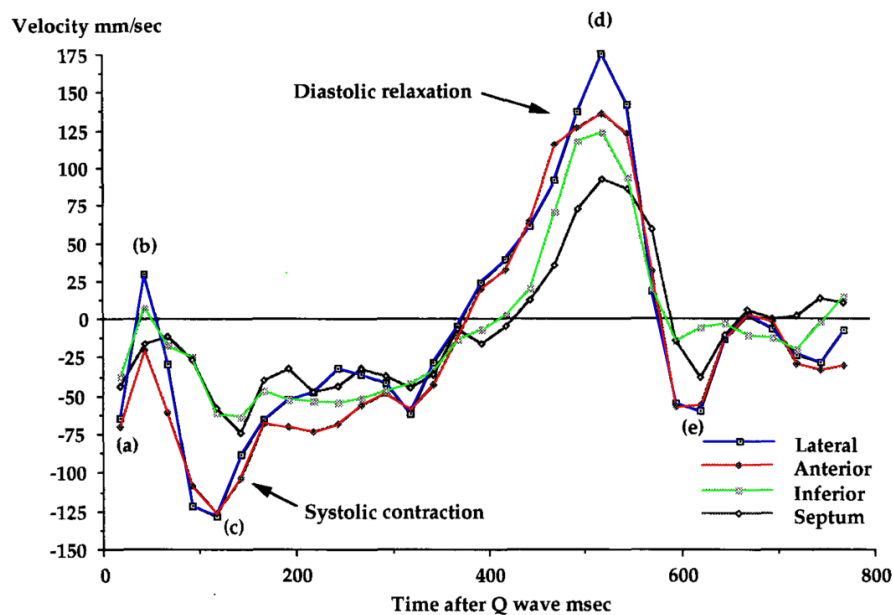
1985) and the onset of the motion in the apex is delayed by around 90ms with respect to that of the base (Leighton et al., 1983). MR phase velocity mapping has been used to quantify the velocity of the LV wall (Karwatowski et al., 1994, Karwatowski et al., 1996, Kvitting et al., 2004, Petersen et al., 2006, Hennig et al., 1998, Arai et al., 1999, Markl et al., 1999, Jung et al., 2004, Jung et al., 2006), (figure 1.12) with such studies demonstrating a systolic peak in velocity and a larger one in diastole with maximum longitudinal velocities of around $140 \pm 40 \text{ mms}^{-1}$ in the lateral wall (Karwatowski et al., 1994) and 51 mms^{-1} in the midventricular endocardium (Petersen et al., 2006).

Table 1.5: Motion of the ventricles in healthy volunteers throughout the cardiac cycle

Chamber	Direction	Section	Base	Mid	Apex
LV	Radial (mm)	Septum	4.5	4.6	4.4
		Anterior	6.2	5.0	3.4
		Lateral	5.8	5.5	4.5
		Inferior	5.4	5.5	5.5
	Longitudinal (mm)	Septum	10.2	6.3	2.1
		Anterior	10.4	6.1	1.8
		Lateral	11.0	7.1	2.8
		Inferior	13.1	8.2	3.6
	Rotation (degrees)		-4.4	5.2	10.0
	Radial Contraction (%)	Midventricular free-wall	15.8	15.9	19.5
	Longitudinal Contraction (%)	Midventricular free-wall	31.2	21.6	28.0

Note: Values are given as the means of those from several sources which are summarized in a review paper by Petitjean et al. (2005). Positive values indicate base-to-apex, radially inward movement or counterclockwise rotation. LV - left ventricle and RV - right ventricle.

Figure 1.12: Motion of the left ventricular free wall assessed using MR phase velocity mapping



Velocity of lateral, anterior, inferior and septal regions of the left ventricle in the long axis direction throughout the cardiac cycle, measured below the mitral annulus in a healthy volunteer. Initially, (a), the heart changes from an ellipsoid to spherical shape and the base moves, before the relatively stationary isovolumic contraction, (b). The base moves towards the apex during systole, (c), away from the apex during diastole, (d), and finally back towards the base, (e). Reproduced from Karwatowski et al. (1994) with permission, copyright Wiley.

The structure and motion of the RV has been studied to a lesser extent. RV contraction is often described as peristalsis like (Armour et al., 1970). Movement of the free wall is primarily longitudinal with an element of radial contraction towards the apex and anterior (Haber et al., 2005) and the slight bulging of the septal wall into the RV also contributes to the ejection of blood (Page et al., 2002).

Motion of the coronary arteries during the cardiac cycle has been extensively investigated due to the difficulties in imaging these small, highly mobile structures which require high spatial and temporal resolution. The motion of the RCA (the most mobile of the coronary arteries) throughout the cardiac cycle is plotted in figure 1.13 and the peak displacements in three orthogonal directions for one MR based study (Al-Kwafi et al., 2006) during breath-holding are summarised in table 1.6. The maximum displacement of the right coronary is around twice that of the left (Mao et al., 2000, Hofman et al., 1998) with two peaks in the vessels' velocity – the first in early or mid systole (during ventricular contraction) and the second in early diastole (during a fast filling period). Motion of the left coronary artery system through the cardiac cycle is predominantly in the superior-inferior (SI) direction ($59 \pm 11\%$ of LAD and $48 \pm 10\%$ of LCX motion is in the SI direction) with around half as much in the left-right (LR) direction ($26 \pm 7\%$ LAD and $33 \pm 7\%$ LCX) and a little in the anterior – posterior (AP) direction ($15 \pm 5\%$ LAD and $19 \pm 5\%$ LCX) (Johnson et al., 2004). In the RCA, the motion is predominantly in the LR direction ($48 \pm 7\%$) with less in the AP and SI directions ($22 \pm 5\%$ and $31 \pm 9\%$ respectively) (Johnson et al., 2004). Along the vessel length the motion of the RCA and LCX is generally greater in the mid and distal sections than proximally

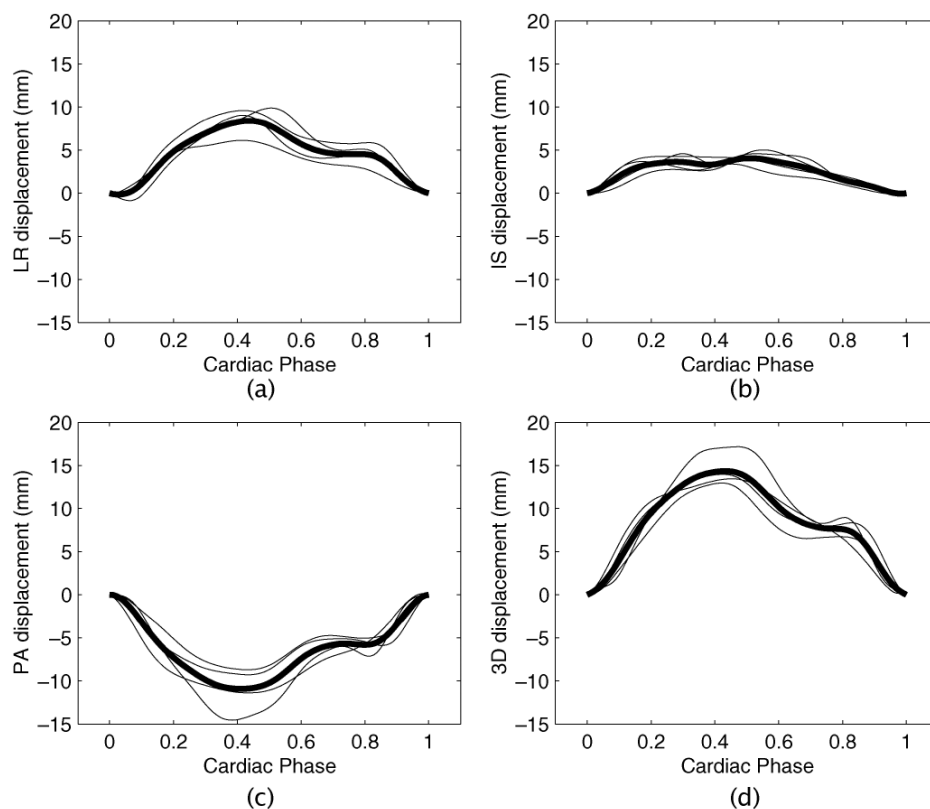
(prox:mid:distal ratio 1:1.6:1.4 and 1:1.5:1.6 for the RCA and LCX respectively), while motion is similar along the whole length of the LAD (1:1.1:1.0) (Johnson et al., 2004). In short periods during the cardiac cycle, coronary artery velocity is reduced or stationary. The rest period was defined by Wang et al. (1999) as the longest period during the cardiac cycle in which the displacement of the vessel in question is less than 1 mm in each of the SI, AP and LR directions and this has been shown to vary substantially between patients. Figure 1.14 plots the rest period as a function of heart rate in the RCA. Typically the rest period of the left coronary artery is longer with an earlier onset (Kim et al., 2001b). However, the rest period onset and duration is fairly invariant on the position along the length of each artery (Johnson et al., 2004). For both the left and right coronary arteries, the motion tends to slow gradually before this period and accelerate rapidly afterward. The onset of the rest period has been established as approximately 750msec after the R-wave of the ECG (Wang et al., 1999), although, in some cases, a relatively longer rest period may be present starting at end systole (around 350-400ms) (Jahnke et al., 2005a), particularly when R-R intervals are short (Lu et al., 2001, Jahnke et al., 2006). Although not commonly applied to MR studies, the duration and time to the onset of the rest period following the R-wave may be increased using β -blockers (Jahnke et al., 2006) as is performed for many x-ray computed tomography studies of the coronary arteries.

Table 1.6: Maximum displacements of the coronary arteries within the cardiac cycle during breath-holding in 8 healthy volunteers

Artery Section	LR (mm)	AP (mm)	SI (mm)
Left Anterior Descending	6.8 $\pm$ 1.7	7.9 $\pm$ 1.5	6.8 $\pm$ 1.9
Left Main	7.9 $\pm$ 1.3	9.0 $\pm$ 1.7	7.1 $\pm$ 1.3
Left Circumflex	9.3 $\pm$ 2.1	12.7 $\pm$ 2.3	10.5 $\pm$ 1.3
Right Coronary Artery – Proximal	9.0 $\pm$ 1.7	10.6 $\pm$ 1.7	11.3 $\pm$ 2.8
Right Coronary Artery – Distal	12.6 $\pm$ 2.2	16.7 $\pm$ 2.9	10.3 $\pm$ 2.4

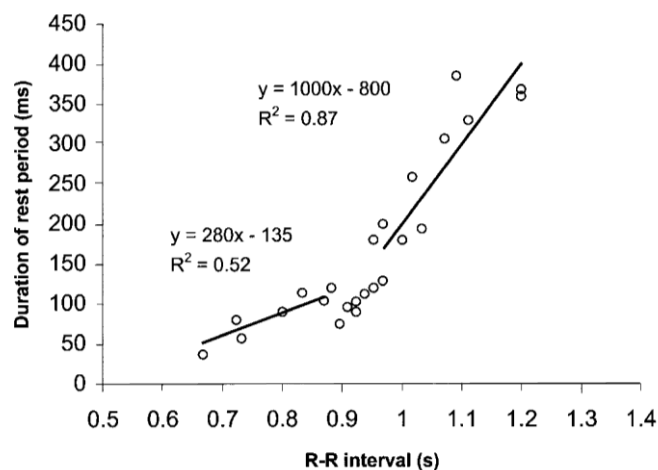
Values are given as the mean of the maximum values ($\pm$ standard deviation) across subjects. From Al-Kwafi et al. (2006).

Figure 1.13: Motion of the RCA origin with the cardiac cycle in 4 patients



Displacements obtained from x-ray coronary angiography in four patients (thin lines) and the average (thick lines) in three orthogonal directions (a-c) and the magnitude displacement (d). Positive displacements were towards left, inferior or posterior. Reproduced from Shechter et al. (2006) with permission, copyright IEEE.

Figure 1.14: Right coronary rest period duration as a function of heart rate



Data from 25 healthy volunteers for the duration of the RCA rest period as a function of RR-interval. The linear regression equations for long and short R-R intervals are superimposed. Reproduced from Kim et al. (Kim et al., 2001b) with permission, copyright Wolter Kluwer Health.

1.c.ii Respiratory induced motion

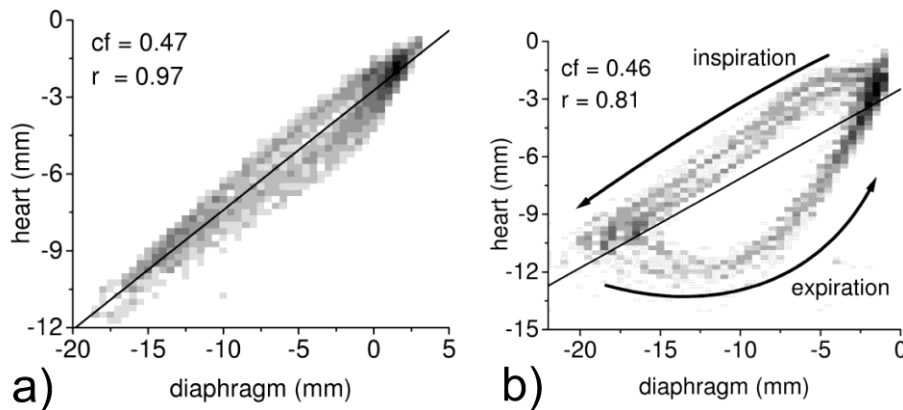
By breath-holding, respiratory motion may be comfortably suspended for 20 - 30s in healthy volunteers. However, Holland et al. (1998) report that the left heart margin at the heart base may drift by 2.7 mm or more during an inspiratory breath-hold and by 1.1 mm or more during expiration (quoted, as in other studies in this section, for a single time point in the cardiac cycle) and suggest that the heart rate increases towards the end of the breath-hold. Residual respiratory motion during a breath hold has been measured at around 0.5mm in the coronary arteries (Fischer et al., 2006). Jahnke et al. (2006) found that in 33% of patients the diaphragm position was irregular and unsteady or drifted continuously during expiratory breath-holding. It should further be noted that inspiratory and expiratory breath-hold positions do not generally correspond with the free-breathing end inspiratory and end expiratory equivalents.

Tidal breathing involves motion of the chest wall and diaphragm, both of which influence the motion of the heart. The relationship between the motion of the heart and SI motion of the diaphragm is approximately linear (Wang et al., 1995c, Nehrke et al., 2001), although highly subject-specific (Taylor et al., 1999b) (discussed further in section 2.b.v) with an element of hysteresis (figure 1.15). Taylor et al. (1997) recorded end inspiratory and end expiratory dwell times during free-breathing in 9 healthy subjects of 1.1 ± 1.6 s and 0.4 ± 0.2 s respectively, with a respiratory period of 4.3 ± 1.1 s, diaphragmatic amplitudes of 14.1 ± 4.8 mm and maximum inspiratory and expiratory velocities of 13.3 ± 5.3 mms⁻¹ and 11.8 ± 4.8 mms⁻¹ respectively. McLeish et al. (2002) studied respiratory induced motion of the heart with both rigid and non-rigid transformation parameters generated from images acquired at various breath-hold positions (table 1.7), demonstrating that the largest component of motion is in the inferior direction during inhalation, with the large standard deviations suggesting high inter-subject variability. Much smaller equivalent displacements and rotations recorded during free-breathing using x-ray coronary angiography (Shechter et al., 2004) may be partially accounted for by the large range of diaphragm displacements found by McLeish et al. (2002) (up to 40 mm), suggesting that the breath-hold positions used were not in the range of normal tidal breathing (around 14 mm (Taylor et al., 1997)). As has been demonstrated by several authors (Manke et al., 2002a, McLeish et al., 2002, Manke et al., 2002b) the assumption of a linear translation of the heart with respiration may be unrealistic. In particular, the motion of the inferior margin of the heart is greater than that of the superior parts of the heart (as demonstrated in the larger LV displacements than RA displacements in table 1.7). As the heart and its surroundings consist of deformable soft tissue non-rigid motion is to be expected.

Non-invasive coronary artery imaging is generally performed at a single time point in the cardiac cycle - hence, cardiac motion is minimised but respiratory motion presents a serious problem. As the arteries traverse a large proportion of the epicardial surface the motion follows that of the epicardium during respiration and is, therefore, non-rigid. Using x-ray coronary angiography, Shechter et al. (2006) demonstrated that motion is primarily in the SI direction (see figure 1.16)

with the relative component in other directions varying widely between subjects. Average maximum displacements over the respiratory cycle are given table 1.8. Respiratory velocities are greater in more distal segments (table 1.9) and inspiratory velocities generally exceed those in expiration, reaching up to 9mm s^{-1} in the proximal RCA (Shechter et al., 2006).

Figure 1.15: Motion of the heart with respiration demonstrating the subject specific and hysteretic nature of the relationship



The superior inferior (SI) respiratory induced movement of the left ventricle (LV) versus that of the right hemi-diaphragm in two volunteers, one with mild hysteresis and one with substantially more. Note that darker squares indicate that this result measurement was more common. The direction of the hysteresis was always found to be in the anti-clockwise direction, as indicated on the right hand image. cf - correction factor (tracking factor) - which is the slope of the linear regression and r - correlation coefficient. Modified from Nehrke et al. (Nehrke et al., 2001) with permission, copyright RSNA.

Table 1.7: Whole heart rigid transformation parameters and selected point displacements between end expiration and end inspiration for a fixed point in the cardiac cycle

Parameter	Breath-hold	Free-breathing
RL translation (mm)	3.8±1.2	-0.4±2.2
AP translation (mm)	7.1±2.9	1.1±1.9
SI translation (mm)	16.4±4.2	4.9±1.9
RL rotation (°)	1.8±1.7	1.6±0.9
AP rotation (°)	3.8±1.8	1.1±1.9
SI rotation (°)	-0.6±3.3	0.4±2.2
RA mid-point displacement (mm)	16.0±4.2	-
RCA mid-point displacement (mm)	17.0±4.0	-
LV apical point displacement (mm)	22.5±4.2	-
Right hemi-diaphragm displacement (mm)	42.7±11.2	-

Note: Angles are given about the stated axis in degrees. Values are given as mean ± standard deviation. RL - right-left, AP - anterior-posterior and SI - superior-inferior, with a positive displacement being towards L, P or I. Free-breathing data was acquired using x-ray coronary angiography and breath-hold with MR. Data from McLeish et al. (2002) and Shechter et al. (2004).

Table 1.8: Maximum displacement of coronary landmarks through the respiratory cycle

Landmark	Displacement (mm)
Proximal RCA	5.0±1.3
Distal RCA	7.2±2.2
Origin of the LM	4.6±1.4
5cm from LM origin on LAD	5.6±2.1
5cm from LM origin on LCX	6.3±1.6

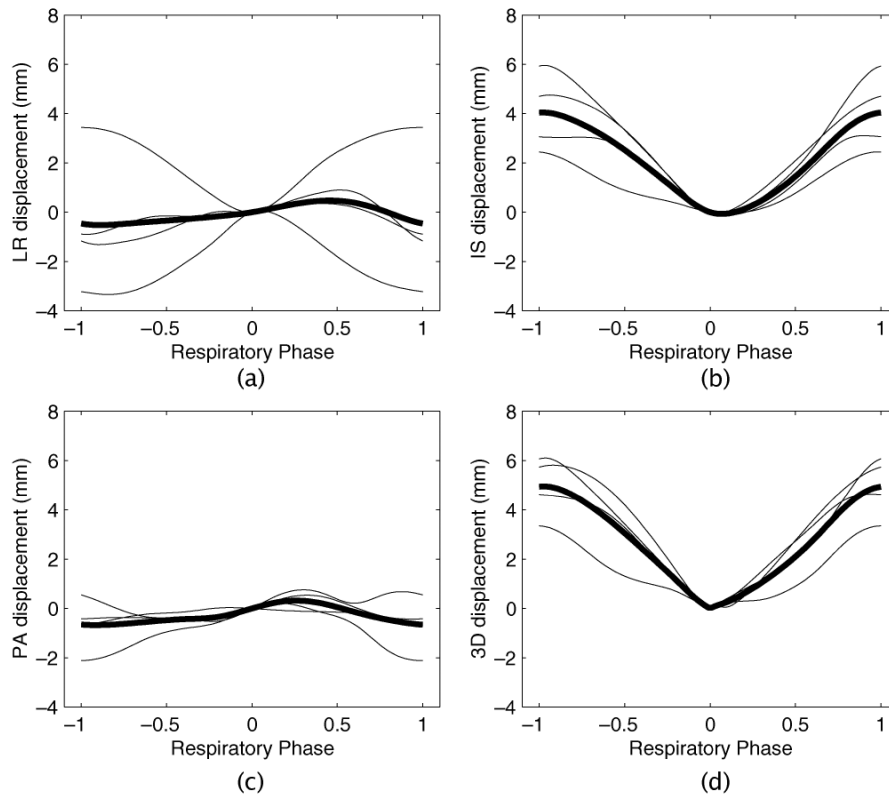
Data given as the average maximum displacement (± standard deviation) over the respiratory cycle obtained using x-ray coronary angiography at a single point in the cardiac cycle, from Shechter et al. (2006).

Table 1.9: Velocity of various points in the coronary artery system during free breathing

Coronary landmark	Expiratory velocity (mms ⁻¹)	Inspiratory velocity (mms ⁻¹)
RCA origin	4.5±1.6	6.6±1.3
RCA mid	5.7±1.6	8.0±2.5
RCA distal	6.4±1.7	9.0±3.1
LM origin	5.5±2.0	6.0±1.8
LM bifurcation	5.7±2.4	6.3±2.0
LAD 5cm from LM origin	7.6±3.9	7.8±3.0
LCX 5cm from LM origin	6.9±3.1	8.5±4.3

RCA mid was approximately one-half the distance from the origin to the acute margin of the heart. RCA distal was the acute margin of the heart. Reproduced from Shechter et al. (2006) with permission.

Figure 1.16: Respiratory motion of the origin of the RCA



Displacements obtained from x-ray coronary angiography in four patients (thin lines) and the average (thick lines) in three orthogonal directions (a-c) and the magnitude displacement (d). Positive displacements were towards left, inferior or posterior. Reproduced from Shechter et al. (2006) with permission, copyright IEEE.

1.d Non-MR based coronary artery imaging

A number of techniques are available for diagnosis and determining both the severity and extent of ischemia or infarction related myocardial injury. Non-imaging based techniques include exercise testing with ECG monitoring, which tests for ischemia related ECG changes (Bruce et al., 1963). The sensitivity and specificity of such tests is, however, limited (Hill and Timmis, 2002) and they are not, therefore, recommended for diagnosis of coronary artery disease (Skinner et al., 2010). Imaging techniques including single photon emission computed tomography (SPECT) (Hendel et al., 1999), positron emission tomography (PET) (Hutchins et al., 1990), ultrasound with microbubble contrast (Heinle et al., 2000) and MR with first pass gadolinium based contrast agents (Schwitter, 2006) have been used to image the perfusion of the myocardium. Such techniques are able to diagnose existing ischemic regions and, in conjunction with knowledge of the regions of myocardium typically supplied by each coronary artery (see figure 1.6), identify a culprit artery. In combination with exercise or pharmacological simulation of exercise, perfusion imaging improves sensitivity over ECG (Hung et al., 1984) and symptomatic monitoring alone (see NICE Report 73 (2003)). Therefore, myocardial perfusion imaging is recommended for use as a diagnostic test in patients with a moderate likelihood of coronary artery disease and unconfirmed angina (Skinner et

al., 2010). However, none of these techniques are able to determine the location of disease within an artery, the severity of the stenosis, the shape of the plaque or detect non-flow limiting disease.

A number of imaging modalities have been employed in imaging the coronary arteries in search of the location, extent and characterisation of disease, which are reviewed below.

1.d.i X-ray contrast angiography

Modern x-ray coronary angiography stems primarily from the work of Sones et al. (1959) and Judkins (1967). Procedures are usually performed without general anaesthetic, but a local anaesthetic is applied to the entry site, typically the brachial or femoral artery. A guide wire is introduced into the artery and through to the descending aorta. Before the guide wire reaches the aortic arch a hollow catheter is inserted using the guide wire. The catheters are shaped to fit the patient specific anatomy with several curves enabling the tip to reach the ostia of the left or right coronary artery. The tip of the catheter contains radio opaque material so it can be tracked using x-ray imaging and is perforated to allow fluids to be injected. Once the catheter is inserted into the ostia of the desired coronary artery system, iodine based contrast agent is injected into the artery through the catheter. Cine angiography using a C-arm or bi-plane x-ray system with an image intensifier is used to image the catheter location and flow of contrast agent into the coronary system. In clinical practice the location, extent and severity of lumen reducing disease is assessed visually by experienced operators. In many centres this procedure automatically becomes a PCI procedure in the presence of significant stenosis (>50% diameter narrowing – see section 1.b.ii). However, despite a high degree of accuracy in the differentiation of mild disease from severe disease, the subjective nature of lesion assessment leads to variations of $\pm 20\%$ in estimation of degree of stenosis from experienced interventional cardiologists when stenoses are 40-70% (Fuster, 2008).

Quantitative coronary angiography (QCA) attempts to remove some of the subjectivity of x-ray coronary angiography by measuring lumen and stenosis size with reference to the known size of the catheter tip. However, inter-observer variability of QCA is around 20% (Fuster, 2008) and the degree of stenosis is generally referenced to an apparently normal section of vessel which is unlikely to be truly disease free in most patients. Other measures attempting to quantify the degree of stenosis include the 4 point TIMI (Thrombosis in Myocardial Infarction study group findings (1985)) score which is a visual estimate of the flow beyond the stenosis (a score of 0 for no flow to 3 for normal flow beyond the stenosis). Counting the cine frames required for the contrast to reach specified landmarks in the coronary circulation beyond the stenosis (Gibson et al., 1996) has also been used as a measure of stenosis severity.

During x-ray angiography procedures, Doppler ultrasound transducer tipped catheters and administration of adenosine may be used to obtain CFR (see section 1.a.iii) measurements, although the large standard deviation of values obtained in healthy and diseased subjects suggests that CFR may not be a definitive measurement of the significance of a stenosis. Alternatively, the

ratio of measurements with a pressure transducer tipped catheter either side of a stenosis after administration of adenosine gives an estimate of fractional flow reserve (FFR) (Fuster, 2008). The FFR indicates the maximum myocardial blood supply available from the artery in question as a fraction of the maximal myocardial blood supply from the same artery without the stenosis.

X-ray contrast angiography is the current gold standard in the diagnosis of significant coronary artery disease (Topol and Califf, 2007): image resolution is high (~ 100 's μm), temporal acquisition windows of 5-20ms minimise motion (Lee and Panting, 2006), there are many experienced operators and, in many centres, diagnostic procedures automatically become therapeutic PCI procedures. It is not, however, without risk; measurements of effective dose to the patient vary between 2 and 16mSv for diagnostic procedures (United Nations. Scientific Committee on the Effects of Atomic Radiation., 2008). The dose for interventional procedures is higher; one study comparing femoral and radial access found average effective doses of 8.6mSv and 13.5mSv for femoral and radial access respectively in interventional procedures vs. 6.8mSv and 9.2mSv for diagnostic procedures (Sandborg et al., 2004). The associated effective dose to the primary operator during interventional procedures was calculated as 3.2 μSv and 4.8 μSv for femoral and radial access per procedure (Lange and von Boetticher, 2006). Picano et al. (2007) presented effective doses as the number of equivalent chest x-rays for the patient in diagnostic coronary angiography (300 chest x-rays) and PCI (1000 chest x-rays) and for the most experienced interventional cardiologists (250 chest x-rays per year). Iodinated contrast agent is toxic, particularly to the kidneys and presents a problem in patients with compromised renal function. Other complications include (Fuster, 2008) stroke, myocardial infarction, serious arrhythmia, aortic dissection, haemorrhage, infection, thrombosis, emboli and injury to the coronary artery. A large multicentre review of diagnostic procedures found an overall complication rate of 7.4 per 1000 and a mortality rate of 0.7 per 1000 (West et al., 2006). In a study of interventional procedures the major adverse cardiac event rate was 42.9 per 1000 and the mortality rate was 11.3 per 1000 (Grossman et al., 2009).

1.d.ii Transthoracic and transesophageal ultrasound imaging

A fundamental property of all ultrasound systems is the trade off between increasing resolution and decreasing penetration at increasing transducer frequencies. In general the depth of the coronary arteries requires relatively low frequency transthoracic transducers (3.5-8MHz (Rigo et al., 2008)) with insufficient resolution and/or penetration for reliable coronary imaging (Pohost, 2000), particularly in distal segments. The limited acoustic window permitted by the inter-rib spacing is also problematic and studies are often unsuccessful. However, transthoracic ultrasound has been used to image the coronary arteries (Zwicky et al., 1988, Rigo et al., 2008) and coronary artery wall thickness has even been evaluated in some studies (Wada et al., 2005, Gradus-Pizlo et al., 2001). However, it is most commonly used to measure CFR, primarily in the LAD (Kenny et al., 1994, Voci et al., 2003, Pizzuto et al., 2003) as this is difficult in the other coronary arteries (Voci et al., 2002, Rigo, 2005). Transesophageal ultrasound (Youn and Foster, 2000) brings the transducer

closer to the heart at the expense of being a minimally invasive procedure. As for transthoracic ultrasound, coronary flow velocities may be obtained in the LAD (Zwicky et al., 1988) and plaque calcification may be identified using transesophageal methods (Wexler et al., 1996). In one review, the success rate for coronary imaging using transesophageal ultrasound was estimated at 80% compared to an estimate of only 20% with transthoracic ultrasound (Baroldi et al., 2004). However, even with transesophageal methods the distal artery is difficult to image, the angle between the LM and LCX is problematic (Erbel, 1991) and RCA imaging is challenging due to its location (Samdarshi et al., 1992).

1.d.iii Intravascular ultrasound imaging

Intracoronary or intravascular ultrasound (IVUS) (Nissen et al., 1991) involves inserting a miniaturised (<1mm diameter) ultrasound probe into the coronary artery tree under x-ray fluoroscopic guidance and is performed in conjunction with x-ray contrast angiography. Tomographic images are generated using either rotating transducers (typically at 30 rev. s⁻¹) or stationary phased array transducers. Such systems operate at between 20MHz and 50MHz resulting in typical axial (radially outward from the transducer) resolutions of ~150µm and lateral (in the circumferential or polar direction) resolutions of ~250µm (at 30MHz) (Schoenhagen et al., 2003). The catheter may be manually manipulated or positioned distally to the anatomy of interest and pulled back past the lesion using a motor (typically at a speed of 0.5mms⁻¹) while imaging to obtain three dimensional data. IVUS studies have demonstrated vessel wall thickening in the absence of luminal narrowing on coronary angiography (Ge et al., 1994) and, unlike QCA, the technique does not rely on a normal segment of artery for reference as vessel wall thickness is measured directly. The quantitative ability of IVUS to measure coronary wall thickness and plaque size means that it is commonly used in the invasive assessment of plaque progression and regression in response to therapy (the REVERSAL trial of statins, for example (Nissen et al., 2004)). However, the interventional nature of the technique and associated radiation dose means that only patients scheduled for angiography can be studied.

Plaque components can often be differentiated from one another using IVUS. Tissue appearing bright with shadowing behind corresponds to calcium, bright tissue without the shadowing corresponds to fibrous tissue and tissue which appears dark corresponds to thrombus or lipid (Nissen and Yock, 2001). However, the accuracy of discriminating between the latter two groups (fibrous tissue vs. thrombus or lipid) is limited (Hiro et al., 1997).

Further information may be obtained from the IVUS signal by analysing the raw data. Integrated backscatter techniques integrate the Fourier transform of the received signal over the frequency spectrum to obtain a mean power (or integrated backscatter) value. Integrated backscatter values from *ex-vivo* samples have been correlated with plaque histology in order to produce normal ranges for calcification, mixed lesions, fibrous tissues, lipid cores and thrombus (Kawasaki et al., 2002, Sano et al., 2006).

Virtual histology (Moore et al., 1998, Nair et al., 2002, Konig and Klauss, 2007) goes further by using multiple parameters obtained from the frequency spectrum (for example peak power, corresponding frequency, minimum power, corresponding frequency, integrated backscatter and others) to automatically classify plaque components. The strong correlation of virtual histology findings with actual histology (Nair et al., 2002) means that vulnerable plaques may be identified. Such techniques, however rely on accurate manual correction of the borders detected and cannot differentiate between soft plaque material and thrombus (Konig and Klauss, 2007).

Different plaque components are expected to have differing mechanical properties which may be differentiated using IVUS elastography or palpography (de Korte et al., 2000, de Korte et al., 2002, Schaar et al., 2006, Schaar et al., 2003). Such techniques involve measuring local radial displacement of the vessel wall due to luminal pressure differences between two points in the cardiac cycle (as determined from the ECG) and, hence, determining radial strain. In particular, studies have demonstrated that vulnerable plaques are likely to have a high strain region in the fibrous cap, commonly surrounded by low strain regions. Regions of high strain are also likely to be macrophage rich (de Korte et al., 2002, Schaar et al., 2003).

In general clinical practice, there is little benefit in routine use of IVUS pre-intervention (Nissen and Yock, 2001) and, in complex cases, operators often prefer the functional information available from Doppler flow or pressure wire measurements. However, IVUS may be used in assessing lesions which are angiographically ambiguous (Nissen and Yock, 2001), for example in the case of intermediate stenoses (typically 40 – 70% diameter) when symptoms are not easily assessed or when there are overlapping structures on the angiogram. Disease in the LM is difficult to assess using x-ray angiography and IVUS may be of use in these cases (Hermiller et al., 1993). In addition, IVUS can be used to aid the choice of device (Stone et al., 1997) in treating a particular lesion and in ensuring that stents are fully expanded with all struts in contact with the vessel wall (Oemrawsingh et al., 2003). Furthermore, in future the additional information from virtual histology or elastography/palpography may aid in the differentiation of vulnerable plaque, but IVUS remains an invasive technique with the associated risks of x-ray coronary angiography.

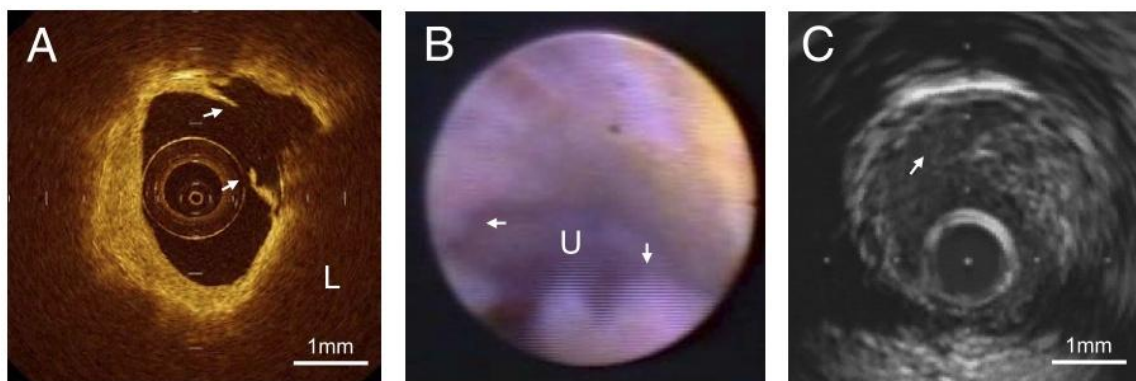
1.d.iv Intravascular optical methods

Several optical based methods for intravascular imaging of coronary artery plaque have been developed, all of which have very limited penetration (≤ 2 mm (Kips et al., 2008)) but very high spatial resolution. In addition, such techniques often require that the vessel is flushed with saline and occluded proximal to the imaging device to avoid the absorption of light by blood.

Angioscopy produces images of the vessel wall and plaque surface using a light source and optical fibre camera catheter inserted into a coronary artery flushed with saline. Once a plaque has been identified using x-ray angiography, angioscopy can be used to detect thrombus (Teirstein et al., 1995) and may provide some indications of the plaque type via the colour appearance (Ishibashi et al., 2006).

Optical coherence tomography (OCT) uses infrared light and the Michelson interferometry principle to reject scattered light and produce high resolution tomographic images of tissue reflectance (Brezinski et al., 1996, Patwari et al., 2000, Jang et al., 2002). The resolution has been measured at $13 \pm 3 \mu\text{m}$ (Jang et al., 2002) which permits imaging of the fibrous cap but the penetration is limited to only 1 – 2mm (Jang et al., 2002). More recently frequency domain OCT (Fercher et al., 1995, Yun et al., 2006, Bouma et al., 2009) has demonstrated greatly increased temporal resolution (from a few frames per second to >100 frames per second (Bouma et al., 2009)) and improved signal to noise ratio (Choma et al., 2003), using a tuneable laser source, enabling a greater length of vessel to be imaged within each saline flush. Figure 1.17 compares images of a ruptured coronary plaque imaged with OCT, angiography and IVUS, highlighting the high resolution but limited penetration of OCT.

Figure 1.17: A comparison of intracoronary imaging techniques



Corresponding images of coronary plaque obtained using OCT (A), angiography (B) and IVUS (C). The lesion is a lipid rich plaque (L) with a rupture of the fibrous cap (arrows), visible as an ulcer on the angiography image (U). Reproduced from Kubo et al. (2007) with permission, copyright Elsevier.

Light may also be used to determine the chemical composition of the vessel wall using the Raman effect. Raman spectroscopy or near infra-red spectroscopy may differentiate plaque components such as lipid, fibrotic and calcified tissue and penetrate to a depth of 1.5 – 2mm (Buschman et al., 2000, Romer et al., 2000, Motz et al., 2006). Studies have, so far been limited by the relatively thick catheters available (Chau et al., 2008).

1.d.v X-ray computed tomography

X-ray computed tomography (CT) of the coronary arteries was initially limited to a few centres with electron beam CT systems (EBCT) (Boyd and Lipton, 1983, Lipton et al., 1984) which were the only scanners fast enough to avoid severe cardiac motion artefacts (reaching up to 50ms temporal resolution). However, they were expensive, required substantial maintenance, had slice thicknesses of 2 or 3mm which was worsened by scatter, had limited electron current (mAs) and were only available from a single vendor (Flohr and Ohnesorge, 2008). EBCT popularity has declined due to the vast technological advances made in multi-detector CT (MDCT) during the last ten years (see Flohr et al. (2008), de Graaf et al. (2010) or Bastarrika et al. (2009)). MDCT scanners have developed from 4-slice to 16-slice then to 64-slice and even 256-slice, enabling whole heart

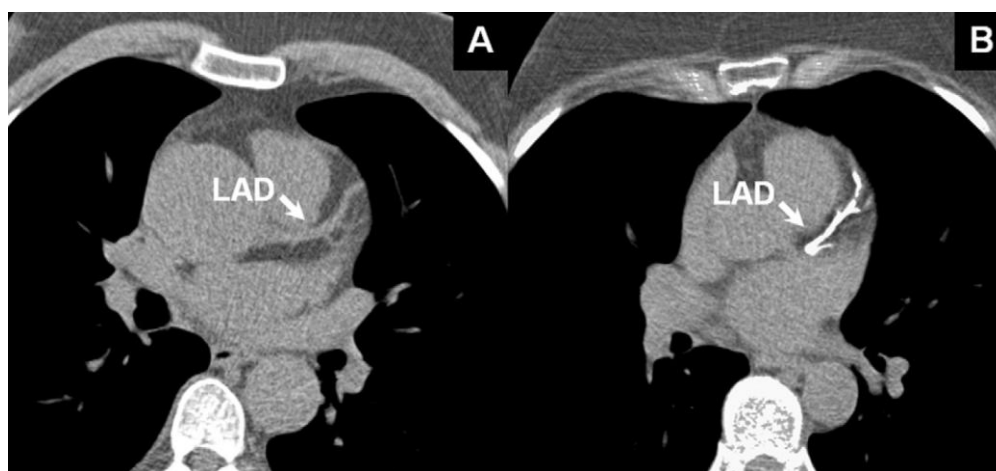
imaging within a short breath hold. The associated in-plane resolution has increased from 1.0x1.0mm at 1.3mm slice thickness with 4-slice MDCT to 0.6x0.6mm at 0.8-1.0mm slice thickness with 16-slice MDCT and to 0.4-0.6mm at 0.6-0.8mm slice thickness with 64-slice MDCT. However, further increases in resolution are likely to result in increased radiation dose in order to maintain signal to noise ratio (Flohr and Ohnesorge, 2008). Recently, 256- and 320-slice scanners were introduced, enabling whole heart coverage within one cardiac cycle with similar resolution to 64-slice scanners and a reduction in typical artefacts (Rybicki et al., 2008, Hsiao et al., 2010). Temporal resolution of MDCT is generally half the rotation time and has also improved from 250ms with 4-slice MDCT to 188-210ms with 16-slice MDCT and to 165-200ms with 64-slice MDCT (similar with 320-slice MDCT). Further increases in temporal resolution are limited by the mechanical limitations of rotating a very heavy gantry (currently limited to $\sim 3\text{rev. s}^{-1}$) and the associated data transfer rates. Recently, however, dual source MDCT which uses a second source and detector rotated by 90° with respect to the first, has been used to improve temporal resolution by a factor of 2, to a quarter of a rotation (83ms) (Flohr et al., 2006, Flohr and Ohnesorge, 2008). In order to minimise motion artefact, coronary artery MDCT imaging is typically retrospectively gated to the coronary rest period using ECG monitoring and beta blockers are used to reduce arrhythmias and high heart rates ($>65\text{BPM}$). Radiation doses for coronary artery CT vary depending on the specific application (discussed below) and scanner technology. However, in general a reduction in radiation dose is possible with x-ray tube current modulation based on the ECG information (Jakobs et al., 2002). More recently, gating the tube current to the expected coronary rest period (an acquisition window of $\sim 200\text{ms}$ starting at a fixed point, typically at 75% of the RR-interval (Earls, 2009)) has been used to reduce dose further (prospective gating), although this does not allow for subject specific variations in rest period onset and duration. While a greater number of slices generally results in an increased radiation dose due to helical oversampling, the single cardiac cycle acquisition enabled by 320-slice MDCT potentially reduces dose (Hsiao et al., 2010).

There are three methods of assessing and/or detecting coronary artery plaque with CT: coronary artery calcium (CAC) scoring which assesses the amount of calcified plaque within the coronary artery system; CT coronary artery angiography which images the lumen of the coronary arteries to detect stenoses; and CT coronary vessel wall imaging which attempts to measure the thickening of the vessel wall due to plaque. All three will be discussed here, starting with CAC scoring.

The high electron density of calcified coronary plaque appears bright on CT images without administration of contrast agents (figure 1.18). The reconstructed images are analysed to produce a CAC score. The most widely known CAC scoring system is the Agatston system (Agatston et al., 1990) whereby the number of calcified pixels (with a value >130 Hounsfield Units) is multiplied by a factor from 1 – 4 based on the peak pixel value within the deposit. Alternatively, the total volume of calcified plaque (>130 Hounsfield Units) can be calculated (Callister et al., 1998) and may be a more reproducible measure. CAC indicates the presence of atherosclerosis (Rumberger et al.,

1995) and an absence of calcified plaque is indicative of a good prognosis (Arad et al., 2000) with an increasing risk of a cardiovascular event with increasing CAC score (Greenland et al., 2007). The sensitivity and specificity for detecting significant stenoses depends on the CAC score cut-off used to define disease (Greenland et al., 2007), with higher cut-offs resulting in reduced sensitivity but increased specificity. In a study of 2115 patients (Knez et al., 2004) referred for x-ray contrast angiography for possible myocardial ischemia, a sensitivity of 100% and specificity of 28% was found when the cut-off score was >0 , whereas a sensitivity of 87% and specificity of 79% was found when using a cut-off score of >100 (using the total volume method of Callister et al. (1998)). These values represent the fact that calcified plaques, while indicative of coronary artery disease, are not necessarily significantly stenotic. Furthermore, not every coronary artery plaque is calcified (Rumberger et al., 1996). Therefore, CAC scoring cannot be used to specifically identify rupture prone or stenotic plaque. American Heart Association (AHA) guidelines (Greenland et al., 2007) suggest that CAC scoring is of most use in screening asymptomatic subjects with intermediate risk factors. Effective radiation doses using a 64-slice MDCT for calcium screening are typically 0.5mSv and 3.7mSv for prospectively and retrospectively gated studies respectively (Horiguchi et al., 2008, Desjardins and Kazerooni, 2004).

Figure 1.18: CAC scoring images

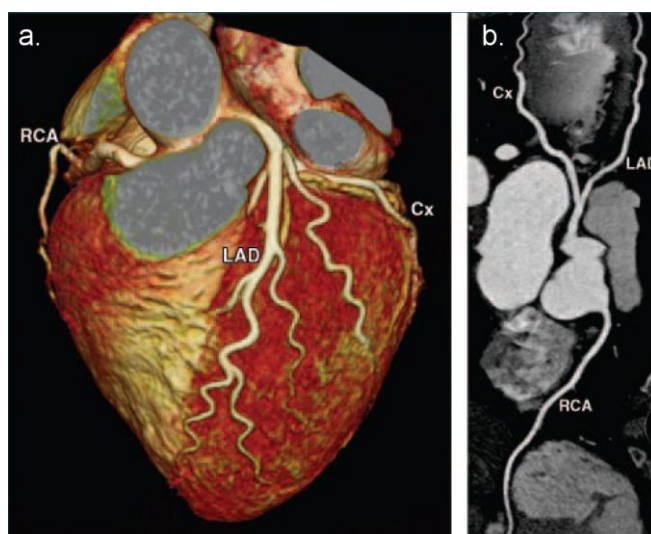


Non-contrast enhanced CT images of the LAD acquired with a 64-slice scanner using prospective ECG gating in subjects with suspected myocardial infarction. No calcium is seen in the first subject (A) whereas there is extensive calcification of the LAD in the second subject (B). Reproduced from Fernandez-Friera et al. (2011) with permission, copyright Elsevier.

CT coronary artery angiography is performed using intravenous injection of iodinated contrast agent in order to provide contrast between soft tissue and blood within the lumen (figure 1.19.b). The images may be reformatted in any plane and the high signal to noise ratio (SNR) available enables volume rendering of the coronary anatomy (see figure 1.19.a). Stenoses are observed as a reduction in lumen area (see figure 1.20), although calcified plaque can result in a blooming artefact, obscuring the artery. A recent meta analysis of 64-slice MDCT studies compared to x-ray contrast angiography or IVUS (Stein et al., 2008) found an average per patient sensitivity of 98%

and specificity of 88%. In individual arteries the sensitivity and specificities were 100% and 99% respectively in the LM, 93% and 95% in the LAD, 88% and 95% in the LCX and 90% and 96% in the RCA. In a pooled analysis of the results on a per segment basis the sensitivity was 90% and specificity 96% (segments defined according to Austen et al. (1975)). In proximal segments (defined according to Stein et al. (2006)) the average sensitivity and specificity was 95% and 93% respectively, in mid segments it was 94% and 90% and in distal segments it was 80% and 97%. Another recent meta-analysis of 64-slice MDCT studies (Mowatt et al., 2008) found a median per patient negative predictive value of 100%, suggesting that CT coronary angiography can accurately rule out flow limiting disease. However, the same meta-analysis found a consistently high level of false positive results (median 10%), caused by an overestimation of the degree of stenosis rather than an incorrect detection of a stenosis when none exists. In contrast to CAC scoring, CT coronary angiography is able to detect both calcified and non calcified stenosis. However CT coronary angiography cannot detect Glagov type positive remodelling, whereas CAC scoring may detect plaque that is calcified but not yet stenotic. In a recent multi-centre study (Hausleiter et al., 2009) the median effective dose in MDCT coronary angiography was 12mSv with a range of median values from 5mSv to 30mSv between sites.

Figure 1.19: Reformatted images from CT coronary angiography



Retrospectively ECG-gated CT coronary angiography in a relatively small 52 year old woman (body mass index 19.2) with chest pain. Images were obtained with a low dose (approximately 5mSv) protocol. A three-dimensional volume rendering (a) is shown with a curved planar reformat (b). In both cases the right coronary artery (RCA), left anterior descending artery (LAD) and left circumflex (LCX) artery are labelled. Reproduced from Bastarrika et al. (2009) with permission, copyright RSNA.

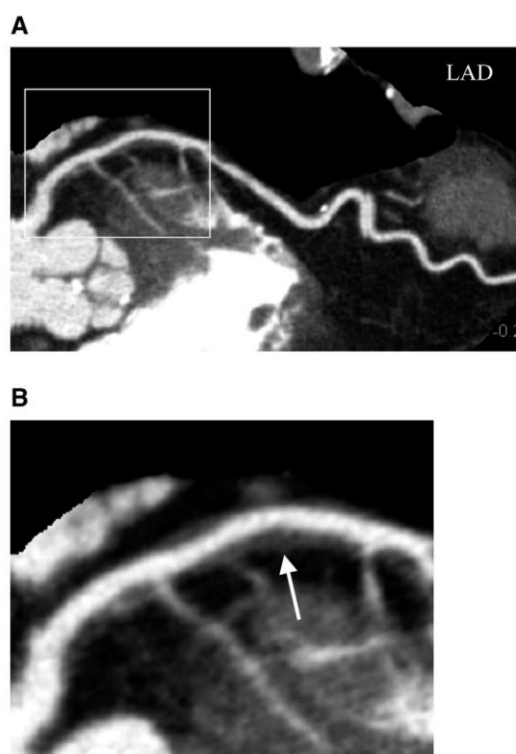
Figure 1.20: Luminography images of a 90% stenosis in the LAD



Equivalent images obtained using x-ray contrast angiography (A), CT coronary angiography (B) and MR angiography (C) all demonstrate an ostial 90% stenosis of the LAD in this 46 year old patient. CT and MR images shown as curved planar reformats. Reproduced from Maintz et al. (2007) with permission, copyright Royal Society of Medicine Press.

There has been recent interest in using CT to image soft coronary plaque (Becker et al., 2000, Schroeder et al., 2001, Leber et al., 2003, Achenbach et al., 2004, Leber et al., 2006, Motoyama et al., 2007, Tanaka et al., 2009b, Matsunaga et al., 2009). Such acquisitions use contrast enhanced acquisitions similar to those obtained for CT contrast angiography. Coronary plaque is identified as an area immediately adjacent to the lumen with reduced signal intensity in the case of a soft plaque (see figure 1.21) or high signal intensity in the case of a calcified plaque. Attempts have also been made to identify plaque components based on pixel intensities in the CT images using a comparison with equivalent IVUS images (Schroeder et al., 2001). One *in-vivo* study compared patients admitted with acute coronary events to those with stable angina by labelling culprit plaques as positive remodelling, calcified or with spotty calcification (Motoyama et al., 2007). Culprit lesions in acute coronary events were more often outwardly remodelling and spotty calcified plaques, whereas those associated with stable angina were more commonly heavily calcified. More recently, Matsunaga et al. (2009), measured maximum proximal coronary artery wall thickness in patients with suspected coronary artery disease and demonstrated a small but significant increase in maximum vessel wall thickness with age. Average maximum coronary wall thickness was also greater in diabetic patients and hypertensive patients. This is a relatively new technique however and like all CT based studies, temporal resolution is restricted by the rotational speed of the gantry and soft tissue contrast is limited. Mixed and soft plaque volumes are underestimated, calcified plaque volume is underestimated and some plaques are missed entirely (Leber et al., 2006). Radiation doses are similar to those from similar retrospectively gated CT coronary angiography studies, typically in the range 9-14mSv (Leber et al., 2006).

Figure 1.21: Coronary vessel wall thickening in the LAD assessed by CT



CT coronary artery angiography images of the LAD in a subject with suspected coronary artery disease. The region highlighted by the rectangle in A is magnified in (B). The arrow indicates the maximum wall thickness in this segment. Reproduced from Matsunaga et al. (2009) with permission.

In conclusion, CT coronary angiography is able to effectively rule out significant coronary artery disease on a per patient basis (sensitivity 98%), although further invasive testing is required to confirm the location and extent of the disease (specificity 88% on a per patient basis). CAC scoring is also able to operate with a very high sensitivity (100% at zero CAC score threshold) but is relatively unspecific (28% at the same threshold). However, effective radiation doses are higher for CT coronary angiography (5mSv on average) compared to CAC scoring (0.5mSv for prospective gating). Dose reductions in CT coronary angiography can be achieved via ECG based tube current modulation, prospective ECG gating and 320-slice whole heart imaging. Spatial resolution is typically 0.4-0.6mm in-plane for 0.6-0.8mm slice thickness and improvements are expected to result in increases in effective dose. Temporal resolution with single source imaging is typically 165ms and is halved to 83ms in dual source imaging. Further reliable improvements in temporal resolution are likely to require substantial improvements to gantry designs. Thickened coronary vessel walls have been also been measured and even categorised with CT, although contrast and temporal resolution limitations currently hinder such studies.

1.d.vi Molecular imaging

Molecular imaging targets the underlying physiological mechanisms involved in the formation, progression and rupture of a plaque (Choudhury and Fisher, 2009). Imaging targets in early

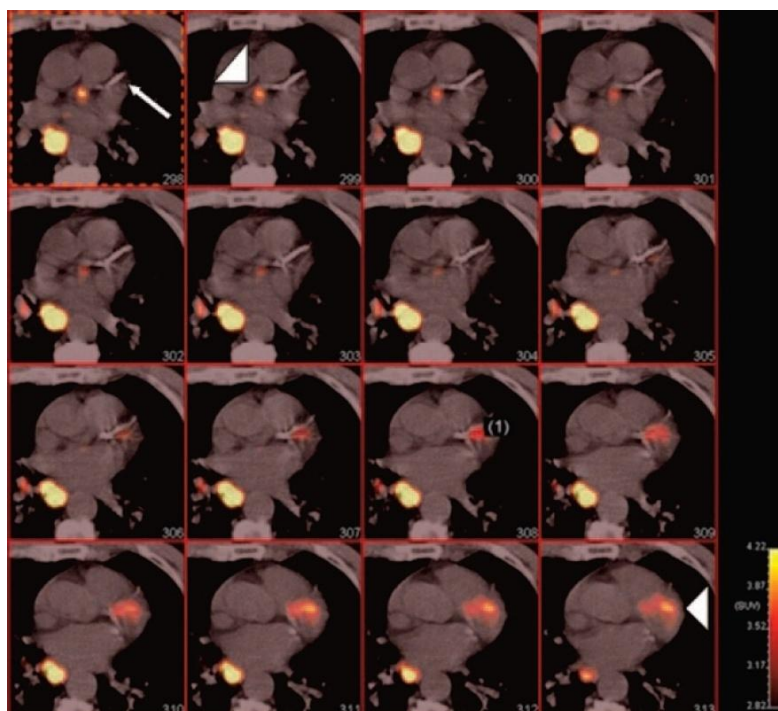
disease include the inflammatory response of the endothelium to the over abundance of LDL in the vessel wall, leukocyte immigration into the vessel wall in response to the inflammation and phagocytosis of the lipid into mature monocytes (Libby et al., 2010). It may also be possible to detect high concentrations of macrophages in the shoulder regions of vulnerable plaques and monitor matrix metalloproteinases (MMP) which are involved in the destabilisation of the plaque (Choudhury and Fisher, 2009). It is also desirable to locate acute thrombus in an acute coronary event for which, activated platelets, fibrin and tissue factor are the imaging targets. All such physiological targets require a targeted contrast agent which may be imaged using nuclear techniques (Davies et al., 2006, Langer et al., 2008) (planar scintigraphy, SPECT or PET), MR (Aime et al., 2002, Briley-Saebo et al., 2007, Sosnovik et al., 2008), ultrasound (Liang and Blomley, 2003, Kaufmann, 2009, Deshpande et al., 2010) or optical fluorescence techniques (Weissleder and Ntziachristos, 2003, Subramanian et al., 2010). Other considerations in contrast agent design include the relative sensitivity of the imaging modality to the contrast agent, the toxicity of the agent and the uptake/clearance kinetics.

Single photon nuclear imaging techniques (planar scintigraphy and SPECT) are limited by their relatively poor spatial resolution (in the order of 10mm) but have demonstrated positive results in targeting several stages of the atherosclerotic process (Davies et al., 2006). In particular LDL accumulation has been successfully targeted by several groups (Iuliano et al., 1996, Tsimikas et al., 2000, Shaw et al., 2001). Apoptosis has been targeted with ^{99m}Tc labelled agents (Kolodgie et al., 2003, Kietselaer et al., 2004) (ideal for SPECT imaging), although PET based tracers probably hold more potential in this area, due to the improved quantitation and anatomical information from adjunct CT. However, very little single photon nuclear imaging work has been performed in humans and even less has targeted the coronary arteries (Langer et al., 2008).

PET imaging has increased tracer sensitivity and spatial resolution (4-5mm) when compared to SPECT, and the commonly used tracer – ^{18}F labelled fluorodeoxyglucose (FDG) demonstrates uptake in arterial inflammation (Bleeker-Rovers et al., 2003). However, the proximity of the coronary arteries to the highly metabolically active myocardium means that coronary artery inflammation is generally obscured. Despite this, *in-vivo* uptake of FDG in the coronary arteries of humans has been demonstrated (figure 1.22) (Dunphy et al., 2005), although almost half the studies were not evaluable due to myocardial uptake of tracer. Other PET tracers may be useful in targeting MMP or apoptosis (Davies et al., 2006).

Respiratory and cardiac motion present problems in cardiac radionuclide imaging. Gating acquisitions may eliminate a large proportion of the motion, yet acquisition durations and/or radiation doses will increase as a result.

Figure 1.22: PET/CT imaging of the LAD with ^{18}F -FDG tracer

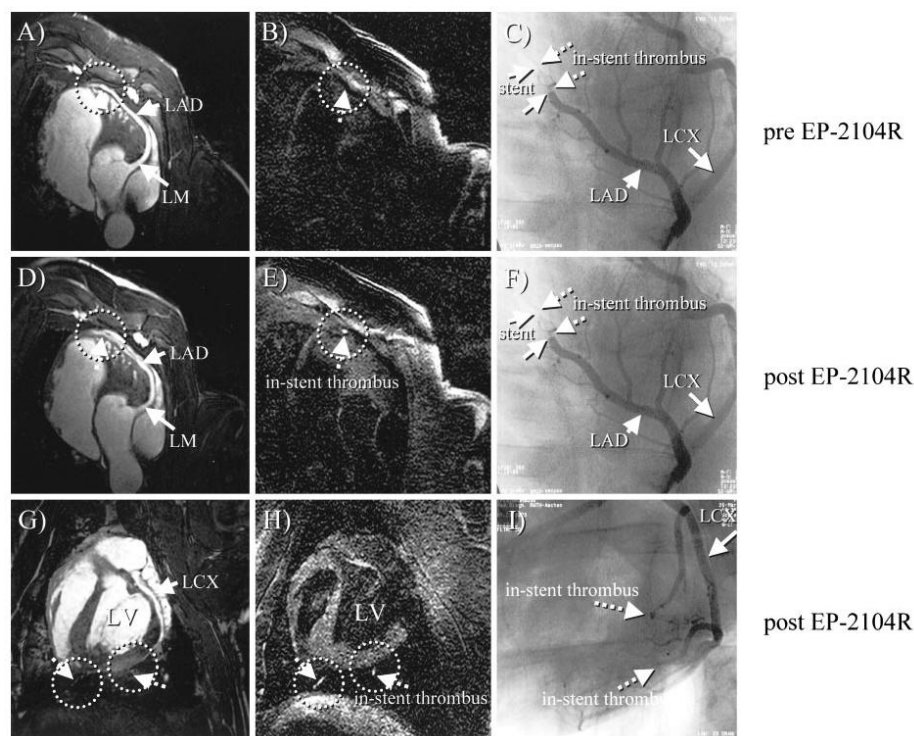


The CT images in greyscale are transparently overlaid with the PET data in a “hot” colour scale. The LAD is heavily calcified (arrow) and there is corresponding uptake of the ^{18}F -FDG tracer in the LM and LAD (arrow heads and (1)). Reproduced from Dunphy et al. (2005) with permission.

Molecular MR imaging (Spuentrup and Botnar, 2006, Makowski et al., 2009) has great potential as it does not use ionising radiation, is intrinsically co-registered with anatomical MR images and has higher spatial resolution than is achievable with radio-isotope based methods. MR contrast agents are most commonly gadolinium (Gd) compounds or iron oxide based particles (Wang et al., 2001b). Gd is a paramagnetic element which is chelated in order to minimise the risks of heavy metal poisoning. Iron oxide is ferromagnetic and formed into nanoscale coated particles, which have properties known as super-paramagnetism (Weissleder et al., 1990). Both agents result in a reduction in T1 (the time constant of longitudinal recovery of magnetisation) and T2 (the time constant of transverse dephasing of magnetisation). The paramagnetic effect of Gd results in a stronger T1 effect than that on T2 (Weinmann et al., 1984). This is observed as a localised increase in signal intensity on T1 weighted imaging. The super-paramagnetic properties of iron oxide agents generally result in a much larger effect on T2 (Weissleder et al., 1990) than T1 and the change in the local magnetic field associated with localised contrast uptake results in a further reduction in T2*. Uptake of iron oxide based contrast agents is observed as a reduction in signal intensity on T2* weighted images, although signal enhancement has been demonstrated in T1 weighted images (Small et al., 1993, Metz et al., 2010) and a number of specialised sequences exist for positive enhancement as a result of reduced T2* (Cunningham et al., 2005, Mani et al., 2006, Stuber et al., 2007). T1 weighted imaging has been used to detect the uptake of extravascular Gd contrast agents in coronary artery plaques (Maintz et al., 2006, Yeon et al., 2007, Ibrahim et al.,

2009) and to detect intrinsic changes in the T1 of plaque (Kawasaki et al., 2009, Tanaka et al., 2009a) (discussed further in section 1.e.ii). Other passive contrast agents include super-paramagnetic particles of iron oxide (SPIOs) and ultrasmall SPIOs (USPIOs) which have been used in human carotid *in-vivo* studies (Metz et al., 2010). These particles are phagocytosed within some plaques, indicating the presence of macrophages (Kooi et al., 2003, Trivedi et al., 2004). Endothelial activation has been targeted in mice and *ex-vivo* human carotids (Nahrendorf et al., 2006) using iron oxide based contrast agents. Formation of new blood vessels within advanced plaques was demonstrated in rabbits using Gd agents (Winter et al., 2006). Early studies have targeted the lipid content of coronary plaque using lipophilic gadofluorine in rabbits (Sirol et al., 2004) and a Gd labelled HDL analogue in mice (Chen et al., 2008). Finally, a number of contrast agents have been developed to target fibrin (figure 1.23) (Botnar et al., 2004a, Botnar et al., 2004b, Spuentrup et al., 2005a, Spuentrup et al., 2007b, Spuentrup et al., 2007a) which is a key component of a thrombus. The majority of such studies have been *in-vitro* and in animals, but recently one agent, EP2104R was used to image non-coronary thrombus in patients (Spuentrup et al., 2008) and has previously highlighted in-stent coronary thrombus in swine (Botnar et al., 2004a).

Figure 1.23: In-stent thrombus imaged with a thrombin targeting contrast agent (EP-2104R) using MR



MR lucent coronary stents containing thrombogenic material were placed into the coronary arteries of a pig using x-ray contrast angiography guidance. Occlusion of the LAD and LCX is evident on the MR coronary angiography (A, D and E) and x-ray contrast angiography images (C, F and I). Blood suppressed images acquired using an inversion-prepared gradient echo technique show the selective uptake of the Gd based EP-2104R contrast agent in the thrombus filled stents (B, E and H). Reproduced from Botnar et al. (2004a) with permission.

While molecular imaging holds great potential for selectively targeting the constituents and physiological processes in atherosclerotic plaque development, so far few studies have been performed in humans, particularly in the coronary arteries. Radionuclide based techniques involve ionising radiation doses and suffer from relatively poor resolution with the compounding effects of motion. MR based techniques offer potentially improved resolution with relatively safe contrast agents, but are some way from reaching full fruition.

1.e MR coronary artery imaging

MR imaging is well established in the assessment of cardiac function, perfusion and viability in ischemic heart disease (Manning, 2006, Sakuma, 2007, Pennell, 2010). However, while MR coronary angiography has undergone extensive development in the last 20 years, it is not yet sufficiently reliable for clinical use in assessment of coronary artery disease. The small size, deep location and mobile nature of the coronary arteries make them a particularly challenging target in MR. The remainder of this chapter will review existing work on MR coronary angiography and MR coronary vessel wall imaging. Motion in cardiovascular MR including MR coronary artery imaging will be fully considered in chapter 2.

1.e.i MR coronary angiography

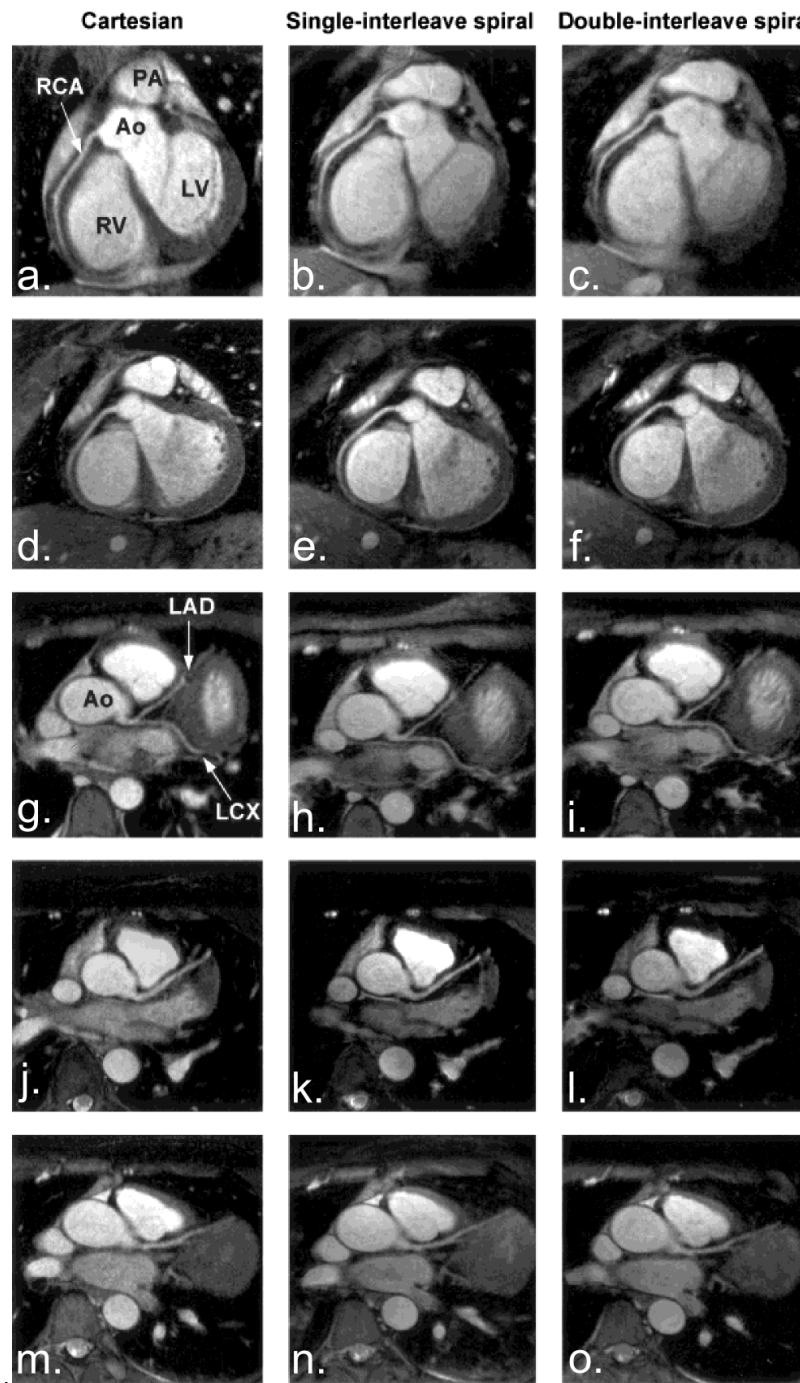
Up to 40% of x-ray angiography studies reveal no significant coronary artery disease (Budoff et al., 1996). Therefore a non-invasive, low risk imaging technique such as MR coronary angiography is a desirable tool in modern cardiology (Stuber and Weiss, 2007).

1.e.i.1 *Imaging sequences*

Numerous MR techniques have been used in attempts to image the coronary arteries. The vast majority gate data acquisition to the cardiac rest period (see section 2.a.ii) and are performed within a breath-hold or with some form of respiratory motion compensation (see section 2.b). However, initial studies were performed with spin-echo sequences (Paulin et al., 1987) without the use of cardiac or respiratory gating and were, therefore relatively unsuccessful. It was not until the advent of segmented imaging (Edelman et al., 1990, Atkinson and Edelman, 1991) that gated techniques and, therefore more reliable imaging, was possible. More reliable spin-echo based sequences have been demonstrated in recent times (Maintz et al., 2004, Stuber et al., 2001), but the negative contrast of the coronary arteries has made them the exception rather than the rule. Spoiled Cartesian gradient recalled echo (GRE) imaging (Edelman et al., 1991b, Pennell et al., 1993, Li et al., 1993, Manning et al., 1993) with fat suppression results in a bright signal from the coronary lumen with suppression of the surrounding epicardial fat. While Cartesian GRE imaging is a relatively robust method of imaging the coronary arteries that is commonplace at 3T (Stuber et al., 2002b, Sommer et al., 2005, Gharib et al., 2007, Liu et al., 2008), Cartesian balanced steady state free precession (bSSFP) techniques are now usually preferred at 1.5T (Deshpande et al., 2001a, Shea et al., 2002, Spuentrup et al., 2002a). Alternatively, many groups have pursued alternative k-space trajectories in order to reduce the cardiac acquisition window and/or improve imaging efficiency. Echo planar imaging (EPI) (Slavin et al., 1998, Botnar et al., 2000b, Deshpande et al., 2001b) is rapid and efficient, yet prone to ghosting, susceptibility and T2* decay artefacts (Edelman et al., 1994). Radial trajectories (Larson et al., 2002, Spuentrup et al., 2004, Stehning et al., 2004, Xie et al., 2010) heavily oversample the centre of k-space making them inherently insensitive to motion (Spuentrup et al., 2004), while the outer parts are usually under-sampled to save time. This is possible as the wrap-around artefacts in radial imaging are less detrimental to

image quality than in Cartesian imaging. Furthermore, in order to improve SNR, radial bSSFP imaging may also be performed, by refocusing rather than spoiling the magnetisation after every radial line. However, the heavy oversampling of the centre of k-space makes radial acquisitions inherently time inefficient. In contrast, spirals are inherently efficient trajectories that share some of the motion resilient properties of radial trajectories. Spiral imaging has been successfully used to image the coronary arteries since the beginnings of MR coronary angiography (Meyer et al., 1992, Bornert et al., 2001b, Bornert et al., 2001a). In head-to-head comparisons, spiral acquisitions outperformed Cartesian GRE (Taylor et al., 2000) and performed as well or better than Cartesian bSSFP techniques (figure 1.24) (Bornert et al., 2001b, Maintz et al., 2004). However, the very careful setup, shimming and fat suppression required to avoid characteristic blurring, as well as the more complex reconstruction means that spirals are not currently a popular choice for MR coronary angiography. As a result, Cartesian bSSFP (Deshpande et al., 2001a, Shea et al., 2002, Spuentrup et al., 2002a) is the current sequence of choice for MR coronary angiography at 1.5T, due to the improvements in SNR over Cartesian GRE and radial techniques (Deshpande et al., 2001a, Spuentrup et al., 2002a, Spuentrup et al., 2004). While banding artefacts appear in bSSFP images as a result of magnetic field inhomogeneities, they can mainly be overcome through careful setup and shimming.

Figure 1.24: A comparison of Cartesian GRE and spiral MR coronary angiography techniques



MR coronary angiography images acquired in healthy subjects using T2-prep. 3D targeted imaging at 0.7x0.7x3.0mm resolution with navigator gating and prospective slice tracking. In each subject acquisitions were performed using a Cartesian GRE sequence (a, d, g, j and m) with a cardiac acquisition window of 81ms and a spiral acquisition using one 20ms spiral interleave per RR-interval (b, e, h, k and n) with a cardiac acquisition window of 26ms and a spiral acquisition using two 20ms spiral interleaves per RR-interval (c, f, i and o) with a cardiac acquisition window of 52ms. SNR was increased in both spiral acquisitions. The Cartesian GRE acquisition was acquired in a similar duration to the spiral acquisition with one interleave per RR-interval whereas the duration was halved when two interleaves per RR-interval were used. Reproduced from Börnert et al. (2001b) with permission, copyright John Wiley & Sons.

1.e.i.2 Contrast mechanisms

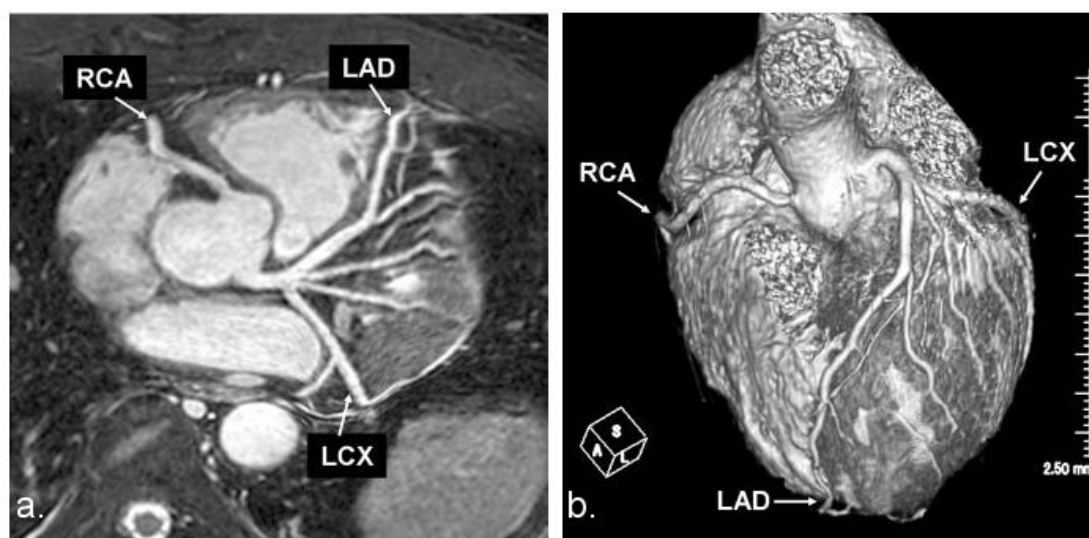
MR coronary angiography is most commonly performed using only endogenous contrast mechanisms. Bright blood contrast is generated in gradient echo based (including bSSFP, spiral and radial acquisitions) 2D and targeted 3D MR coronary artery acquisitions using the inflow of fresh blood to generate high blood signal (Edelman et al., 1991b), while fat suppression is used to null the signal from the epicardial fat surrounding the coronary arteries. Many studies also use preparatory RF pulses to generate T2 weighting (T2-prep) (Brittain et al., 1995, Botnar et al., 1999) which suppresses the myocardial signal relative to that from oxygenated blood. Other, less frequently employed pre-pulses that make use of endogenous mechanisms to enhance coronary lumen/background contrast include magnetisation transfer contrast (Li et al., 1993) and arterial spin labelling (Wang et al., 1991, Stuber et al., 2002a, Katoh et al., 2008, Katoh et al., 2009).

Exogenous contrast agents in the form of either extracellular (Goldfarb and Edelman, 1998, Li et al., 2001) or intravascular Gd based agents (Wielopolski et al., 1998, Li et al., 1998, Stuber et al., 1999b) have been used to increase blood/background signal via T1 shortening. Extracellular agents are more commonly available, but quickly diffuse from the vessels into the extracellular space, therefore rapidly diminishing the positive contrast effect. This is particularly problematic during long 3D acquisitions. As a result, extracellular agents require first pass imaging techniques or the use of more complex slow infusion methods (Li et al., 2001). Intravascular agents are unable to easily pass through the vessel wall and so remain in the blood pool for much longer (typically >1hr (Stuber and Weiss, 2007)), but very few are available for routine use. Recently there has been much publicity of the risks of potentially fatal nephrogenic systemic fibrosis (NSF) (Marckmann et al., 2006, Grobner, 2006, Thomsen, 2006, Rofsky, 2008) from certain Gd based contrast agents. However, the risk of such complications is extremely low, and NSF is not known to have occurred in subjects with healthy kidneys. As a result, renal function is measured and as a precaution Gd based contrast agent is generally not administered if the estimated glomerular filtration rate is <30ml min⁻¹ (Rofsky, 2008).

1.e.i.3 Whole heart vs. targeted imaging

At the present time, MR coronary angiography is almost universally performed as a 3D acquisition for ease of setup and improved SNR efficiency. Whole heart studies (Weber et al., 2003, Stehning et al., 2004) image the whole coronary artery system in one 3D acquisition; therefore minimising preparatory imaging time, enabling whole heart surface renderings (see figure 1.25) and, in general, requiring less skill in planning. However, the large imaging volume results in a variation of the in-flow enhancement effect across the imaging volume and a corresponding loss of contrast to noise ratio (CNR) (Bi et al., 2006, Chang et al., 2008). For this reason, 3D slabs targeting each coronary artery may be preferable in some circumstances.

Figure 1.25: Whole heart MR coronary angiography images



Whole heart 3D MR coronary angiography images acquired in a total study time of less than 30 minutes using a bSSFP sequence with T2-prep and navigator gating. Curved planar reformatting (a) and surface rendering (b) is used to produce images similar to those obtained with CT (see figure 1.19). The left anterior descending (LAD), left circumflex (LCX) and right (RCA) coronary artery labelled in both cases. Reproduced from Sakuma et al. (2005) with permission, copyright RSNA.

1.e.i.4 Comparison with CT coronary angiography

MR coronary angiography may be the clinical choice for imaging anomalous coronary arteries in congenital heart disease (Post et al., 1995) and is a useful tool in subjects with Kawasaki disease (Greil et al., 2007b, Greil et al., 2002, Takemura et al., 2007), but it is not in current routine clinical use for the assessment or detection of coronary artery stenoses. The rapid technological advance of MDCT and dual source CT has resulted in CT becoming the current modality of choice for non-invasive coronary angiography, despite the associated ionising radiation dose, due to the shorter acquisition durations, improved spatial resolution and superior diagnostic accuracy possible (Schuetz et al., 2010).

Although MR coronary angiography has been acquired at up to $0.7 \times 0.7 \times 0.9$ mm resolution in patients (Klein et al., 2008), resolutions of $1.3 \times 1.3 \times 1.7$ mm – $1.0 \times 1.0 \times 1.5$ mm used in recent studies (Pouleur et al., 2008, Kato et al., 2010) are more typical, which compares poorly to the resolution available with MDCT (see section 1.d.v). And while the average duration of a whole heart coronary angiography acquisition in a recent head-to-head comparison was 20s using 16-slice MDCT, it was 14min using MR (Maintz et al., 2007). Most crucially, however, the diagnostic accuracy of MDCT is superior. A recent meta-analysis compared the diagnostic performance of CT coronary angiography with MR coronary angiography in ruling out significant coronary artery disease (Schuetz et al., 2010) when both were compared to x-ray contrast angiography as a gold standard. The authors reviewed substantially more CT studies than MR studies, reflecting the balance of the number of publications in these fields. They calculated sensitivities of 87.1% and 97.2% in MR and

CT studies respectively and specificities of 70.3% and 87.4% respectively on a per-patient basis ($p < 0.001$ in both cases). No subgroup analysis was performed on the MR data to provide sensitivities and specificities on a per-vessel or per-segment basis and both the CT and MR studies were heterogeneous in the protocols they used (16-320 slice MDCT with single and dual source, GRE and bSSFP MR sequences, with and without contrast agents, both breath-hold and free-breathing). In a direct head-to-head comparison of 77 patients (Pouleur et al., 2008), whole heart 3D MR coronary angiography using bSSFP imaging with T2-prep was compared to 40- or 64-slice MDCT. Imaging was successful in all 77 patients using MDCT but MR coronary angiography failed in 9 (12%) patients due to poor respiratory efficiency using navigator gating (see section 2.b). While, on a per patient basis, sensitivity was similarly high using both techniques (100% vs. 94% for MR and CT respectively), specificity was lower using MR (72% vs. 88%). On a pooled per vessel basis, sensitivity was 95% using both techniques, whereas specificity was 79% vs. 92% for MR vs. CT respectively. On a pooled per segment basis sensitivity was 96% vs. 98% for MR vs. CT respectively and specificity was 68% vs. 92%. In the most recent multicentre trial of MR coronary angiography 138 patients with chest pain suggestive of significant coronary disease (Kato et al., 2010) were examined. Imaging failed in 11 subjects (8%) due to poor navigator gating performance. Sensitivity and specificity were 88% and 72% respectively on a per patient basis, 83% and 90% per vessel, 77% and 90% in the RCA, 100% and 100% in the LM, 91% and 82% in the LAD, 69% and 97% in the LCX and 81% and 98% on a per segment basis.

While coronary MR angiography does not suffer from the same artefacts caused by calcified plaque in CT coronary angiography, a considerable number of navigator gated MR studies fail due to irregular respiratory patterns (typically 8% (Kato et al., 2010) to 14% (Sakuma et al., 2006)). Metallic coronary stents also generate MR artefacts whereas CT may be able to assess disease within the stent (Cademartiri et al., 2008), although MR lucent coronary stents have been demonstrated in swine (Buecker et al., 2002, Spuentrup et al., 2005b). The use of beta-blockers to reduce a subject's heart rate is common in CT coronary angiography although rare in MR studies (Schoepf et al., 2007, Schuetz et al., 2010). This is primarily because tube rotation speeds in CT limit the temporal resolution to approximately 165ms (half this in dual source CT). In contrast the acquisition window is readily defined on a subject specific basis in MR imaging, and may be reduced to a few tens of ms in subjects with high heart rates (Hofman et al., 1998), although at the expense of imaging efficiency. Coronary vasodilators such as nitroglycerin which are used in some MR studies (Kim et al., 2001a, Hu et al., 2010, Kato et al., 2010) and are more common in CT (Schoepf et al., 2007, Schuetz et al., 2010), increase the SNR, vessel diameter (and hence, conspicuity) and sharpness, but could result in inaccurate assessment of the degree of stenosis due changes in vessel distensibility in the diseased region (Rafflenbeul et al., 1980).

1.e.i.5 Future outlook

Future developments in MR technology may reduce the gap between MR and CT in resolution, SNR and, therefore, diagnostic accuracy. Much new MR work in this area is performed at 3T where field

inhomogeneities (Zur et al., 1988, Stuber et al., 2002b, Kaul et al., 2004) and increased RF power deposition have so far limited the use of bSSFP techniques, but recent developments including wideband SSFP (Nayak et al., 2007, Lee et al., 2010) and VIPR trajectories (Xie et al., 2010) may push this sub-field forward. Coronary artery imaging at 7T has also been demonstrated (van Elderen et al., 2009) and initial results comparing coronary angiography at 7T to 3T were promising (van Elderen et al., 2010). Acquisition duration and the number of failed studies are expected to reduce with improved respiratory motion correction techniques (see section 2.b) such as described by Nehrke and Börnert (2005), the CLAWS method of Jhooti et al. (2010) and the one developed later in this thesis. Furthermore, imaging may be accelerated with parallel imaging techniques (Pruessmann et al., 1999, Weber et al., 2003, Larkman and Nunes, 2007) in one or more dimensions (Nehrke et al., 2006). However, there is an associated loss of SNR with this acceleration, which may be recovered by imaging at 3T (Huber et al., 2004).

1.e.ii MR coronary vessel wall imaging

While MR coronary angiography may one day provide a radiation free method for ruling out significant disease, other methods are required for the assessment of sub-clinical disease. MR coronary artery wall imaging, if accurate, reliable and reproducible, would permit assessment of the progression or regression of sub-clinical disease in longitudinal studies and clinical trials.

1.e.ii.1 Blood signal suppression

Meyer et al. (1998) presented the first human *in-vivo* coronary artery vessel wall images in 1998 using a 2D spiral acquisition sequence with a dark blood preparation pulse and spatial/spectral binomial excitation pulses (Meyer et al., 1990). The dark blood preparation is a non-selective 180° pulse, inverting all magnetisation, followed immediately by a slice selective 180° pulse to reinvert the tissue within the imaging plane (Edelman et al., 1991a). Imaging is performed after an inversion time (TI), selected to match the zero crossing point of the blood magnetisation, as defined by:

$$TI = T1_{\text{blood}} \cdot \left\{ \ln 2 - \ln \left(1 + e^{\left(\frac{-TR}{T1_{\text{blood}}} \right)} \right) \right\} \quad 1.1 \text{ (Fleckenstein et al., 1991)}$$

where TR is the sequence repetition time and $T1_{\text{blood}}$ is the T1 longitudinal relaxation time constant for arterial blood. Blood that starts outside the imaging slice and flows in during the inversion time, appears dark, whereas the tissue within the imaging volume appears bright. In order to ensure that the reinverted tissue contains the imaging slice after cardiac motion occurring during TI, the reinversion thickness is typically two to three times wider than the imaging slice. However, for 3D acquisitions TI may be insufficient for full replacement of the blood within the reinverted slab. As a result, 3D studies utilise either a user positional selective reinversion slab (Priest et al., 2005, Katoh et al., 2006a, Bansmann et al., 2007, Keegan et al., 2007) or a user defined “pencil beam” 2D RF pulse (Stuber et al., 2004, Botnar et al., 2001, Kim et al., 2002, Desai et al., 2005, Katoh et al., 2006b). Both of these techniques selectively reinvert the tissue surrounding the coronary artery of interest whilst minimising reinversion of the aorta and left ventricle, where the in-flowing blood originates. While the pencil beam reinversion reduces the spatial extent of the reinverted tissue relative to the slab reinversion, the latter results in a more even spatial distribution of the reinversion (Katoh et al., 2006a).

Meyer et al. (1998) acquired data every cardiac cycle (1RR gating), but a majority of dark blood coronary artery studies have gated acquisitions to alternate cardiac cycles (2RR gating). The latter is accompanied by a factor of 2 loss in imaging efficiency, but an increase in SNR (of approximately 20% (Botnar et al., 2000a)), due to greater longitudinal relaxation of both the vessel wall and myocardial tissue, and an increased resilience to variations in RR-interval due to more complete recovery of the longitudinal magnetisation of blood between sequence repeats. For a heart rate of 60BPM, equation 1.1 gives a TI of 400ms for 1RR gating and 625ms for 2RR gating. However,

should the TI be insufficient for blood signal nulling (but long enough for inverted blood to flow into the imaging volume), phase sensitive reconstruction can be used to correct the complex data (Abd-Elmoniem et al., 2010) and potentially increase the CNR of the lumen/vessel wall, even when compared to an acquisition at the TI given by equation 1.1.

Alternative methods for blood signal suppression include improved motion sensitising driven equilibrium (iMSDE) which uses large unipolar gradients either side of a refocusing pulse (similar to diffusion encoding) to dephase magnetisation within moving tissue (Wang et al., 2009, Gerretsen et al., 2010b). Despite avoiding the inversion time and in-flow requirements of double inversion recovery pulses, so far there have only been limited demonstrations of this technique in the coronary arteries due to their extremely mobile nature and the inherent sensitivity of this technique to motion. One recent study (Tanaka et al., 2009c) acquired a whole heart coronary angiography study with fat saturation and T2-prep followed by an equivalent whole heart water suppressed dataset (although the resolution of the images is not quoted). The lumen appears bright in the angiography study while the vessel wall and surrounding fat are suppressed. In contrast, the fat appears bright in the water suppressed dataset while the lumen and vessel wall are suppressed. A maximum intensity projection of the fused images is generated and the coronary vessel wall appears dark as a result. While this technique potentially permits visualisation of the coronary artery wall in a whole heart dataset, albeit with negative contrast, the two sets of images must be acquired with perfect registration, which may be problematic.

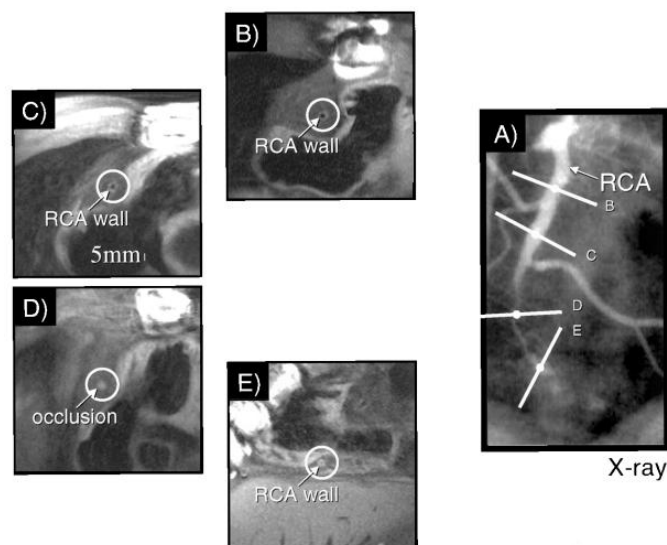
Despite the potential advantages available from 1RR gating, phase sensitive reconstruction and alternative blood suppression techniques, the reliability of double inversion recovery techniques with 2RR gating means they remain the most commonly used preparation for coronary vessel wall imaging.

1.e.ii.2 Imaging sequences

The thin wall, highly mobile nature and position of the coronary arteries deep within the chest require high spatial resolution, short acquisition windows and high SNR techniques. Imaging within the subject-specific coronary rest period is mandatory (Kim et al., 2001a) to eliminate motion artefacts. Turbo spin echo (TSE) readouts are commonly used for 2D coronary vessel wall acquisitions (Fayad et al., 2000, Botnar et al., 2000a, Hazirolan et al., 2005, Macedo et al., 2008) at 1.5T (see figure 1.26), whereas for 3D acquisitions, a stack of segmented spirals trajectory is more common (Botnar et al., 2001, Kim et al., 2002, Desai et al., 2005, Keegan et al., 2007). Spiral k-space trajectories are inherently efficient and short spiral readout durations (~10 – 20ms) can be used to reduce off-resonance blurring and minimise the effects of cardiac motion. TSE acquisitions require fat suppression in the form of a chemical shift selective saturation pulse or spectrally selective inversion recovery, whereas spiral techniques may use water selective excitation (Hore, 1983, Meyer et al., 1990, Meyer et al., 1998, Keegan et al., 2007, Abd-Elmoniem et al., 2010). In a MR coronary angiography study spectrally selective inversion recovery and binomial water selective

excitation were found to be equally effective in suppressing fat. However, water selective excitation is more time consuming than standard RF pulses, but this is less of a problem in spiral imaging, where typically only one or two interleaves are acquired per cardiac cycle. Saturation or inversion recovery based fat suppression techniques may suffer from recovery of the fat magnetisation during long acquisition windows in subjects with low heart rates. While TSE images may be T2 weighted to maximise CNR between smooth muscle and epicardial fat (Botnar et al., 2000a), spiral acquisitions with 2RR gating are proton density weighted.

Figure 1.26: Coronary vessel wall imaging and x-ray contrast angiography



Multiple 2D MR right coronary vessel wall images obtained using navigator gated TSE imaging. Images obtained at locations corresponding to B, C and E in the x-ray angiography image (A) appear to show a patent vessel lumen, whereas at the location of the suspected stenosis (D), no lumen is visible. Reproduced from Botnar et al. (2000a) with permission.

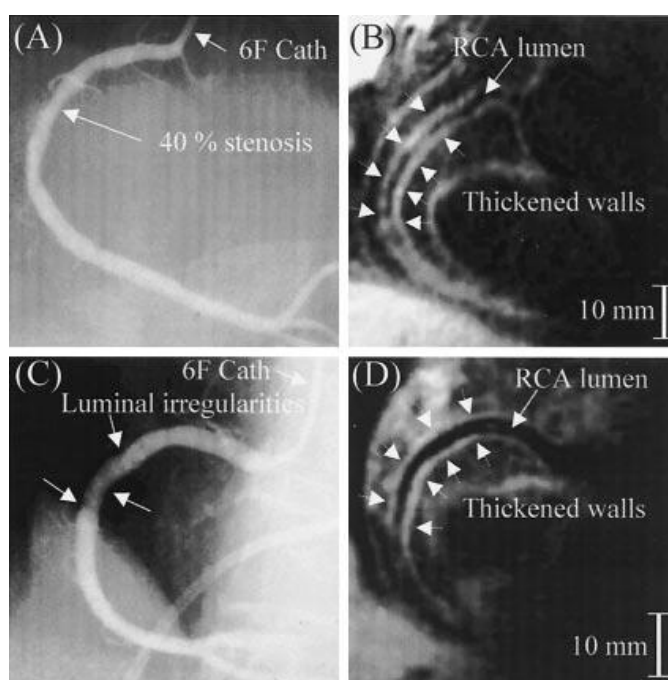
Katoh et al. (Katoh et al., 2006a, Katoh et al., 2006b, Priest et al., 2007) have investigated the use of a stack of radial lines trajectory for 3D coronary artery wall acquisitions. In a comparison with a 3D stack of spirals acquisition, both using navigator gating, Katoh et al. (2006a) found significantly increased image sharpness and subjective image scores using radial trajectories but a trend for increased vessel wall to epicardial fat contrast and vessel wall SNR using spiral trajectories. They also observed some ghost like spiral artefact and blurring which they suggest was caused by uncorrected respiratory motion within the navigator gating window. This artefact was not present in the equivalent radial acquisitions and it is possible that such blurring may be reduced with shortened spiral readouts (TR was 30ms in this study). The radial acquisition in this work was also less efficient – a longer cardiac acquisition window was used (104ms vs. 60ms) than in the spiral acquisition for approximately the same acquisition duration (8min 15s vs. 7min 49s). A separate study compared coronary vessel wall imaging using Cartesian GRE, radial GRE and radial bSSFP acquisitions (Katoh et al., 2006b). Both radial acquisitions were found to be generally superior to Cartesian GRE with lower levels of artefact and higher SNR and CNR. The radial bSSFP acquisitions

were more susceptible to failure than the radial GRE acquisitions and although the SNR and CNR were slightly improved using radial bSSFP over radial GRE acquisitions, subjective image quality was not.

1.e.ii.3 Respiratory motion compensation and improving efficiency

Breath-hold studies are limited to single slice 2D acquisitions (Fayad et al., 2000, Hazirolan et al., 2005, Macedo et al., 2008), whereas free-breathing studies with respiratory motion compensation (typically navigator gating (Botnar et al., 2001)) permit 3D imaging. The multiple, thin contiguous slices achievable with 3D techniques enable in-plane imaging of the coronary artery wall (see figure 1.27) or the acquisition of a stack of cross-sectional images (Botnar et al., 2001) with reduced partial volume effect. However, as discussed in section 2.b.iii, the efficiency of navigator gated acquisitions is low and highly variable. In combination with the short cardiac acquisition windows required and 2RR gating, this can lead to long acquisition durations. As an alternative, Keegan et al. (2007) acquired data with 100% respiratory efficiency using a novel beat-to-beat respiratory motion correction (B2B-RMC) technique, (which forms the basis for the rest of this thesis), and 1RR gating. Phase sensitive double inversion recovery (as also discussed in section 1.e.ii.1) has also been used (Abd-Elmoniem et al., 2010) to enable the acquisition of data through a longer part of the cardiac cycle and then the reconstruction of multiple 2D slices. However, this acquisition scheme is primarily limited to multi-slice 2D studies in order to allow sufficient blood in-flow time. It also acquires data while the artery is moving rapidly, therefore relying on a very short acquisition window to “freeze” cardiac motion.

Figure 1.27: In-plane images of diseased RCAs



RCA images acquired in two patients referred for x-ray coronary angiography. The x-ray contrast angiography images for the first subject (A) show a 40% stenosis and the in-plane MR coronary vessel wall images (B) show a thickened vessel wall (arrows). In the second subject, luminal irregularities with ~10% stenosis on the x-ray contrast angiography images (C) correspond to a thickened vessel wall (arrows) on the MR coronary vessel wall images (D). The in-plane MR coronary vessel wall images were acquired with a 3D spiral sequence with navigator gating. Reproduced from Kim et al. (2002) with permission, copyright Wolter Kluwer Health.

1.e.ii.4 Accuracy and reproducibility

Clearly for MR coronary vessel wall imaging to be of use in directly quantifying vessel wall thickness and for use in longitudinal studies, measurements must reflect the true wall thickness and demonstrate a high degree of reproducibility. In general, MR measurements of coronary vessel wall thickness over-estimate the true thickness as assessed by histology (see table 1.10). There may be two reasons for this: firstly, residual motion during the acquisition may result in blurring; and secondly, the imaging resolution of the techniques may be insufficient. In a comparative study of pig hearts however, Worthley et al. (2001) found no difference between coronary vessel wall thickness measurements obtained using a high resolution (0.39-0.47mm in-plane resolution) 2D TSE sequence acquired *in-vivo* (breath-holding) and *ex-vivo*. This suggests that in cooperative subjects who are able to completely suspend respiration, respiratory motion does not result in increased vessel wall thickness measurements. However, diaphragmatic drift is common during breath-holding and high resolution 3D studies cannot be performed within the duration of a breath-hold. Using numerical simulations and phantom experiments, Schaar et al. (2003) found that with resolutions of less than 4 pixels per vessel wall thickness, vessel wall area was severely over-estimated due to partial volume effects. The same work also found that respiratory motion within the navigator gating window can degrade the delineation of different vessel wall

components, particularly when spatial resolution is insufficient. So far *in-vivo* MR coronary vessel wall imaging studies have been unable to differentiate plaque components although some work has been performed on distinguishing different plaque types using T1 weighted imaging (section 1.e.ii.6).

Studies of the reproducibility of vessel wall thickness measurements have been performed for both cross-sectional (Hazirolan et al., 2005) and in-plane (Desai et al., 2005) coronary vessel wall imaging. Hazirolan et al. (2005) compared wall thickness from multi-slice 2D cross-sectional TSE acquisitions (0.7x0.6x3mm resolution) in 12 healthy subjects on two occasions. A high degree of reproducibility was observed: the inter-observer difference was 0.07 ± 0.14 mm and the inter-study difference was 0.02 ± 0.20 mm. Desai et al. (2005) compared wall thickness from in-plane 3D spiral acquisitions with navigator gating (0.8x0.8x2mm resolution) in 8 healthy subjects imaged on two occasions. While the mean vessel wall thickness (1.6 ± 0.2 mm) was greater than that observed in studies using cross-sectional imaging (see table 1.10), the intra-class correlation coefficients (MacLennan, 1993) for intra-observer, inter-observer and inter-study reproducibility were excellent at 0.97, 0.92 and 0.86 respectively. There has however, thus far, been no direct comparison of reproducibility between the various techniques employed in coronary vessel wall imaging.

Table 1.10: Coronary vessel wall thickness obtained using MR and other measurement techniques in normal subjects

Study	Technique	Stated acquired resolution	Thickness $\pm$ SD (mm)
Fayad et al. (2000)	MR – Breath-hold cross-sectional 2D TSE	0.5-0.8mm in-plane 3-5mm slice thickness	0.75 ± 0.16
Botnar et al. (2000a)	MR – Breath-hold cross-sectional 2D TSE	0.5x1.0mm in-plane 5mm slice thickness	1.0 ± 0.2
Hazirolan et al. (2005)	MR – Breath-hold cross-sectional 2D TSE	0.7x0.6mm in-plane 2mm slice thickness	1.14 range (0.63 – 1.75)
Koktzoglou et al. (2005)	MR – Breath-hold cross-sectional 2D TSE at 3T	1.2x0.8-0.9mm in-plane 4-5mm slice thickness	0.88 ± 0.18
	MR – Navigator gated cross-sectional 2D TSE at 3T	0.8-1.0x0.7-0.8mm in-plane 4-5mm slice thickness	0.79 ± 0.23
Desai et al. (2005)	MR – Navigator gated in-plane 3D spiral	0.8x0.8x2mm (3D) 20 slices	1.6 ± 0.2
Macedo et al. (2008)	MR – Breath-hold cross-sectional 2D TSE	1.1x1.1mm in-plane 4mm slice thickness	1.8 $\pm$ 0.3 range(1.32-2.33)
	MR – Navigator gated cross-sectional 2D TSE	1.0x1.0mm in-plane 5mm slice thickness	
Gradus-Pizlo et al. (2001)	Transthoracic ultrasound	0.25mm	0.9 ± 0.1
Gradus-Pizlo (2003)	Open chest epicardial ultrasound	0.1mm	1.0 ± 0.2
	Transthoracic ultrasound	0.25mm	1.0 ± 0.1
Ozolanta et al. (1998)	Autopsy – microscopy of 121 male subjects (20 – 39 years)	0.01mm	0.68 ± 0.20 RCA 0.75 ± 0.24 LCA See table 1.2

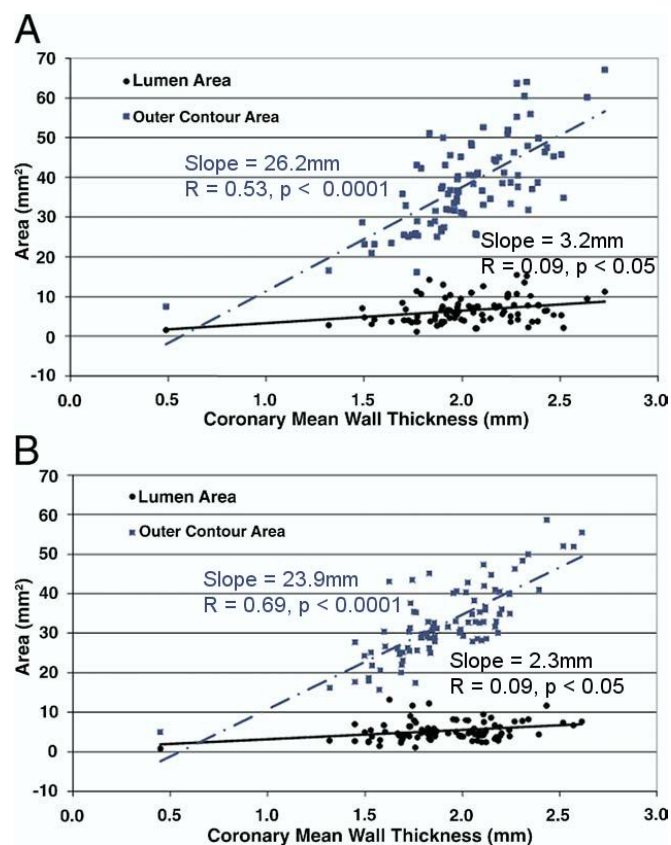
1.e.ii.5 Application in patient cohorts

That MR coronary vessel wall imaging can detect wall thickening in a cohort of atherosclerotic vs. normal subjects is now well established (Fayad et al., 2000, Botnar et al., 2000a, Kim et al., 2002, Kim et al., 2007, Macedo et al., 2008, Gerretsen et al., 2010a). Fayad et al. (2000) compared vessel wall thickness in eight normal subjects and five patients with $\geq 40\%$ coronary stenosis, confirmed by x-ray angiography, using breath-hold cross-sectional TSE acquisitions. Average maximum coronary vessel wall thickness was greater in patients than in normal subjects (4.38 ± 0.71 mm vs. 0.75 ± 0.17 mm $p < 0.0001$). Similarly Botnar et al. (2000a) compared coronary vessel wall thickness in five healthy subjects and five patients with x-ray angiography confirmed disease using a 2D cross-sectional navigator gated TSE acquisition. Average vessel wall thickness proximal to the coronary stenoses was significantly greater than that observed in normal subjects (1.5 ± 0.2 mm vs. 1.0 ± 0.2 mm $p < 0.005$), which is suggestive of a diffuse disease process. Kim et al. (2002) compared six healthy subjects to six patients with coronary artery stenosis (10-50% of vessel diameter) using an in-plane 3D spiral sequence with navigator gating (see figure 1.27). The average vessel wall thickness obtained from four cross-sectional images at 10mm intervals was significantly greater in the patients with CAD compared to the normal subjects (1.7 ± 0.3 vs. 1.0 ± 0.2 mm, $p < 0.01$), while the average lumen diameter and lumen area were not increased. This was presented as evidence of Glagov like (Glagov et al., 1987) outward remodelling of the vessel wall. The same author later studied a larger group of patients with type I diabetes (Kim et al., 2007) without symptoms of coronary artery disease. The cohort was divided into those with sufficient kidney function ($N=37$ imaged) and those without ($N=37$ without), as those with nephropathy have higher rates of cardiovascular incidents (Astrup et al., 2005). Using 3D MR coronary vessel wall imaging the study found mean and maximum vessel wall thickness were increased in the patients with nephropathy (mean 1.7 ± 0.3 mm vs. 1.3 ± 0.2 mm and max 2.2 ± 0.5 vs. 1.6 ± 0.3 mm, both $p < 0.001$). They also found coronary plaque (defined as a focal thickening of the vessel wall on the MR images) in significantly more of the nephropathy cohort (76% vs. 15%, $p < 0.001$).

Several MR coronary artery vessel wall imaging studies have been performed on sub-cohorts of the Multi-Ethnic Study of Atherosclerosis (MESA) (Macedo et al., 2008, Malayeri et al., 2009, Miao et al., 2009). This was a large study ($N=6500$) of subjects without a history of atherosclerosis aged 45-84 years investigating the use of pre-clinical markers of coronary heart disease (Bild et al., 2002). Macedo et al. (2008) imaged 48 subjects from MESA using multiple cross-sectional 2D images at $1.1 \times 1.1 \times 4$ mm or $1.0 \times 1.0 \times 5$ mm resolution. Subjects with 2 or more risk factors (high total cholesterol, low HDL, high blood pressure, diabetes, smoking, old age) had, on average, higher maximum coronary vessel wall thickness (2.59 ± 0.44 mm vs. 2.36 ± 0.30 , $p = 0.05$). They also found significantly greater maximum LM wall thickness in subjects with low levels of HDL and significantly greater mean vessel wall thickness in subjects with a history of smoking. These subjects also had CT CAC scoring. The study observed wall thickening in the absence of calcification and found that mean and maximum vessel wall thickness were significantly greater in

subjects with 2 or more risk factors when only those subjects without coronary calcifications were considered. Miao et al. (2009) imaged 179 MESA subjects and measured lumen area, vessel wall area and outer wall area (lumen + wall area). A significant relationship was observed between both outer wall area and lumen area with vessel wall thickness, but the slope of the relationship with outer wall area was significantly greater, even after normalising for left ventricular mass or body mass index (BMI). This was claimed to indicate Glagov type outward remodelling. In another study (Terashima et al., 2010), of subjects without a history of cardiovascular disease (aged 60-72), 223 subjects (150 successfully, see below) were imaged using a breath-hold 2D spiral technique with 1RR gating. While a significant relationship was found between outer wall area and vessel wall thickness, there was no significant relationship between lumen area and vessel wall thickness. This was claimed to indicate Glagov type outward remodelling. In addition, a multivariate analysis found that diabetes was significantly associated with increased vessel wall thickness and increased outer wall area; vessel wall thickness was significantly associated with the ratio of total cholesterol to HDL. However, age, gender, BMI, hypertension and smoking were not associated with outer wall area or vessel wall thickness.

Figure 1.28: Vessel wall remodelling using MR coronary artery vessel wall imaging



Outer wall area (lumen+vessel wall) and lumen area plotted with mean vessel wall thickness in men (A) and (B) women from the MESA study. In both cases, outer wall area and lumen area show a significantly increasing relationship with coronary vessel wall thickness. However, the increase in outer wall area with vessel wall thickness is significantly greater, suggesting outward remodelling. Reproduced from Miao et al. (2009) with permission, copyright Elsevier.

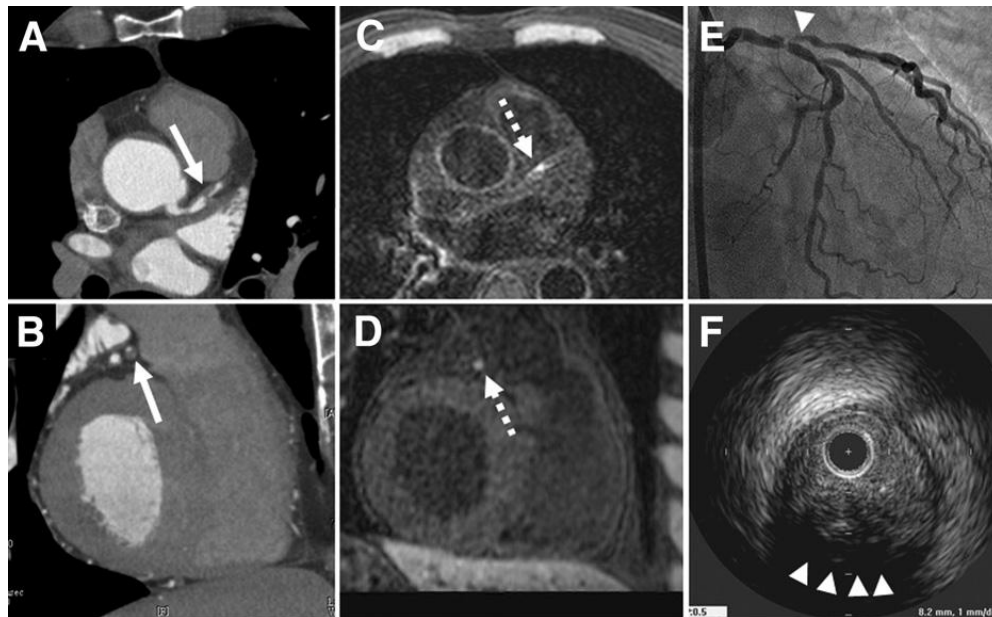
Larger scale MR coronary vessel wall imaging studies in patients have contained a relatively high number of rejected images. For example, in the work by Miao et al. (2009) all 179 subjects completed MR coronary vessel wall imaging. Seven coronary segments were targeted for each subject (1 in the LM, 3 in both the RCA and LAD), yet only 365 images were available for analysis. In the study by Terashima et al. (2010) 33% (73 of 223) of images were of insufficient quality. The determinants of image quality were considered in a sub-cohort of MESA (N=76) (Malayeri et al., 2009) following on from Macedo et al. (2008). Coronary vessel wall imaging was unsuccessful in 10% (9) of subjects due to irregular ECGs or respiratory motion. For the subjects with successful studies, 215 of 234 segments (92%) were imaged, but 43% (93) were considered insufficient (poor) quality for further assessment. In total only 47% of all coronary segments in all recruited patients were successfully imaged. The highest proportion of the best rated images were acquired in the RCA. Increased SNR was significantly associated with better subjective image scores in the RCA and LM; a similar relationship was present between CNR and image score in the LM. Image quality, SNR and CNR were all significantly better in male subjects. The average heart rate was significantly higher and rest period duration was significantly lower in female subjects, both of which were associated with reduced subjective image scores. The SNR was also significantly greater in subjects with CT evidence of calcification, which is probably the result of increased vessel wall thickness in these subjects.

1.e.ii.6 T1-weighted contrast- and non-contrast-enhanced imaging

Several recent studies (Maintz et al., 2006, Yeon et al., 2007, Wessely et al., 2007, Ibrahim et al., 2009, Kawasaki et al., 2009, Tanaka et al., 2009a) have used T1 weighted black blood imaging, with or without Gd-DTPA contrast agent, in attempts to differentiate plaque types. Images are acquired with 3D inversion prepared fat suppressed GRE sequences and use a prior Look-Locker T1 mapping sequence (Look and Locker, 1970) to determine the correct inversion time for blood suppression. Typically, such studies are performed with slightly lower resolution than MR coronary artery vessel wall acquisitions (~1.0x1.0x3.0mm (Maintz et al., 2006)), use navigator gating for respiratory motion and 1RR cardiac gating. Maintz et al. (2006) imaged 9 patients with known coronary artery disease using non-contrast enhanced T1 weighted black blood coronary vessel wall acquisitions and performed the same acquisitions 3 hours after contrast administration. Plaques either demonstrated no enhancement, enhancement only after contrast administration or enhancement both before and after contrast. Yeon et al. (2007) imaged 6 healthy subjects and 14 patients with previous x-ray contrast angiography studies, CT coronary angiography studies and one or more risk factor for coronary artery disease, ~60 min after contrast administration. None of the healthy subjects demonstrated vessel wall contrast enhancement whereas it was observed in all patients. While contrast enhancement was more common in soft plaques (as determined by CT) than in regions without plaque, it was even more common in calcified plaque. Non-contrast enhancement using a T1 weighted black blood sequence, was observed in three calcified stenotic plaques. However, no clear cut relationship was observed between plaque type and enhancement.

Ibrahim et al. (2009) imaged 10 patients using contrast enhanced imaging an average of six days after acute MI and again, an average of 93 days after the infarction. Another nine patients were imaged as controls after elective x-ray angiography. Significantly more enhancement was observed in the acute MI patients and contrast enhancement was significantly correlated with the severity of luminal narrowing. A CNR threshold for detection of stenotic segments was calculated with a sensitivity and specificity of 70% and 86% respectively. In the delayed follow up imaging, there was a significant decrease in signal intensity and the spatial extent of the enhancement. However, Gd-DTPA uptake in plaque is non-specific; inflammation, edema and fibrosis are all associated with enhancement. Therefore, while T1 weighted coronary vessel wall imaging both with and without contrast agent may be a useful tool for plaque characterisation, current results lack sufficient specificity. The work of Kawasaki et al. (2009) attempts to address some of these issues for non-contrast enhanced T1 weighted black blood imaging. 24 patients with angina were successfully imaged with CT coronary angiography, x-ray contrast angiography, IVUS and non-contrast enhanced T1-weighted black blood MR coronary vessel wall imaging (see figure 1.29). 18 lesions from 17 subjects were classified as hyperintense, whereas 7 lesions from 7 patients were classified as non-hyperintense. Lesions defined as hyper-intense on the MR images were often found to originate from plaques which appeared to be positive remodelling with “spotty” calcification on CT coronary angiography images. When assessed with IVUS, the hyper-intense lesions were often found to be strongly attenuating. The authors of the study suggest that these features are to be expected from vulnerable plaques, although a larger cohort with follow up data and post-mortem histology is required for corroboration.

Figure 1.29: Hyperintense plaque on non-contrast enhanced T1 weighted black-blood MR imaging



LAD images acquired in a patient with angina using CT coronary angiography (A and B), T1 weighted black blood GRE MR imaging (C and D), x-ray contrast angiography (E) and IVUS (F). A severe stenosis in the LAD (arrow head, E) corresponds to a large soft plaque on the CT images (solid arrows), ultrasound attenuation on the IVUS images (arrow heads, F) and hyperintensity on the MR images (dotted arrows on C and D). Reproduced from Kawasaki et al. (2009) with permission, copyright Elsevier.

1.e.ii.7 Future outlook

Improvements in vessel wall SNR are expected at 3T, which should permit increases in resolution, and a number of studies have demonstrated MR coronary vessel wall imaging at this increased field strength, although the majority of recent published studies still use 1.5T. Initial work at 3T (Botnar et al., 2003b) used 2D Cartesian GRE sequences with navigator gating. Subsequently 2D TSE (Koktazoglou et al., 2005), 3D Cartesian GRE (Priest et al., 2005), 3D radial (Bansmann et al., 2007), 2D spiral (Abd-Elmoniem et al., 2010) and 3D spiral (Lagemaat et al., 2009) acquisitions have been demonstrated. Bansmann et al. (Bansmann et al., 2007) compared navigator gated Cartesian and radial 3D GRE acquisitions at 3T. No significant differences were observed between the sequences, but subjective image quality scores were significantly higher using the radial technique. A comparison between 1.5T and 3T (Peel et al., 2010) using spiral imaging suggested that SNR and CNR may be increased at 3T, but image sharpness, the length of vessel visualised and subjective image quality were greater at 1.5T, while artefacts were more severe at 3T.

Initial studies have investigated the possibility of intra-vascular MR coronary vessel wall imaging (Botnar et al., 2003a) using miniaturised receive coils inserted into the coronary arteries. High quality images were obtained in swine. However, no such studies have so far been performed in

man and the inherent invasiveness means that, like IVUS, it could not be used for longitudinal studies.

Current MR coronary vessel wall imaging techniques are inefficient. For a free breathing, navigator gated technique, with 2RR gating and a 50ms cardiac acquisition window, assuming a respiratory efficiency of 40% and a heart rate of 60BPM, only 1% of the acquisition duration is used to acquire data which is subsequently reconstructed. Initial studies suggest that respiratory efficiency may be increased to near 100% by using B2B-RMC rather than navigator gating. Acquisition duration can be halved by using 1RR rather than 2RR gating and, although there are theoretical advantages to using 2RR gating, no study has yet performed a direct comparison between 1RR and 2RR gating for coronary vessel wall imaging. Furthermore, spiral imaging allows short readout durations while efficiently covering k-space. These issues with those of reproducibility and accuracy will become increasingly important with the recent increases in the number of studies using coronary vessel wall imaging to assess disease in patient cohorts.

1.f Summary and conclusions

The heart is an intricate, complex and vital organ which, by necessity, is continuously moving with both the cardiac and respiratory cycles. As a result it requires an adequate and uninterrupted blood supply, which is provided by the coronary arteries. Unfortunately, these arteries are susceptible to atherosclerotic disease, which is the inflammation and accumulation of mainly lipid within the vessel wall. Atherosclerotic plaques may cause stenoses or occlusions of the coronary arteries which can lead to death or require complex interventional measures. The serious nature of coronary artery diseases has led to a wealth of diagnostic tests for its detection. However, the majority of such tests are lumenographic and, therefore, fail to diagnose many outward remodelling plaques, or are invasive techniques with non-negligible risks. The non-invasive, ionising radiation free nature and flexible image contrast available with MR imaging potentially make it an excellent choice for assessment of coronary artery disease. Yet the small size, deep location and mobile nature of these arteries present a challenge for MR imaging. In addition, the rapid acceleration of MDCT technology to large numbers of detectors and higher temporal resolution has resulted in higher diagnostic accuracy for detecting significant stenoses than is available with MR. As a result, CT is the current modality of choice for non-invasive coronary angiography. However, for the early detection of sub-clinical disease and the assessment of the progression or regression of coronary artery disease in response to therapy, selective imaging of the vessel wall is preferable. While coronary vessel wall thickness has been measured from CT coronary angiography images, the positive contrast, flexible temporal resolution and lack of both ionising radiation and contrast agents when using MR vessel wall imaging, mean that it is potentially a more powerful technique for this application. A number of imaging techniques and contrast mechanisms have been employed for MR coronary artery vessel wall imaging, but double inversion dark blood preparation is most commonly used with 2RR-gating and navigator gating to minimise respiratory motion artefacts. TSE or spiral imaging techniques are often used for 2D

acquisitions, while 3D acquisitions are most commonly obtained with spiral imaging. MR coronary artery vessel wall imaging has been used in a number of clinical studies to show outward remodelling of the vessel wall and vessel wall thickening due to, or as a pre-cursor to, disease. Such studies require high resolution, high accuracy, highly reliable and highly reproducible techniques. However, in patient studies, existing techniques have resulted in poor quality images or failed acquisitions in up to 53% of studies. One of the key reasons for these failures is poor and inefficient respiratory motion compensation. Existing techniques are highly inefficient due to the low respiratory efficiencies available from navigator gating and due to the large proportion of dead time required for both longitudinal signal recovery and to minimise cardiac motion artefacts. This thesis will address the efficiency and robustness of MR coronary vessel wall imaging with a particular focus on respiratory motion compensation.

2. Motion in MR imaging

The primary motion of concern in cardiovascular MR imaging is that caused by the cardiac and respiratory cycles, which is described in section 1.c. Excess motion during data acquisition results in a degradation of the resultant images. The severity and type of degradation depends on the imaging sequence and parameters used, but the effects include blurring, ghosting and mis-registration (Schultz et al., 1984). The first two parts of this chapter (2.a and 2.b) are based on part of a recently published review article (Scott et al., 2009) and concentrate on the various strategies available to minimise these effects, with a particular focus on techniques applicable to MR coronary angiography and coronary artery wall imaging. Section 2.c describes the beat-to-beat respiratory motion correction (B2B-RMC) technique, as first demonstrated by Keegan et al. (2007), which forms the focus of the remainder of this thesis.

2.a Motion from the cardiac cycle

2.a.i Cardiac gating

With the advent of rapid MR imaging techniques it is now possible to acquire low resolution single-shot real-time images without ECG gating. Such techniques have been used in interventional MR applications (Serfaty et al., 2000, Razavi et al., 2003, Zhang et al., 2006), rapid assessment of LV function (Yang et al., 1998c, Zhang et al., 2006) and both angiography and flow measurement (Pat et al., 1998, Nayak et al., 2000, Macgowan et al., 2005, de la Pena et al., 2006). However, higher resolution techniques acquire image data over a number of cardiac cycles and therefore require the data acquisition to be triggered. Triggering may be achieved using pulse oximetry (Denslow and Buckles, 1993), auscultatory monitoring, laser Doppler or plethysmograph peripheral pulse monitoring (Lanzer et al., 1984). However, ECG triggering is generally preferable as the former techniques are unable to trigger from the beginning of the cardiac cycle, there are variable delays from the R-wave to the trigger and motion artefacts are common (Lanzer et al., 1984, Soulen and Higgins, 1985). Despite this, auscultatory based gating has recently been used at 7T to avoid the increased ECG artefacts at higher field strengths (Frauenrath et al., 2010).

Several studies have directly extracted information on the cardiac phase directly from MR data (Spraggins, 1990, Kim et al., 1990, Hardy et al., 2000, Sussman et al., 2002, Crowe et al., 2004, Larson et al., 2004, Brau and Brittain, 2006) for gating or motion compensation. A sub-group of such techniques, known as cardiac self-gating (Crowe et al., 2004, Larson et al., 2004, Brau and

Brittain, 2006), derive an ECG like signal from cardiac induced periodic variations in a line of k-space repeatedly acquired without phase encoding. This information may be used in a similar manner to the ECG, without the need for careful electrode placement or potentially hazardous metallic conductors in the scanner bore. ECG gating, however, remains the most commonly used technique as such alternatives have several limitations: rapid online processing is required for prospective gating and they, therefore are mainly used as retrospective techniques; they are not easily implemented; they have limited accuracy; and the morphology of the self-gating signal varies with image plane orientation. Recent developments in ECG gating include real-time gradient artefact correction (Odille et al., 2007) and algorithms used with vector cardiograms (VCG) (Fischer et al., 1999) which increase the accuracy of R-wave detection in the presence of magnetic field distortions and artefacts due to gradient switching, RF interference, blood flow and motion. ECG gated acquisitions can also be improved, in some cases, by implementing arrhythmia rejection algorithms (Leiner et al., 2005) that exclude data acquired during R-R intervals which deviate by more than -10% or +50% from the average period of the last eight accepted intervals. Implementing these techniques, however, can result in an increased and unpredictable scan duration which may be problematic for acquisitions acquired during a breath-hold.

2.a.ii Selection of the acquisition window

For imaging at a single time point in the cardiac cycle – in applications such as coronary artery imaging (angiography and vessel wall) – prospective ECG triggering is normally used to acquire a number of k-space lines (a segment) in a time which is short with respect to cardiac motion. The heart is relatively still during the middle of the diastolic phase of the cardiac cycle, which is most often used as the acquisition window for coronary imaging. It is also possible to image the coronary arteries in systole (Duerinckx and Atkinson, 1997) and this may be preferable when the diastolic rest period is very short. Empiric suggestions for the delay from the R-wave to the onset of the optimum acquisition window in mid-diastole, are based on measurements of the length of the systolic phase averaged over a population. Fixed delays of 350msec (Stuber et al., 1999a) and heart rate (HR) dependent delays of 550msec – 0.002HR (HR in BPM) (Weissler et al., 1968, Wang et al., 2001a) have been suggested. However, there is a large variability in both the onset and duration of the rest period between subjects (Hofman et al., 1998, Wang et al., 1999) and, particularly for high resolution imaging, the best approach is to tailor the acquisition parameters to the individual subject. In coronary imaging the optimal timing and duration of the acquisition window is determined either by pre-scanning (Wang et al., 2001a) or from a cardiac motion study (Wang et al., 1999, Kim et al., 2001b). Long acquisition windows may be used in subjects with slow heart rates, resulting in an increased scan efficiency without detriment to image quality (Wang et al., 1999, Plein et al., 2003). Alternatively, the trigger delay and potentially, the acquisition window, may be adjusted in real-time in each cardiac cycle based on the average duration of previous R-R intervals and information from pre-scanning inputted into a generic motion model (Roes et al., 2008). Another approach, cardiac motion-matched k-space sampling (Wang and Ehman, 2000), acquires the central lines of k-space (which are more sensitive to motion) during

the period of minimum motion in diastole and the outer lines of k-space during less stationary periods. Using this technique in application to contrast enhanced 3D MR coronary angiography, the cardiac acquisition window was extended (333 ms vs. around 100 ms) with an associated increase the imaging efficiency without loss of image quality. Alternatively, the acquisition window may be extended by acquiring multiple image segments per cardiac cycle and using intersegment motion correction based on epicardial fat-tracking (Stehning et al., 2005a).

Selection of the acquisition window is also important in dark blood-prepared imaging, as is used for coronary artery vessel wall imaging, which uses a double inversion pulse to null blood signal and, optionally, a further inversion pulse to null signal from fat (Simonetti et al., 1996). The delay after the double-inversion pulse must be adjusted to null signal from blood and to avoid signal drop out from mis-registration of the myocardium between the dark-blood preparation (soon after the R-wave) and the imaging segment (in the diastolic rest period of the same cardiac cycle). Mis-registration errors can, in part, be reduced by increasing the slice thickness of the double inversion pulse preparation, although this can reduce the effectiveness of the dark-blood suppression, particularly in the presence of slow moving blood. Alternatively, signal loss may be reduced by offsetting the slice selective component of the preparatory pulses from the imaging plane to take into account the expected motion (Keegan et al., 2006). Additional issues in dark blood prepared cardiac imaging may occur when the systolic rest period contains the optimal stationary period. In this situation, the delay from the R-wave, and therefore the dark blood preparation, to the systolic rest period is likely to be insufficient for optimal blood signal nulling. As a result, the dark blood preparation must be located in the prior cardiac cycle and techniques such as Kalman filtering must be used to predict the optimal temporal location of the preparatory pulse (Fernandez et al., 2010).

2.b Respiratory motion

2.b.i Simple breath-holding

Early CMR studies were performed during free-breathing with no respiratory motion compensation and consequently suffered from blurring and ghosting (Steiner et al., 1983, Alfidi et al., 1982, Higgins et al., 1985). Improvements in scanner technology and sequence design, however, have enabled many acquisitions to be completed within a single breath-hold (Atkinson and Edelman, 1991) (usually at end expiration as it is more stable, more reproducible and blood flow is similar to that during free-breathing (Sakuma et al., 2001)). For many applications, acquisitions cannot be completed with sufficient SNR or resolution within the comfortable breath-hold period of 20 - 30s for a healthy volunteer, less for many patients. One alternative is to use multiple breath-holds (Feinberg et al., 1995) and acquire segments of k-space or a sub-set of slices in each, but if breath-hold reproducibility is poor, this may result mis-registration artefacts. Some studies (Noble et al., 2005, Chandler et al., 2008), have registered multiple breath-hold short axis images, to a breath-hold long axis image to correct for mis-registration between short-axis images.

Other studies (McCarthy et al., 2003, Danias et al., 1999, Marks et al., 1997) have extended breath-hold duration using supplementary oxygen, or hyperventilation. In one study, for example (Danias et al., 1998), breath-holds were extended by 40% using hyperventilation, 24% using supplemental oxygen and 59% using hyperventilation and oxygen. However, all breath-holding schemes require patient co-operation, which can be problematic, and may suffer from respiratory drift during the breath-hold period (Danias et al., 1998).

2.b.ii Monitoring respiration

Various methods for monitoring respiration have been suggested along with ways of gating, triggering or compensating for the motion detected. Systems that monitor the motion of the chest wall include belts across the patient (Ehman et al., 1984), electrical impedance between ECG electrodes (Felblinger and Boesch, 1997), bellows (Wang et al., 1995a, McConnell et al., 1997a) or optical compression devices (Bailes et al., 1985). Methods which monitor the expired and inspired gas include capnography, temperature sensors in oxygen masks or nasal cannulas (Ehman et al., 1984) and spirometers. Techniques that monitor the diaphragm include navigators, discussed below, and M-mode ultrasound imaging used during the CMR scan (Feinberg et al., 2010). The biggest disadvantages of these systems are complicated setup, poor patient tolerance and the assumptions made regarding the relationship between the output signal and the motion of the heart.

Techniques utilizing MR acquired data are generally known as navigators. The most common forms are a column of tissue excited using either a 2D spiral RF pulse (Danias et al., 1997) or a slice selective 90° RF pulse followed by a non-coplanar 180° slice selective pulse (Ehman and Felmlee, 1989). The 2D RF pulse has the disadvantage of requiring a complex pulse design and may have a poorly defined excitation profile in regions of poor shim. The 90°-180° pulse combination is more robust, but causes saturation artefacts if either of the excitation planes intersects the imaging volume. In either case, a frequency encode gradient is applied along the length of the excited column to provide a profile through the moving structure of interest. This type of navigator may be placed on the chest wall, directly on the heart or on the diaphragm. The peak of the dome of the right hemi-diaphragm (RHD) is the most common position for ease of setup and diaphragm edge sharpness (McConnell et al., 1997a, Stuber et al., 1999a). The position of the diaphragm, which is clearly delineated by the liver - lung interface on the RHD, can be extracted from the reconstructed navigator profiles using either edge detection (Liu et al., 1993), correlation or least-squares methods. It has been suggested that the edge detection method is unsuitable for use with most navigator profiles (with the exception of those using external markers) due to insufficient SNR and edge definition (Wang et al., 1996a). However, the efficacy of edge detection has been improved by smoothing and thresholding the navigator profiles (Du et al., 2004). Correlation and least-squares methods are more computationally demanding with the least squares technique shown to be more robust in the presence of noise and profile deformation (Wang et al., 1996a). It should also be noted that the SNR of the navigator signal, and hence the accuracy of the derived information, may

also be affected by preparatory pulses in the sequence. For example, in the case of double inversion dark blood preparation for vessel wall imaging, an additional reinversion pulse may need to be applied to the column of tissue used for the navigator signal in order to retain navigator SNR (Stuber et al., 2001). During imaging, one navigator is typically acquired before, after each imaging segment. Alternatively two navigator echoes, one placed temporally either side of the imaging segment can be used to reject data acquired during rapid motion and reduce the associated blurring (Wang et al., 1996b). Rapid processing of the navigator and feedback to the imaging sequence is essential for prospective correction, as demonstrated by Spuentrup et al. (2002b) who showed a significant increase in image quality as the time from the navigator echo to the acquisition window was decreased from 100msec to 20msec.

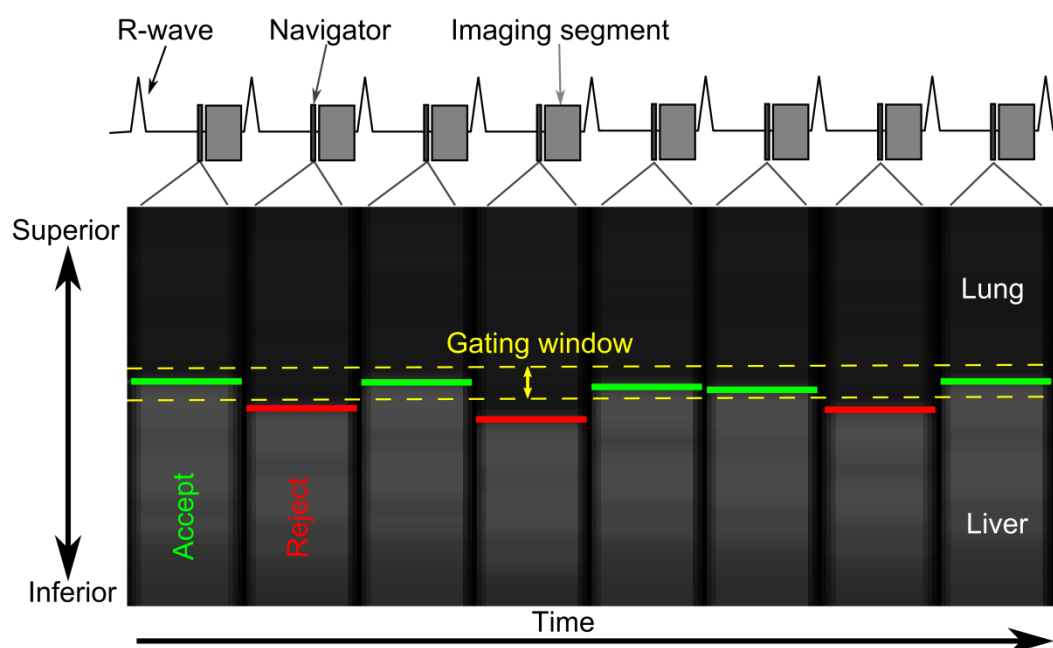
2.b.iii Using displacement information to guide and gate acquisitions

Prospective techniques can only be used with respiratory information acquired prior to the acquisition window in the cardiac cycle and, as mentioned above require rapid processing and feedback of the respiratory signal. Alternatively, retrospective techniques are used. The original retrospective respiratory gating (RRG) technique (Li et al., 1996), acquired each line or segment of k-space multiple times (typically a factor of 5 was used). The modal respiratory position was then determined from a histogram of the respiratory data stored with the image data. Image reconstruction was performed with data acquired over the minimum range of diaphragm positions about the modal value. This approach decreases the range of motion present in the final image when compared to free-breathing. However, the residual motion within the reconstructed data varies and may be large in the presence of respiratory drift. Furthermore, the low respiratory efficiency (defined as the proportion of the acquired data accepted for reconstruction, 20% in this case) is such that this technique would generally only be used if prospective methods were not possible. Prospective techniques have been used to acquire data over multiple consistent breath-holds or during free-breathing. In the former, the navigator position is fed back to the subject via a visual (Liu et al., 1993, Gatehouse et al., 2001) or an audible indicator (Wang et al., 1995a) in order to guide the breath-hold position. The acquisition starts after the subject has suspended respiration within an operator-defined window after a short settling period (Wang et al., 1996b). Although techniques such as these have been successful in increasing inter-breath-hold reproducibility in studies of healthy volunteers, the cooperation required from patients is usually prohibitive (Taylor et al., 1999a).

The prospective acceptance/rejection algorithm (ARA) (Sachs et al., 1994, Oshinski et al., 1996), reconstructs free-breathing data acquired when the diaphragm position lies within a user determined gating window about a reference position, typically end expiration (figure 2.1). Larger gating windows clearly result in more data being accepted and hence a higher respiratory efficiency but also lead to reduced image quality. In contrast to the RRG technique where the range of motion in the final study is unknown but the acquisition duration is fixed, the ARA technique acquires images with a pre-defined range of motion but in a variable acquisition duration.

Although early ARA studies demonstrated similar results to breath-holding (Oshinski et al., 1996), temporal changes in breathing patterns during the data acquisition are frequent and may result in a drastic loss of respiratory efficiency and ghosting (Taylor et al., 1997). As described in the next sections, additional techniques are often employed in combination with ARA to improve respiratory efficiency and/or image quality.

Figure 2.1: Accept/reject navigator gating



Every R-R interval a 1D image of a column of tissue (a navigator) over the lung-liver interface is acquired immediately before or after the imaging data. Data acquired in a pre-defined window around end-expiration (a gating window) is accepted for reconstruction whereas data acquired outside this window is rejected and reacquired in a subsequent cardiac cycle. Originally published in Scott et al. (2010).

2.b.iv Methods of improving respiratory efficiency in prospectively gated free-breathing acquisitions

Respiratory efficiency and/or image quality in free-breathing ARA images may be improved by implementing a real-time k-space ordering which is dependent on the respiratory position. Such techniques rely on the fact that movement during acquisition of the outer k-space lines is less detrimental to image quality than the same movement during the acquisition of the central k-space lines (Maki et al., 1996). Various algorithms exist, such as respiratory ordered phase encoding (ROPE) (Bailes et al., 1985), where phase encode lines are ordered as a slowly varying function of diaphragm position. Centrally ordered phase encoding (COPE) (Haacke and Patrick, 1986), acquires the central region of k-space at end-expiration and the remaining lines are acquired symmetrically about the centre of k-space. Hybrid ordered phase encoding (HOPE) (Jhoo et al., 1998) combines the best features of these two algorithms. The centre of k-space is acquired at the most common diaphragm position (as for COPE), and from a histogram of respiratory positions,

areas of k-space are distributed to histogram bins – thereby maintaining the monotonic relationship between respiratory position and phase encode line (as for ROPE). This work was later extended to 3D imaging and improved by using a dual gating window of 5 mm for the central 75% of k-space and 10 mm for the remainder (Jhooti et al., 1999). In a direct comparison with ARA, HOPE was shown to maintain image contrast and quality while resulting in much improved respiratory efficiency (72% vs. 48%). However, all of these techniques require a gating window and will, therefore result in low respiratory efficiency in the presence of respiratory drift.

A number of techniques exist which do not require the definition of a gating window, thereby reducing the problems associated with respiratory drift. The diminishing variance algorithm (DVA) (Sachs et al., 1995) initially acquires a complete set of data during free-breathing and the modal diaphragmatic position is determined from a histogram. During the remainder of the acquisition, in each RR-interval the segment previously acquired at the greatest displacement of the diaphragm from the modal value is reacquired, efficiently reducing the variance of the diaphragm displacements as the acquisition progresses. This technique has been extended to 3D (Sachs et al., 2000) using 3 orthogonal navigators (SI over the RHD, AP on the chest wall and LR on a posterior region of the heart). Another technique, motion adapted gating (MAG) (Weiger et al., 1997, Sinkus and Börner, 1999) acquires phase-encoding lines according to a weighting function which varies with diaphragm displacement from the modal value. The weighting function describes a maximum diaphragm displacement at which every phase encode line may be acquired. Phase encode lines closer to the edge of k-space may be acquired at diaphragm displacements further from the mode. Phase ordering with automatic window selection (PAWS) is an alternative technique aimed at combining the advantages of DVA and ARA. The range of respiratory positions is binned and each bin assigned a starting point in k-space. Once three adjacent bins are fully acquired, k-space is completely covered and data is reconstructed with a maximum range of respiratory positions equal to the combined bin widths. 3D motion adapted gating (3D MAG) (Hackenbroch et al., 2005) extends the PAWS technique to 3D. When applied to coronary artery imaging, image quality was comparable to ARA but the scan efficiency was significantly improved (Langreck et al., 2005). A further extension of PAWS, continuously adaptive windowing strategy (CLAWS) (Jhooti et al., 2010), orders phase encode lines so that data is acquired in the most efficient 5mm navigator gating window. In a direct comparison with ARA, respiratory efficiency using CLAWS was found to be $14.4 \pm 20.9\%$ greater whilst maintaining equivalent image quality. However, phase ordering techniques aim to minimise the effects of the motion (or limit its magnitude in the case of PAWS or CLAWS like techniques) during the acquisition rather than eliminating or correcting for the effects of the motion. Furthermore, while the lack of a pre-defined gating window means such techniques are usually able to cope with respiratory drift, the final reconstructed image may not be at end-expiration.

2.b.v Slice tracking and motion correction

Several techniques improve respiratory efficiency by correcting for the measured motion within a larger gating window. Adaptive navigator correction (Ehman and Felmlee, 1989, Korin et al., 1990) is a retrospective technique which applies a phase shift to the measured data to correct for respiratory motion. The size of the phase shift is determined by the diaphragm position as measured by a navigator and the Fourier shift theorem (see for example Weisstein (2011)). More recently, a similar retrospective technique was used with linear interpolation of the respiratory signal between pre and post imaging-segment navigators to correct for respiratory motion during the acquisition window in 3D MR coronary angiography images (Wang and Ehman, 2000). The image quality achieved using this technique and an 8.4 mm gating window was similar to that achieved using a standard ARA gated acquisition and a 2.8 mm gating window with a corresponding increase in respiratory efficiency by a factor of 3.0.

Both retrospective and prospective correction techniques require accurate tracking factors to relate the motion of the heart to that of the diaphragm. This relationship is approximately linear, although not one-to-one. Work by Wang et al. (1995c) related the respiratory motion of the diaphragm to that of the heart. Assuming rigid body motion, the position of the mid-point of the left hemi-diaphragm and the position of various landmarks within the heart were measured on 2D coronal and sagittal images at different inspiratory positions. The results led to slice tracking factors of 0.57 in the SI direction and 0.09 in the AP direction being commonly accepted.

Subsequent work used these values in developing the prospective slice tracking technique for MR coronary angiography with multiple guided breath-holds (McConnell et al., 1997b, Shea et al., 2001). This technique shifts the imaging volume in each R-R interval by an amount determined by the slice tracking factors and the diaphragm position. Slice tracking is more commonly performed during free-breathing (Danas et al., 1997), correcting for motion within an ARA navigator gating window. Using the SI and AP tracking factors from Wang et al. (1995c), one study (Danas et al., 1997) found that slice tracking enabled an increase of gating window from 5 mm to 7 mm with a reduction in imaging time of 13% but without a discernable loss in image quality. However, extending the gating window further and using the same slice tracking factors resulted in a decrease in image quality, highlighting the inadequacy of such a non-subject-specific and simple model. Many studies use only an SI correction (Oshinski et al., 1998, Botnar et al., 2000a, Bornert et al., 2001a, Stuber et al., 2001, Weber et al., 2003) and apply the navigator at the RHD during free-breathing. In contrast, the original work by Wang et al. (1995c) used breath-holding and the left hemi-diaphragm as a reference. During breath-holds the relationship between chest wall and abdominal motion may change relative to free-breathing. As a result, when deriving tracking factors from multiple breath-holds, it is likely that a larger range of diaphragm positions are used than are found during normal tidal breathing. In addition to the differences in location and technique for measuring diaphragm displacement, this may account for the inconsistencies in average tracking factors reported by different groups (Wang et al., 1995c, Danas et al., 1999, Taylor et al., 1999b, Keegan et al., 2002) (table 2.1). All of these studies, however, quote large

standard deviations in the measured tracking factors, suggesting high inter-subject variability. The subject dependence of the slice tracking factor may be partly resolved by calculating a subject-specific tracking factor in the SI direction (Taylor et al., 1999b, Nagel et al., 1999, Manke et al., 2002a). One study (Taylor et al., 1999b) for example, used both two-point (inspiration and expiration) and seven-point (navigator guided) breath-hold images to relate RHD movement to that of the coronary arteries in the SI direction. The subsequent study demonstrated that image quality was significantly improved over ARA when the subject-specific tracking factor was used. Furthermore, there was no significant loss of image quality going from a 6mm to a 16mm gating window when using the subject specific slice tracking factor, corresponding to an increase in mean respiratory efficiency from $49 \pm 17\%$ to $81 \pm 22\%$.

A potential problem with all motion correction techniques is the artefact generated by structures not moving with the region of interest. This may be reduced by applying spatial saturation bands over static structures such as the chest wall. Alternatively, a zonal imaging technique whereby a 2D RF pulse is used to excite a restricted region of tissue for 3D imaging has been demonstrated (Yang et al., 1998b). The advantages of such a technique are that imaging time is reduced as fewer phase encode lines are required to sample the excited region and stationary structures outside the excited region do not generate artefacts. This technique was subsequently used (Gatehouse et al., 2001) with a 20 mm gating window and subject-specific tracking in the SI and AP directions to demonstrate similar image quality to that obtained using navigator guided breath-holds with a 5 mm gating window. The respiratory efficiency was correspondingly increased from a mean of 61% to 95%.

Although linear tracking factors are commonly used, the motion of the heart during respiration is not that of a rigid body and hysteretic effects (Nehrke et al., 2001, Fischer et al., 2006) are seen between inspiration and expiration (see figure 1.15). A recent approach to this has been to develop subject-specific prospective respiratory motion models. These techniques model the motion of the heart as a 2D or 3D translation or as an affine transformation (Manke et al., 2002b, Manke et al., 2003, Nehrke and Börnert, 2005, Fischer et al., 2006, Jahnke et al., 2007) which also includes linear scale, shear and rotation. The non-rigid parameters are used to correct for respiratory induced deformation of the cardiac anatomy. Subject-specific model parameters are usually determined in a low resolution pre-scan using either multiple guided breath-holds (Manke et al., 2002b, Manke et al., 2003) or free-breathing (Nehrke and Börnert, 2005, Manke et al., 2002a, Jahnke et al., 2005b). The multiple images acquired at different respiratory positions are registered to one image selected as a reference, typically using a block-matching technique. To derive the model parameters for the transformation, simple linear regression may be used in the case of a single navigator (Manke et al., 2002b). However, if multiple navigators are used in different anatomical locations, more complex techniques, typically Gauss-Newton optimization, are required (Manke et al., 2003). Prospective motion correction requires real-time modulation of the imaging gradients and, in the case of non-Cartesian imaging, of the RF waveform (Nehrke and Börnert, 2005) (figure

2.2). Retrospective non-rigid corrections do not require real-time sequence control but do need advanced reconstruction schemes (Batchelor et al., 2005, Odille et al., 2008a). For example, the generalised reconstruction by inversion of coupled systems (GRICS) (Odille et al., 2008b, Odille et al., 2010) technique can retrospectively extract and correct for a non-rigid motion model from free breathing imaging data.

Table 2.1: Slice tracking factors relating the SI, AP and LR motion of different regions of the heart to the SI motion of the diaphragm

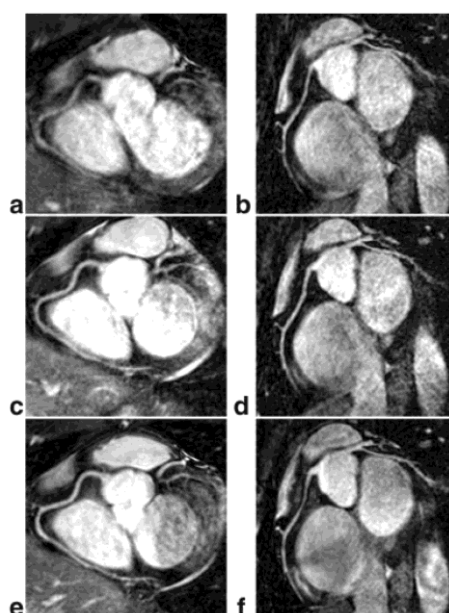
Study	Factor SI/AP/LR	Tracked location	Method
Wang et al. (1995a)	0.57 / 0.09 / -	RCA root	Imaging two perpendicular slices including the LHD and heart with breath-holding.
	0.70 / 0.85 / -	Prox. LAD	
	0.81 / 0.07 / -	Apex	
	0.62 / - / -	SHM	
	0.92 / - / -	IHM	
Danias et al. (1999)	0.6 / - / -	Left main	Imaging of the RHD and coronary in the same slice during free-breathing.
Taylor et al. (1999b)	0.49 / - / -	Prox. RCA	Navigator on RHD and imaging of heart during breath-holding.
	0.59 / - / -	Prox. LCA	
Nagel et al. (1999)	0.62 / - / -	ILV	Imaging of RHD and heart in a separate slice during breath-holding
	0.27 / - / -	LCA	
Keegan et al. (2002)	0.25 / 0.04 / 0.12	RCA root	Navigator on RHD and imaging of RCA during free-breathing.
Fischer et al. (2006)	0.38 / - / -	Prox. RCA	Navigator on RHD and imaging of heart during free-breathing.
	0.59 / - / -	Dist. RCA	
Jahnke et al. (2007)	0.45 / -0.01 / 0.02	Whole heart	Navigator on RHD and 3D imaging of heart during free-breathing in patients.

Note: The tracking factors are quoted where given in the original work ("- " is used otherwise) with the method used to derive the factor. SHM and IHM – Superior and Inferior Heart Margins respectively, LCA - Left Coronary Artery, ILV - Inferior LV wall, prox. - proximal and dist. - distal.

As discussed above, multiple navigators may be used in subject specific models. A precursory navigator, which is an additional navigator collected some time before the main navigator, enables

correction for hysteretic motion (Manke et al., 2003). In tests on a moving circular phantom this technique was demonstrated to reduce motion induced blurring in the circumferential (or polar) direction (Nehrke and Börnert, 2005). Including the square of the navigator position (a quadratic navigator) in the model reduced blurring in the radial direction and both modifications were found to reduce ghosting. In an extension to this work, precursory navigators and a 2D subject-specific affine model were applied to MR coronary angiography (Fischer et al., 2006). Using this model, respiratory efficiencies were around 30% greater and a similar level of residual coronary motion was found using a 10 mm gating window compared to 2D subject-specific linear slice tracking using the same navigators and a 5 mm window. All such techniques however, fix the motion model at the beginning of the scan and do not adapt to changes or short term variability in the breathing pattern as the scan proceeds, which may cause problems over long acquisition durations.

Figure 2.2: A comparison of navigator based respiratory motion correction techniques



Reformatted MR images of right coronary arteries in two volunteers. Images were acquired with (a, c, e) a Cartesian sequence and (b, d, f) a spiral sequence. Images were acquired with (a, b) simple slice tracking and 20-mm gating window; (c, d) 20-mm gating window and prospective correction with calibrated affine model, resulting in markedly improved image quality; and (e, f) 5-mm gating window and simple slice tracking, requiring substantially increased acquisition time when compared with a–d. Reproduced from Nehrke and Börnert (2005) with permission, copyright John Wiley & Sons.

2.b.vi Image based corrections and self-gating

A large number of motion correction techniques have used physiological data extracted from the imaging data itself or from additionally acquired images rather than respiratory information derived from navigators or external devices. These techniques require no tracking factor as the respiratory motion is detected from the structure of interest itself. A number of these techniques are summarised here.

2.b.vi.1 Self-gated and related techniques

Self-gating techniques extract motion information directly from the imaging data, as described in section 2.a.i for cardiac self-gated techniques (Kim et al., 1990, Brau and Brittain, 2006, Stehning et al., 2005b, Uribe et al., 2007, Buehrer et al., 2008). Some of these techniques and others that similarly acquire repeated SI projections of the cardiac anatomy are described in this section.

- Stehning et al. (2005b) – **Radial self-gating.**
 - Respiratory motion information is derived from repeated SI projections in a radial acquisition.
 - This was demonstrated for MR coronary angiography.
- Uribe et al. (2007) – **Self-gated Cartesian bSSFP.**
 - A phase encode line through the centre of k-space (an SI projection) in a 3D Cartesian bSSFP acquisition is repeatedly interleaved with the imaging data.
 - This was originally implemented for 3D whole heart cine imaging.
- Lai et al. (2008) – **Dual projection respiratory self-gating.**
 - Two SI projections are repeatedly acquired with a carefully chosen phase encode gradient applied to the second.
 - The resulting sinusoidal sensitivity modulation is used to suppress chest wall signal which, may otherwise produce an additional unwanted component in the projection data.
- Lai et al. (2009) – **Dual projection respiratory self-gating with a floating navigator.**
 - Dual projection respiratory self-gating was combined with the floating navigator concept (Kadah et al., 2004), which uses phase encoding perpendicular to the readout gradient to encode motion in two dimensions.
 - This technique was used to retrospectively correct for residual motion in a 9mm gating window for MR coronary angiography.
 - While this method shares some similarities with self-gated techniques, as the SI projections are acquired before the main imaging segment this is not truly self-gating.
- Nguyen et al. (2003) – **The cardiac fat-navigator.**
 - This technique selectively excites the epicardial fat around the heart and coronary arteries before acquiring self-gating like projections in one or more directions using non-phase encoded readouts.
 - The motion of the heart can be extracted from these projections and in coronary artery imaging, results were improved when compared to simple diaphragmatic navigators (Nguyen et al., 2006, Nguyen et al., 2008).
 - In imaging frames subsequent to the cardiac fat navigator, fatty tissue is saturated and so the need for additional fat suppression may be avoided in many instances.

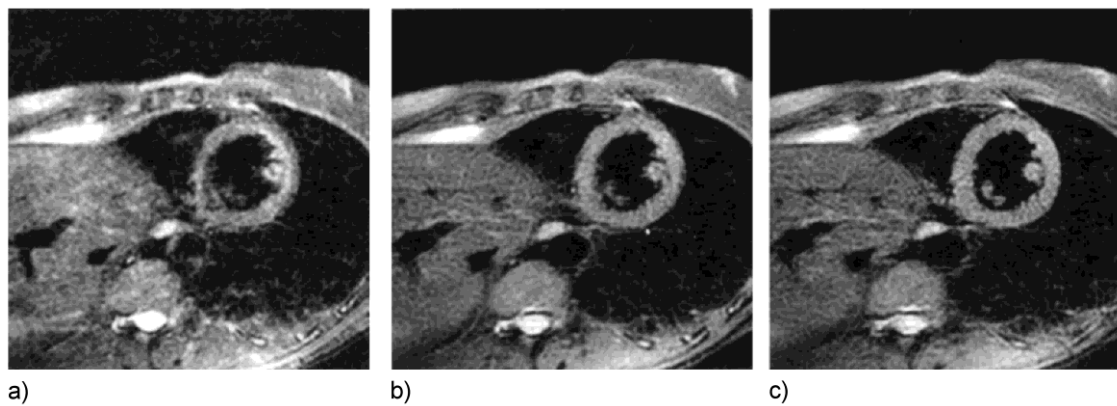
The interleaved nature of the projections used in true respiratory self-gating (i.e. not the techniques of Lai et al. (2008, 2009) and Nguyen et al. (2003)) means that the respiratory motion information is highly temporally relevant. However, in most of these techniques using projection data the respiratory motion information is one-dimensional and may be corrupted by signal from the chest wall.

2.b.vi.2 Techniques using sub-images

A number of techniques have reconstructed low resolution, low SNR or heavily aliased images (sub-images) from the main imaging data and extracted respiratory motion information from them.

- Hardy et al. (2000) – **Adaptive averaging.**
 - An interleaved spiral or echo planar acquisition is performed without cardiac gating and an image is generated every interleaf – either a full image using a sliding window reconstruction or an aliased sub-image from the undersampled data.
 - 2D respiratory and cardiac motion information is extracted from the images and is used to gate or compensate for motion before averaging.
 - Resulting MR coronary angiography images with combined cardiac and respiratory efficiencies of around 35% were demonstrated, but with long cardiac acquisition windows (~380ms).
- Hardy et al. (2003) – **Breathing autocorrection with spiral interleaves (BACSPIN).**
 - A spiral ECG gated breath-hold reference MR coronary angiography acquisition is acquired followed by an equivalent free-breathing main acquisition.
 - Each spiral interleaf is reconstructed to form a heavily aliased sub-image, which is cross-correlated with the equivalent sub-image from the breath-hold acquisition.
 - The results are used to retrospectively gate the acquisition and derive 2D respiratory motion information.
- Larson et al. (2005) – **2D radial self-gating.**
 - Respiratory motion information is extracted from low resolution sub-images reconstructed from a subset of the full radial bSSFP data set.
 - The respiratory motion information is then used to correct a high resolution 2D cine acquisition reconstructed from the same radial profiles.
- Pipe (1999) – **Periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER).**
 - A set of parallel lines are acquired in each R-R interval and the pattern is rotated after every R-wave.
 - A central region of k-space is fully sampled in each R-R interval and may be reconstructed to form a low resolution image, which can then be used to extract respiratory motion information for use in gating and motion correction.
 - An example of motion correction with PROPELLER for dark blood, T2-weighted TSE imaging is shown in figure 2.3.
 - Also see (Pipe and Zwart, 2006, Tamhane and Arfanakis, 2009).
- McLeish et al. (2004) – **Motion correction from undersampled radial images.**
 - Heavily undersampled radial sub-images are acquired in each R-R interval and used to determine 2D respiratory motion information.
 - Rigid and non-rigid correction of the full radial bSSFP image (reconstructed from the sub-images) was demonstrated.
 - Navigators were used to perform slice tracking in the third dimension.
- Sussman et al. (2002) – **Variable-density adaptive imaging.**
 - A modified interleaved spiral trajectory is acquired without cardiac gating. Each interleave has a high density central part and lower density outer part.
 - Subsets of the spirals may be used to reconstruct a fully sampled low resolution image using only the higher density inner part.
 - Respiratory motion information is extracted from the low resolution images and was used to gate and correct for respiratory motion before averaging the 2D MR coronary angiography images.

Figure 2.3: Example of PROPELLER based respiratory motion correction



Short-axis dark-blood-prepared T2-weighted turbo spin-echo MR images acquired in a healthy volunteer during free breathing: (a) conventional Cartesian acquisition, (b) with PROPELLER k-space trajectory and no motion correction, and (c) with PROPELLER trajectory and motion correction. Reproduced from Pipe et al. (1999) with permission, copyright John Wiley & Sons.

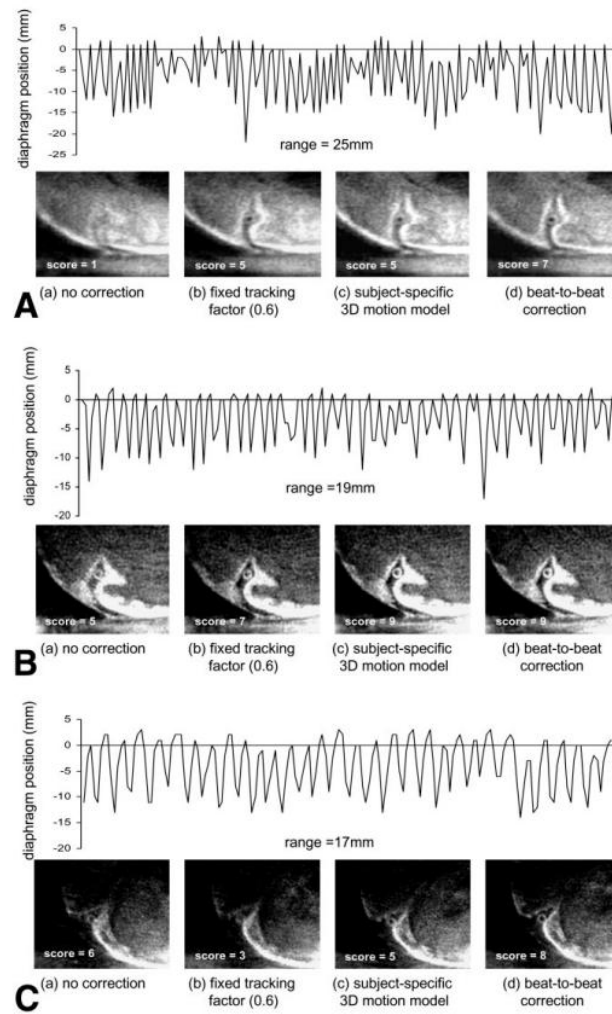
2.b.vi.3 Techniques acquiring additional low resolution images

Another sub-group of techniques (Keegan et al., 2007, Dewan et al., 2008, Hess et al., 2009, Hess et al., 2010, Tisdall et al., 2009) acquire additional rapid fully sampled low resolution images and use these to correct for the motion of the anatomy of interest.

- Dewan et al. (2008) – **Low resolution perpendicular images for coronary artery tracking.**
 - Two orthogonal low resolution 2D images are repeatedly acquired throughout the cardiac cycle.
 - The combined cardiac and respiratory motion of the coronary arteries is tracked in these images to predict the optimal cardiac acquisition window.
 - During the predicted cardiac rest period the low resolution acquisitions are paused and a segment of a high resolution 3D coronary artery imaging sequence is acquired.
 - Respiratory gating and slice tracking is also performed from this same data.
- Keegan et al. (2007) – **Beat-to-beat respiratory motion correction (B2B-RMC).**
 - Every cardiac cycle a full 3D low resolution stack of single-shot spirals with fat selective excitation is acquired, in addition to a single spiral interleave of a 3D high resolution image with selective water excitation.
 - The 3D coronary displacements determined from the low resolution images of the epicardial fat are subsequently used to retrospectively correct each high resolution interleaf.
 - Figure 2.4 compares the high-resolution water images reconstructed without motion correction and corrected for motion in one, two and three directions using the 3D spiral fat navigator information.
 - Preliminary results in 6 healthy volunteers showed that B2B-RMC produced images with better quality than a retrospective subject-specific 3D translation model in 5 cases and with equivalent quality in 1. These results were achieved with data acquired during free-breathing over the entire respiratory range. A further advantage is that the high resolution water image is not affected by the low resolution 3D spiral fat images, yet the same anatomical region is imaged in both.

Such techniques hold great potential for 3D respiratory motion compensation in applications where there is unused time within the cardiac cycle. The latter work described above (Keegan et al., 2007) is described in more detail in section 2.c and forms the focus of the remainder of this thesis.

Figure 2.4: Comparison of B2B-RMC with no correction and navigator based correction in coronary artery vessel wall imaging



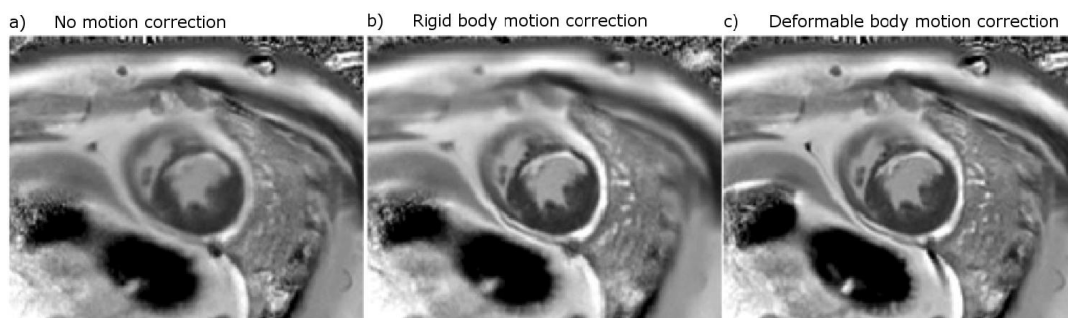
Example coronary vessel wall images obtained in three healthy subjects (a-c) shown with the diaphragmatic navigator trace and the range of diaphragm motion (upper panel). One slice is shown with the respective subjective image score for each volunteer without motion correction (a), with a fixed navigator correction (tracking factor 0.6) (b), with a pseudo subject-specific motion model correction, obtained from the low resolution images (c) and corrected using B2B-RMC (d). Reproduced from Keegan et al. (2007) with permission, copyright John Wiley & Sons.

2.b.vi.4 Techniques using co-registration of multiple full images

Another group of techniques non-rigidly co-register fully sampled rapid images acquired every cardiac cycle during free-breathing.

- Ledesma-Carbayo et al. (2007) – **Automatic registration of multiple low SNR images.**
 - Low SNR images are rapidly acquired, co-registered and then averaged to improve SNR in late-enhancement myocardial imaging.
 - The use of a non-rigid correction reduced edge blurring when compared to both no motion correction and a rigid body correction, as demonstrated in figure 2.5.
- Bidaut and Vallée (2001), Kawakami et al. (2004), Stegmann et al. (2005), Kellman et al. (2008) – **Automatic registration of dynamic images.**
 - Registration of free-breathing first pass myocardial perfusion images aids quantification and enables direct image-to-image comparison (Bidaut and Vallée, 2001, Kawakami et al., 2004, Stegmann et al., 2005). Also see Yang et al. (1998a) for a related technique.
 - A similar methodology has been used for free-breathing short axis cine images (Kellman et al., 2008).

Figure 2.5: Motion correction of multiple images acquired during free-breathing



Delayed gadolinium-enhanced MR images in patient with chronic myocardial infarction. Images were acquired during free breathing and averaged over 30 frames with (a) no motion correction, (b) rigid body motion correction derived by registering user-defined region around LV in each image to same region in one frame used as reference, and (c) nonrigid motion correction derived by using automatic full field-of-view registration. Reproduced from Ledesma-Carbayo et al. (2007) with permission, copyright John Wiley & Sons.

These techniques promise high performance in a number of areas where multiple images of similar anatomy can be acquired sequentially. One present limitation, however, is that corrections are limited to the in-plane directions.

2.b.vii Conclusions

A number of techniques are available for cardiac and respiratory motion compensation in MR. While for subjects with moderate, stable heart rates, without arrhythmia, imaging within the subject specific cardiac rest period is adequate, more advanced techniques and/or medication may be preferable in many patients. For respiratory motion compensation however, breath-holding is simply inadequate in many applications, including MR coronary angiography and coronary artery vessel wall imaging. The preferred alternative of diaphragmatic navigator gating is also

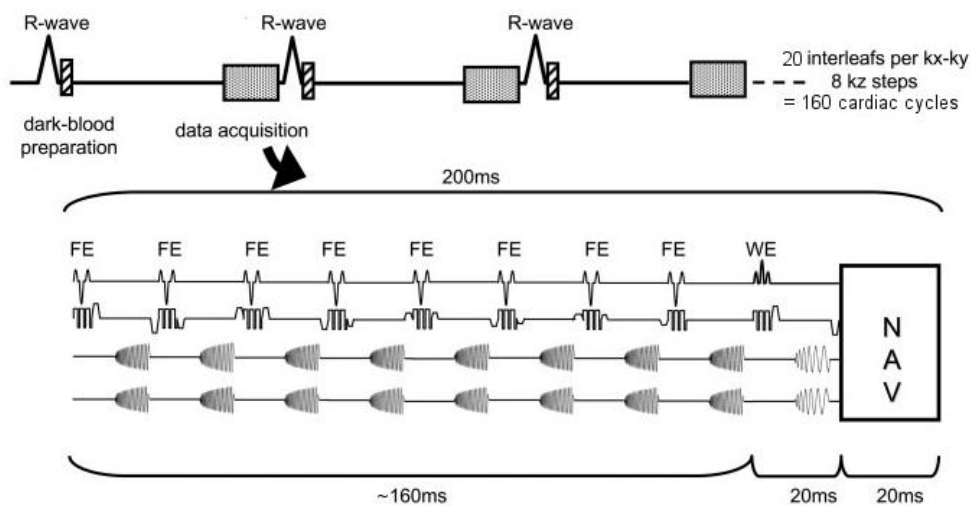
unsatisfactory, as this results in a low and highly variable respiratory efficiency and, as a result, an unpredictably long acquisition duration. In addition, the highly subject-specific relationship between the diaphragm and heart motion means that motion models require calibration scans, which may fail if the relationship changes during the acquisition. Model free, image based techniques are, therefore, an attractive prospect. The B2B-RMC technique (Keegan et al., 2007), requires no training acquisition, does not rely on a model, obtains 3D respiratory motion information directly from the anatomy of interest and is the only technique of its type to be applied to coronary vessel wall imaging. The remainder of this thesis will focus on the development of this technique and its use in a number of MR coronary artery imaging applications.

2.c Beat-to-beat respiratory motion correction

A number of respiratory motion correction techniques have been developed for or applied to MR coronary angiography. However, with the exception of the study by Keegan et al. (2007), all MR coronary vessel wall imaging has been performed with breath-holding for short 2D studies or navigator gating for longer studies. The resolution and SNR requirements of this challenging imaging target result in long acquisition durations and sensitivity to residual motion (Schär et al., 2003). Therefore, an accurate and efficient respiratory motion correction technique would be highly beneficial.

The original sequence (Keegan et al., 2007) is shown in figure 2.6. In every RR interval, a fully sampled low resolution 3D spiral dataset is acquired with binomial fat selective excitation. One interleaved of an interleaved high resolution 3D spiral dataset with water selective binomial excitation is acquired immediately after the low resolution data. Blood signal suppression is provided by double inversion recovery preparation with slab selective reinversion. Acquisitions were performed with 1RR gating. A standard crossed-pair navigator on the RHD is acquired after the high resolution data for comparison with the respiratory translations derived using B2B-RMC. The low resolution acquisition used a stack of single shot spirals (4096 points acquired over 10ms) and 8 kz phase encode steps, resulting in an acquisition window of 160ms. Reverse centric phase ordering was used to place the central kz phase encode step temporally close to the high resolution data acquisition. For the low resolution fat images, the acquired resolution was 6x6x3mm over a 250mm field of view, which was reconstructed to 0.5x0.5x1.5mm using zero filling. The high resolution acquisition used a stack of segmented 3D spirals, each of which was 10ms long (4096 points). A total of 20 spiral interleaves were required to fill each kx-ky plane and 8 kz phase encode steps were acquired, resulting in a total acquisition duration of 160 cardiac cycles. The acquired in-plane resolution was 0.8-0.94mm depending on the field of view and the slice thickness was 3mm, reconstructed to 1.5mm. Including the water selective binomial excitation, the high resolution acquisition window was 20ms. The navigator was used to monitor the diaphragm position only and all data was accepted for reconstruction.

Figure 2.6: The original B2B-RMC sequence for dark blood coronary artery vessel wall imaging

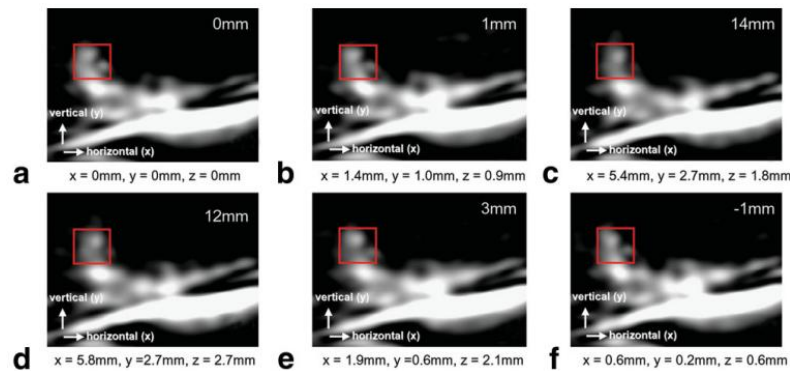


Every cardiac cycle a fully sampled low resolution 3D spiral dataset is acquired with fat selective excitation (FE) followed by a single interleave of a segmented high resolution 3D spiral acquisition with water selective excitation (WE). Blood suppression is provided with slab selective double inversion recovery preparation and acquisitions were performed with 1RR gating. A standard diaphragm navigator is also acquired for comparison with the 3D respiratory information. Reproduced from Keegan et al. (2007) with permission, copyright John Wiley & Sons.

Using this technique, cross-sectional coronary vessel wall images were acquired in a straight section of the RCA in six healthy subjects. Images were reconstructed and processed offline. An end expiratory volume was selected as a reference using the diaphragmatic navigator information and a 2D reference region of interest (ROI) was defined around the right coronary artery. 3D respiratory translations were obtained using a normalised sub-pixel cross-correlation of the 2D reference ROI with a 3D search ROI in every low resolution data set. The 3D translations were used to correct the corresponding high resolution data using the Fourier shift theory. Images were subsequently analysed using a subjective measure of image quality.

Example low resolution fat images used to obtain the respiratory translations are shown in figure 2.7 and example high resolution coronary artery vessel wall images are shown in figure 2.5. When the B2B-RMC technique was compared to a fixed 1D correction based on the navigator information and a pseudo-subject specific model, the B2B-RMC achieved the highest image quality score in all subjects with the exception of one, where B2B-RMC and the subject specific model achieved equally high scores.

Figure 2.7: Example low resolution images obtained in six consecutive cardiac cycles demonstrating beat-to-beat respiratory translations of the epicardial fat.



A single slice from the fully sampled low resolution 3D volume acquired every cardiac cycle, shown for 6 consecutive cardiac cycles (a-f). The diaphragm displacement in each of the cardiac cycles is shown in the top right of the images and the in-plane (x and y) and through-plane (z) beat-to-beat respiratory displacements are given below the relevant images. Reproduced from Keegan et al. (2007) with permission, copyright John Wiley & Sons.

While this feasibility study suggested that B2B-RMC has potential, further work was required before it may be widely accepted as an accurate and efficient respiratory motion correction technique. The remainder of this thesis presents work performed in developing, validating and applying B2B-RMC in MR coronary artery imaging based applications. The results presented will demonstrate that this may be a reliable, reproducible, accurate and efficient technique in MR coronary artery vessel wall imaging.

3. Development of the B2B-RMC technique

3.a Aim

The aim of this work was to develop the acquisition and reconstruction techniques presented originally by Keegan et al. (2007) for 3D spiral coronary vessel wall imaging with B2B-RMC. While this initial implementation demonstrated the potential of the technique, further development and optimisation was required to produce reliably high quality images at similar resolution to that demonstrated in the literature with navigator gated acquisitions (typically 0.6-1.0mm in-plane, 2-5mm through plane). In this chapter, developments are described which increase the robustness of B2B-RMC, enabling subsequent phantom (chapter 4) and *in-vivo* (chapter 5) validation of performance and latterly *in-vivo* applications (chapters 6-8).

3.b Implementation

All sequences were developed in the Siemens IDEA pulse sequence programming environment and all imaging (in this and subsequent sections) was performed on a Siemens Avanto 1.5T MR scanner. The original implementation was based on a Siemens phase velocity mapping sequence in an older version of the scanner software. To ease the transition to future scanner software updates, the sequence was redeveloped based on a standard skeleton fast low angle shot (FLASH) sequence. All processing and reconstruction of the B2B-RMC data was performed offline. The original reconstruction and processing was implemented in the C language. For simpler image display, user interface creation, access to pre-written libraries (toolboxes) and rapid compilation free code modifications, the reconstruction and processing software were rewritten in MATLAB (The Mathworks, Natick, MA, USA).

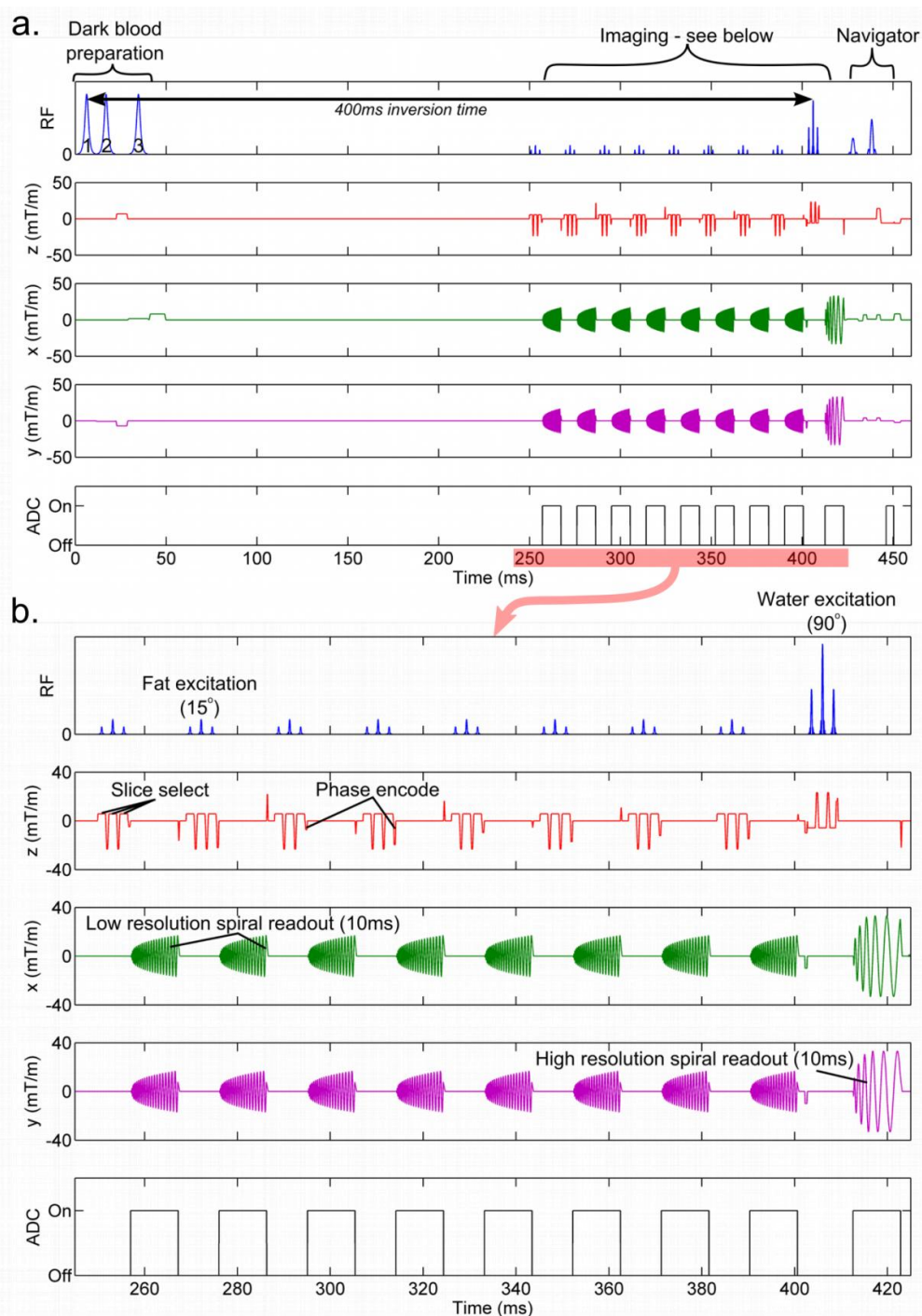
3.b.i Basic sequence implementation

To convert the basic Siemens skeleton FLASH sequence into a B2B-RMC sequence for 3D coronary vessel wall imaging the following modifications were made:

1. Standard crossed pair diaphragmatic navigators were added.
2. Double inversion dark blood preparation was added and modified to enable orientation of the reinversion slab via the user interface.
3. The standard excitation RF pulses were swapped for binomial excitation pulses.
4. The readout gradients were swapped for spiral gradients, designed using existing code written at the Cardiovascular Magnetic Resonance Unit, The Royal Brompton Hospital by Dr Peter Gatehouse. This results in gradient waveforms that are slew rate limited until the maximum gradient amplitude is reached, and gradient amplitude limited (constant linear velocity spirals) thereafter, the latter being preferable for speed and more uniform k-space coverage (Hardy and Cline, 1989, Meyer et al., 1992, Delattre et al., 2010).
5. The looping and timing structure was modified to obtain a stack of low resolution spirals immediately before the high resolution spiral at the user specified dark blood inversion time.

The complete sequence diagram is shown in figure 3.1.

Figure 3.1: The sequence diagram for the original B2B-RMC implementation



The original B2B-RMC sequence for 3D spiral coronary vessel wall imaging. The dark blood preparation (shown in a) includes three 180° RF pulses: the initial pulse (1) is a non-selective inversion; the second pulse (2) is a selective reinversion pulse to reinvert a slab of tissue selected by the user, covering the coronary artery of interest (the large slab thickness results in a very small slice select gradient); the final pulse (3) is a navigator restore pulse which reinverts the tissue that is later excited by the 90° navigator pulse, thus improving navigator SNR (Stuber et al., 2001). The imaging part of the sequence, highlighted on the time axis of part (a) and shown in part (b), includes a stack of eight 10ms single shot spirals with through plane phase encoding (combined with the final slice-rephasing gradient) and fat selective excitation (although the phase of the RF pulses is not shown), followed by a single 10ms interleave of a high resolution 3D stack of interleaved spirals acquisition with water selective excitation.

3.b.ii Reconstruction, processing and analysis tools

A series of tools were developed in MATLAB for reconstruction, processing and analysis of data acquired using the B2B-RMC technique which are described in the following sections.

3.b.ii.1 Reconstruction

All data from the B2B-RMC was retrospectively reconstructed and processed offline. A graphical user interface (GUI), and associated code, was developed for sorting of the raw data files and reconstruction of the images. Initially the single raw data file obtained from the scanner is sorted into navigator data, low resolution data and high resolution data. If required (see section 3.c.iii), the navigator information is used to eliminate data acquired outside of a wide pre-set gating window. The data is then saved into intermediate files; one file per coil per low resolution volume and similarly, one file per coil for the high resolution volume. Phase shifts may be applied to the raw spiral data for image space displacement, including motion correction, according to the Fourier shift theorem (Ehman and Felmlee, 1989):

$$f(x) \xrightarrow{FT} F(k)$$

$$f(x - a) \xrightarrow{FT} F(k)e^{-ika} \quad 3.1$$

where x is the coordinate in image space, k is the spatial frequency and a is the shift in image space. Reconstruction is performed by gridding the spiral data onto a Cartesian matrix followed by an inverse fast Fourier transform (iFFT) and finally, sum of squares coil combination.

A variety of techniques exist for re-sampling non-Cartesian data onto a regular Cartesian grid (gridding) before the iFFT is applied. The most common of these techniques involves a convolution with a Kaiser-Bessel kernel with compensation for the shape of the kernel and the density of the convolved data (Jackson et al., 1991). However, the original work on B2B-RMC (Keegan et al., 2007) used an unpublished algorithm, developed by Professor Guang-Zhong Yang at the Royal Brompton Hospital, London, 1992 and referred to here as the Yang method. This technique was found to perform well and was subsequently used in all reconstructions performed in this thesis. The Yang method convolves the data with the kernel:

$$c(r, u, v) = e^{-\left(\frac{\alpha \cdot 20 \cdot r^2 (0.1 + \beta \cdot D(u, v))}{w^2}\right)} \quad 3.2$$

where r is the distance from the centre of the kernel placed at the spiral data point to the Cartesian grid point (u, v) , $D(u, v)$ is an estimate of the spiral sampling density at the point (u, v) , w is the radius of the extent of the kernel and α scales the width of the peak of the kernel. In contrast to other kernels used in gridding non-Cartesian MR data, the peak of this gridding kernel has a variable width depending on the spiral sampling density $D(u, v)$. At the centre of k-space where there is a high density of sampling points, the width of the peak in the kernel is much narrower than at the

edges of k-space where $D(u,v)$ is much less. The degree to which $c(r,u,v)$ is dependant on $D(u,v)$ is controlled by β . Small values of β result in a more uniform convolution kernel across k-space. $D(u,v)$ is estimated by replacing the raw data with 1 at each spiral k-space point and convolving this with a “top-hat” function. However, the $D(u,v)$ term in equation 3.2 does not fully compensate for the changing sampling density across k-space and an additional correction is performed after the convolution based on summing $c(r,u,v)$ over every relevant raw data point for every value of u and v . No correction is performed for the shape of the convolution kernel (intensity correction). As a result, there is apodization of the reconstructed images, the magnitude of which is dependent on α , β and w . Optimal values of $\alpha=1.5$ and $\beta=1.0$ for a value of $w=1$ (chosen for rapid reconstruction speed), were estimated by iterating around values used in the previous work (Keegan et al., 2007) and comparing the reconstructed images visually.

Based on the use of a high performance workstation (with two quad core Intel(R) Xeon(R) 2.40GHz processors and 12GB of RAM without parallelisation of the code) with raw data from two receive coil channels, sorting of the raw data takes ~12s, reconstruction of the high resolution data takes ~30s (based on 75 spiral interleaves with 4096 points each and 8 kz phase encode steps without motion correction) and reconstruction of the low resolution data takes ~5s per volume (based on single-shot spirals of 6144 points each with 6 acquired kz phase encode lines).

3.b.ii.2 Processing

Respiratory motion information for B2B-RMC is extracted from low resolution 3D fat images acquired before every high resolution imaging segment. Software and a GUI dedicated to the extraction of the motion information from the low resolution data sets was developed in MATLAB. However, the low resolution fat images can be difficult to interpret as the coronary artery is not usually evident. Figure 3.2 shows MR images of the relevant anatomy when B2B-RMC is used for cross-sectional RCA imaging. The breath-hold 2D spiral images (figure 3.2a and 3.2b) show the right coronary artery in the AV groove (a) and the fat within the AV groove (b), with an equivalent low resolution fat acquisition (c) demonstrating the relatively little detail available in the low resolution fat images acquired for B2B-RMC. Movie S.1 in the supplementary material shows 9 of the 16 low resolution slices acquired in each RR-interval moving with respiration. Figure 3.3 highlights the equivalent anatomy in an *ex-vivo* human heart.

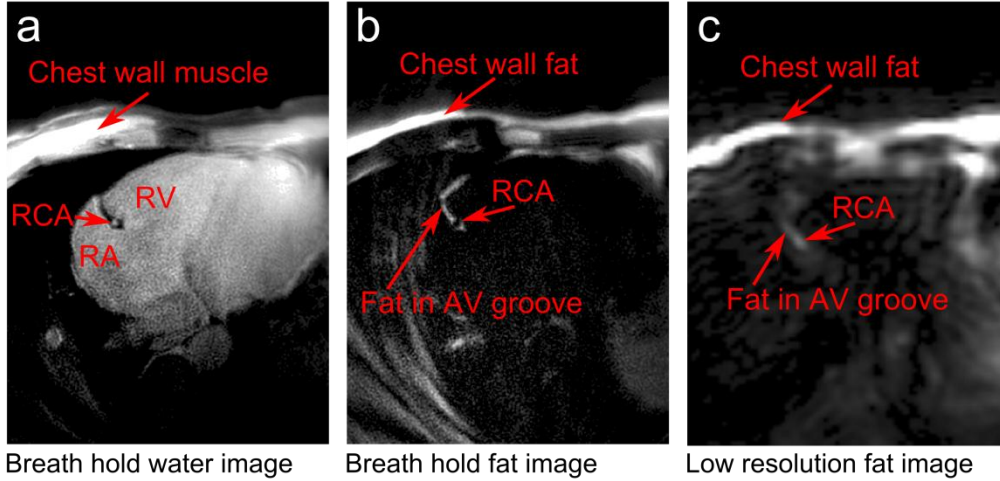
Initially, an end-expiratory low resolution data set is chosen as a reference using the diaphragmatic navigator trace. This chosen low resolution volume is then overlaid on the uncorrected high resolution water volume, as shown in figure 3.4 (also see movie S.2 in the supplementary material), in order to aid identification of the fat surrounding the coronary artery (note the correlation with the *ex-vivo* anatomy in figure 3.3). A rectangular reference region of interest (ROI) is drawn on a central slice of the reference end-expiratory volume (see movie S.3 in the supplementary material) of a size large enough to encompass the artery’s cross-section and a small amount of immediately adjacent fat (typically 10-20 x 10-20mm). The extent of the reference ROI in the through-plane

direction (not shown in figure 3.4) was defined as 3 slices (4.5mm) in order to encompass some change in the epicardial fat distribution. A larger search ROI is also defined on the end-expiratory reference dataset of sufficient size to encompass the expected respiratory motion of the reference ROI, typically 20-40 x 20-40mm in-plane and 7.5-12mm through plane. This search ROI is copied to each of the low resolution datasets acquired for B2B-RMC and linearly interpolated in three dimensions by factors set within the GUI (4 in all directions for the examples in this thesis). Each of the interpolated search ROIs is compared to the reference ROI using the normalised cross correlation coefficient, r :

$$r = \frac{(\sum OS - N\bar{O}\bar{S})}{\sqrt{(\sum O^2 - N\bar{O}^2)(\sum S^2 - N\bar{S}^2)}} \quad 3.3$$

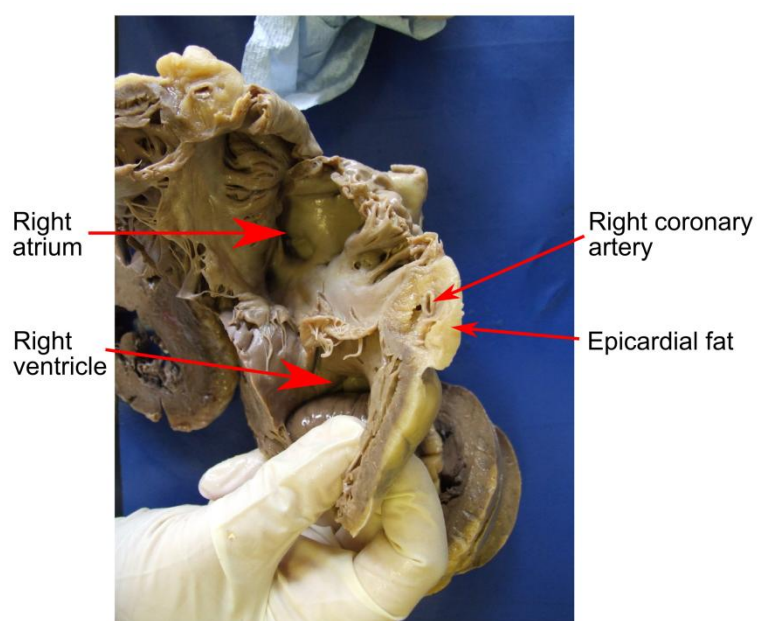
where O and S are the two matrices (the reference ROI and relevant part of the current search ROI), each with number of elements N , to be cross-correlated. The normalisation allows for cases when the most similar part of the search ROI may lie in an area of low signal intensity due to, for example, changes in the through-plane slice profile. The reference ROI is shifted about the search ROI in 3D to generate a volume of r -values, the maximum of which corresponds to the 3D respiratory displacement for that acquisition. This is referred to as normalised sub-pixel cross-correlation (NSPCC) and is represented (in 2D for clarity) in figure 3.5. The GUI also permits interactive adjustment of the ROI sizes and automatic plotting of the displacement results, as discussed in section 3.c.ii.

Figure 3.2: Cross-sectional anatomy imaged in the B2B-RMC technique



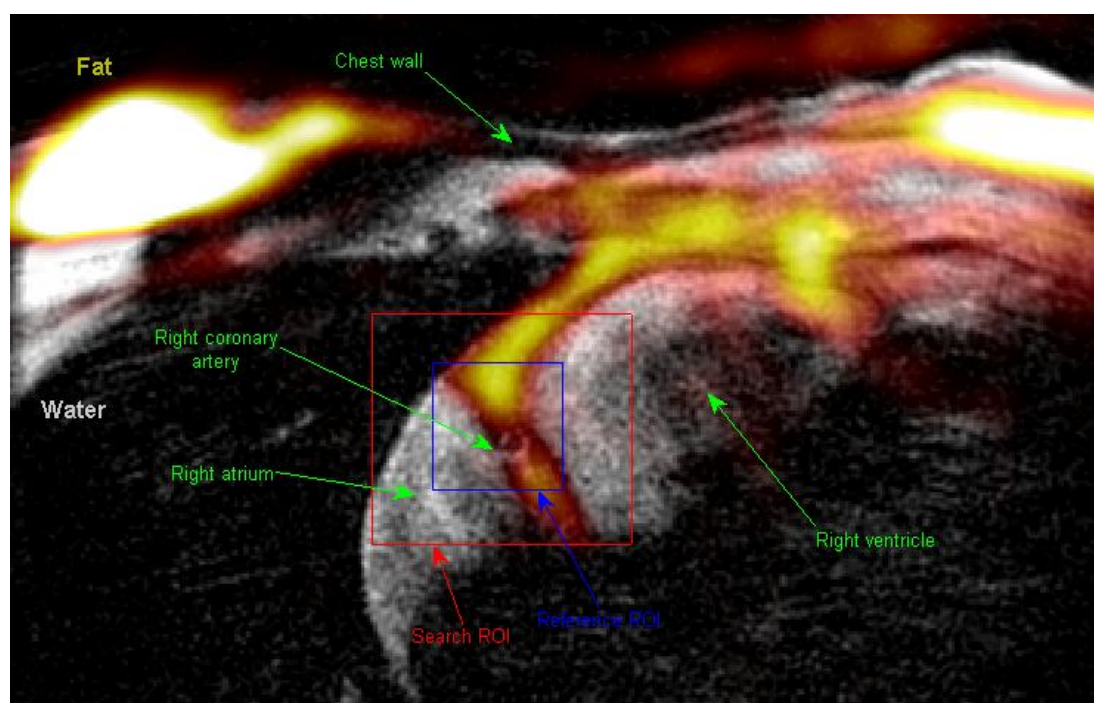
Cross-sectional right coronary artery images obtained in a healthy subject using spiral imaging. Breath hold 2D images at 1.0x1.0x6mm resolution were obtained with a binomial water selective excitation (a) and a fat selective excitation (b). An equivalent slice of a 3D low resolution data set acquired with fat selective binomial excitation at 4.8x4.8x3mm resolution in one cardiac cycle (c). While the major anatomy is recognisable in the low resolution images (c), the signal void corresponding to the coronary artery in the right atrioventricular groove is barely visible (arrows). RCA – right coronary artery, RA – right atrium, RV – right ventricle.

Figure 3.3: An ex-vivo human heart showing the RCA within the right AV groove



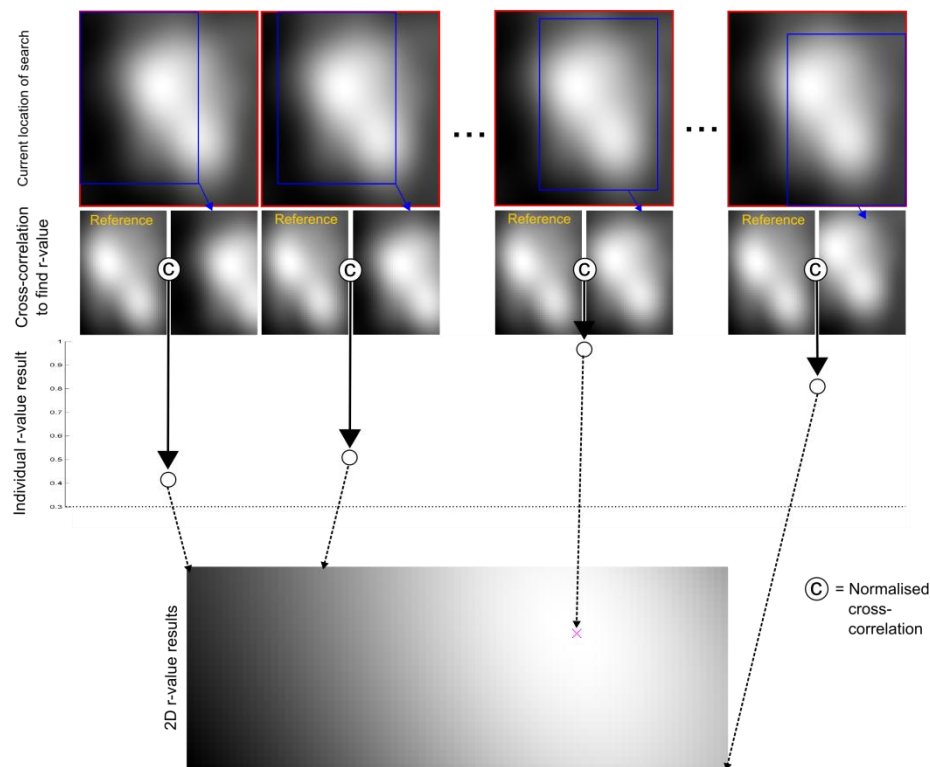
An ex-vivo human heart with a healthy RCA. The absence of pressure within the coronary arteries causes the lumen to collapse. Image courtesy of Dr Mary Sheppard, Director of the CRY Unit for Cardiac Pathology, Imperial College London.

Figure 3.4: Coloured overlay of the low resolution fat data onto the high resolution water data



An end-expiratory low resolution fat volume is transparently overlaid in a “hot” colour scale onto the uncorrected high resolution water volume, shown in a grey colour scale. This display is used to aid identification of the fat within the AV groove which assists the positioning of the reference and search ROIs for the NSPCC. Although shown here in 2D for clarity, both the search and reference regions extend across multiple slices.

Figure 3.5: Schematic representation of the 3D sub-pixel cross correlation shown in 2D.



As depicted in the top line, for each low resolution volume, the ROI (blue) to be correlated with the reference ROI is shifted around the search ROI (red) in all three dimensions (only the two in-plane directions are shown here for clarity). At each shift, the normalised correlation coefficient (r) is calculated between the reference ROI and the ROI at the current shift (second line from the top). The value of r indicates the similarity of the ROI at the current shift and the reference ROI (as shown in the third line); a value of 1 indicates a perfect match. A volume of r -values is generated, the maximum of which indicates the shift of the region most similar to the reference ROI (shown as a purple cross in the 2D representation shown in the bottom image). This NSPCC process is performed for each low resolution volume acquired (1 per RR-interval) in order to extract the motion due to respiration.

Based on a typical (for a cross-sectional RCA acquisition in a healthy subject) reference ROI of size $23 \times 40 \times 3$ pixels ($12 \times 20 \times 4.5$ mm), in x, y and z respectively and a search ROI of size $48 \times 60 \times 7$ pixels ($24 \times 31 \times 10.5$ mm) the NSPCC takes 13s per volume on a high performance workstation. However, multiple NSPCCs can be performed simultaneously on a multi-processor workstation using a parallel “for” loop. This reduces total NSPCC time by a factor equal to the number of processors used.

3.b.ii.3 Analysis

Each B2B-RMC acquisition results in one high resolution dataset and a large number (160 in the original implementation) of low resolution fat datasets. Two interactive tools were developed with MATLAB GUIs for analysis of the images produced in the B2B-RMC process. The first is an image viewer used to display single high or low resolution volumes reconstructed by the software described in 3.b.ii.1 and the second is a measurement viewer allowing the user to step through

multiple slices and multiple volumes of the low resolution data acquired for B2B-RMC. Screen captures of these tools are shown in movies S.2 to S.8 in the supplementary material.

The image viewer has options for: (1) in-plane Fourier or binomial interpolation, (2) Hamming filtering, (3) image zooming (cropping and nearest neighbour interpolation), (4) image rotation and reflection, (5) window and level adjustment, (6) phase image display, (7) generating parallel maximum intensity projections (see movie S.4), (8) curved planar reformatting (movie S.5), (9) 3 point plane description, (10) displaying perpendicular planes in 3D, (11) length measurement, (12) in-plane and through plane intensity profiles and (13) interfaces for saving one image or a montage of images from multiple slices and multiple volumes to one image file. The image viewer also provides the interface for (i) the MR coronary angiography analysis tools (see chapter 5 and movie S.6), (ii) the coronary vessel wall measurement tools (see sections 6 and 7 and movie S.7) and (iii) the coloured overlay of the low resolution fat images onto the high resolution data as shown in figure 3.4 (also see movie S.2).

The measurement viewer is able to create montages of multiple slices in multiple volumes and movies of montages of multiple slices stepping through the volumes which demonstrate the motion of the fat with respiration (see movie S.1). This tool also enables the user to overlay the search ROI, reference ROI and the reference ROI shifted by the respiratory displacements obtained using NSPCC, onto each low resolution volume (see movie S.8).

3.c Improving motion detection and correction

3.c.i Developments to the low resolution acquisitions

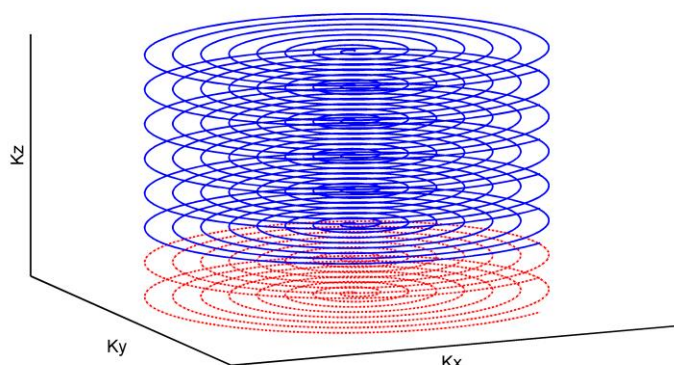
For B2B-RMC, respiratory displacements are extracted from the low resolution images. In the original implementation of B2B-RMC, each low resolution volume acquired every cardiac cycle was obtained in an acquisition window of 160ms and had an acquired resolution of 6.0x6.0mm in-plane and 3.0mm through-plane. Accurate respiratory information is vital to fully correct for respiratory motion in the high resolution data and improvements in accuracy are expected with increases in the resolution of the low resolution images. In general however, any increase in the resolution of the low resolution images must be traded for an increased acquisition window, potentially leading to increased cardiac motion artefacts and, therefore, reduced accuracy of the motion detection. Alternatively, SNR may be traded for increased resolution using a reduced field of view (FOV) or parallel imaging techniques. Reducing the FOV beyond the size of the imaged anatomy results in wrap artefacts. Parallel imaging techniques such as SMASH (Sodickson and Manning, 1997) or SENSE (Pruessmann et al., 2001, Pruessmann et al., 1999) use additional data available from multiple coils to enable the unwrapping of aliased images, therefore reducing acquisitions durations or increasing image resolution. While SNR appeared to be more than sufficient in the original implementation of B2B-RMC, the added reconstruction complexity and therefore reconstruction time required meant that parallel imaging was not a practical option in this project. Another option for reducing acquisition duration in Cartesian imaging is partial Fourier imaging,

which asymmetrically samples k-space in the phase encode direction, thus maintaining resolution and FOV. Partial Fourier data may be reconstructed by using the conjugate symmetry of k-space and Homodyne reconstruction (Noll et al., 1991). However, the simplest partial Fourier reconstruction zero-fills the empty k-space data with an associated penalty of increased Gibbs ringing and some suppression of high spatial frequency information.

In this section it is proposed that the low resolution data and hence, motion detection, can be improved using an increased spiral duration (with superior spatial resolution) in combination with partial Fourier acquisition in the through-plane phase encode direction (to maintain acquisition duration) (figure 3.6). Images were obtained in a stationary water filled resolution phantom using the original B2B-RMC sequence modified to acquire 10ms, 15ms and 20ms spiral durations with in-plane resolutions of 6mm, 4.8mm and 3.75mm respectively. Images were also obtained with the 15ms spiral duration and 6/8ths partial Fourier encoding in the through plane direction, which should result in a loss of SNR by a factor of $\sqrt{6/8}$. Partial Fourier reconstruction was performed with simple zero-filling. The associated acquisition windows for the 3D low resolution volumes were 148ms, 187ms, 230ms and 140ms for the 10ms spiral, 15ms spiral, 20ms spiral and 15ms spiral with partial Fourier respectively. For these phantom acquisitions, the low resolution acquisitions were modified to obtain water selective images. An approximate measurement of SNR was calculated for each acquisition using an ROI placed in a region of uniform signal and one placed in an artefact free noise region (see 3.d.ii for details), both in the central slice of the volume. One representative slice from the low resolution 3D acquisitions is shown in figure 3.7. The increased spatial resolution as a result of the longer spiral duration results in visually sharper edges and increased visibility of the resolution test patterns. There are changes in the Gibbs ringing artefacts due to the changes in acquired resolution. Approximate SNR was similar between the acquisitions at: 48, 10ms spiral; 46, 15ms spiral; 50, 20ms spiral; and 45, 15ms spiral with partial Fourier.

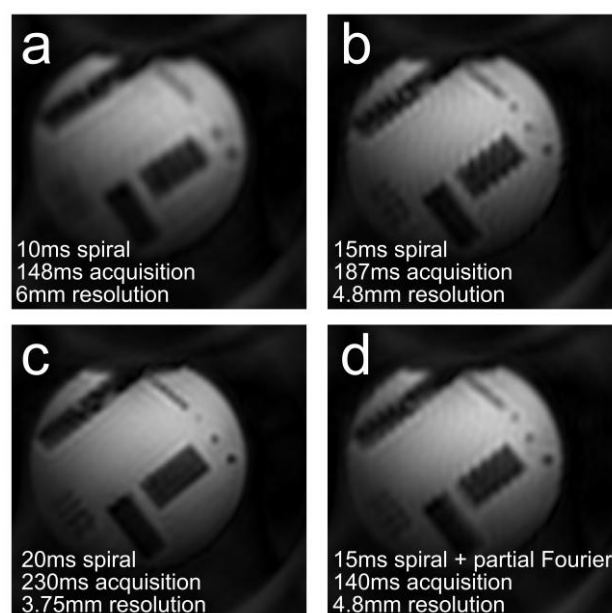
Table 3.1 compares the original low resolution acquisition parameters with those chosen as optimal in this work. Using a combination of increased spiral acquisition duration and through-plane partial Fourier encoding, in-plane resolution of the low resolutions may be increased from 6.0mm to 4.8mm (20% increase), with no increase in acquisition window (148ms vs. 140ms). While further increases in in-plane resolution may be achieved with even longer spiral acquisitions, the increased acquisition window required together with the increased image blurring associated with longer spiral readouts means that further increases are unlikely to be beneficial. The basic zero-filling partial Fourier reconstruction introduces Gibbs ringing in the partial Fourier (through-plane) direction. However, this is unlikely to be a problem in the anatomy of interest as the fat within the AV groove changes slowly from slice to slice, minimising the effect. In addition, any ringing artefacts that are present should move rigidly with respiratory displacement of the AV groove. The expected loss of SNR associated with partial Fourier acquisition was not observed here. This could be a result of the basic method used to measure SNR or the zero-filling reconstruction used.

Figure 3.6: A schematic of the low resolution acquisition with partial Fourier acquisition



The low resolution acquisition has 8 through plane phase encode steps. At each phase encode value a single shot 2D spiral is acquired. With 6/8ths partial Fourier acquisition, six (the solid blue lines in the figure) of the eight spirals are acquired. The final two spirals (red dotted lines) were zero-filled in the reconstruction.

Figure 3.7: A comparison of low resolution phantom images acquired with varying spiral length and in-plane resolution



Example slices from low resolution acquisitions obtained in one simulated cardiac cycle. With increasing spiral length and therefore in-plane resolution, increasing edge sharpness is observed, although the frequency of the Gibbs ringing artefact also changes. With the use of partial Fourier techniques, images with 4.8mm in-plane resolution can be obtained in a similar duration to those obtained at 6mm in-plane resolution without partial Fourier.

Table 3.1: A comparison of low resolution imaging parameters used in the original work and those chosen here

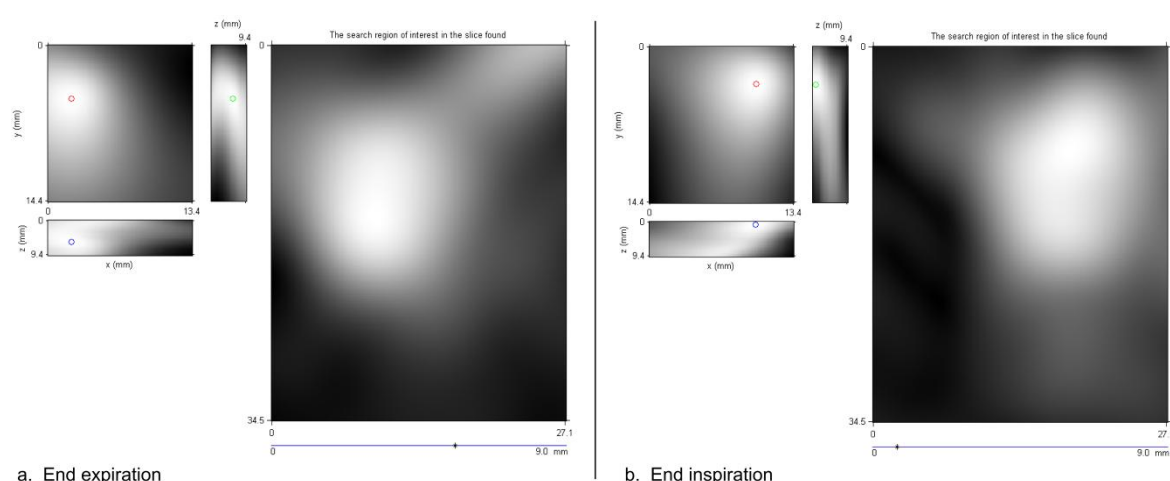
Parameter	Original value	New value
Excitation	15° binomial fat selective	15° binomial fat selective
Spiral readout duration	10ms	15ms
Dwell time per spiral point	2.5 μ s	2.5 μ s
Points per spiral readout	4096	6144
TE/TR	3.9ms/19ms	3.9ms/23ms
In-plane resolution	6.0x6.0mm	4.8x4.8mm
In-plane field of view	220x220mm	260x260mm
Through-plane phase encode steps (reconstructed)	8 (16)	8 (16)
Partial Fourier factor	8/8	6/8
Slab thickness	24mm	24mm
Acquired slice thickness (reconstructed)	3.0mm (1.5mm)	3.0mm (1.5mm)

3.c.ii Selection and evaluation of the search and reference ROIs used in the normalised sub-pixel cross-correlation

In the B2B-RMC technique, NSPCC is used to determine 3D respiratory displacements of the imaged coronary artery on a beat by beat basis. Appropriate selection of the reference and search ROIs is crucial to determine accurate motion information. The reference ROI must encompass fat moving rigidly with the coronary artery and the search ROI must be large enough to encompass the motion of the coronary artery through the respiratory cycle. However, selection of an excessively large search ROI will lead to unnecessarily long processing times and an increased likelihood that the NSPCC will select an incorrect (but similar) region of fat contained within the search ROI.

As discussed in section 3.b.ii.2 and shown in figure 3.5, the NSPCC produces a volume of cross-correlation coefficients (r) for each low resolution volume acquired. The results of the NSPCC may be assessed using a visualisation technique developed as part of this work and demonstrated in figure 3.8 and movie S.9. For each of the low resolution datasets, the values of r are displayed in the 3 orthogonal planes, i.e. x-y, x-z and y-z, containing the peak r -value and the peak in each plane is highlighted. The search ROI in the slice corresponding to the peak r -value is also shown together with a plot of the through-plane position of that slice. This display is converted into a movie with one frame per low resolution volume which shows the in-plane and through-plane motion of the tracked region of fat over time. A movie showing the search ROI after correction for motion in each of the low resolution volumes is also generated (see movie S.10) – if well corrected, the fat around the artery within the search region should be of a fixed shape and position in each frame.

Figure 3.8: Visualising the NSPCC results



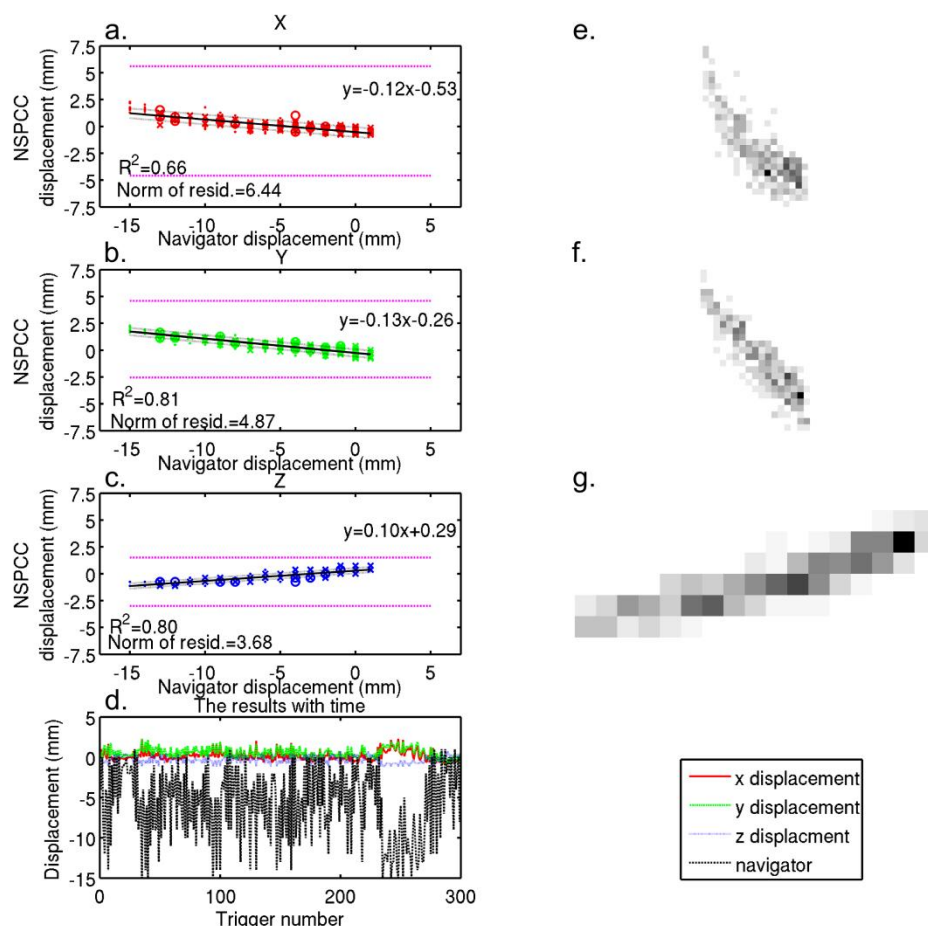
A visualisation of the NSPCC results for one example dataset, shown at end expiration (a) and end inspiration (b). The three left panes of each visualisation show the r -values obtained with NSPCC in the x - y plane (top left), y - z plane (central upper pane) and x - z plane (bottom left). Each of these planes passes through the maximum r -value (circled in each). The right-hand pane shows the search ROI at the through plane displacement obtained from the NSPCC (which is indicated as a cross on the line below) and therefore shows only in-plane shifts. Also see movie S.10 in the supplementary material.

In the example shown in figure 3.8, at end expiration (a) the peak r -value lies well within the boundaries of the search ROI. At end inspiration (b) the peak r -value has moved relative to end expiration. The displacement is in the direction of increasing y and increasing x , corresponding to in-plane displacements towards the chest wall and the right hand side of the image as viewed, respectively. The peak r -value has also moved to a smaller z position (corresponding to a through-plane displacement, approximately towards the feet). This method of visualising the NSPCC output effectively demonstrates how the epicardial fat around the coronary artery is moving with respiration. By watching the shape of the fat at the through plane displacement detected it can be used to detect occasions when the NSPCC selects a similar but incorrect region of fat. It may also be used to detect when the search ROI has been defined inappropriately, in which case the peak r -value may jump erratically across the display as an incorrect region of fat is selected or repeatedly select displacements at the boundary of the search ROI. This visualisation technique was invaluable in the initial stages of this project when experience in defining the search and reference ROIs was limited. However, the process of analysing the output is time consuming and it has become less necessary with more experience in positioning of the ROIs.

As an alternative to the display method described above, the respiratory displacements obtained from NSPCC may be plotted against the diaphragmatic navigator displacements, as demonstrated in figure 3.9 (a-c). Two dimensional histograms of this data are also generated (figure 3.9 (e – g)), with darker points representing a greater number of results (Nehrke et al., 2001), which are useful for discerning hysteric loops (see chapter 4). By adding the search limits of the NSPCC to the plots of respiratory displacement vs. navigator displacement, the size of the reference ROI can be

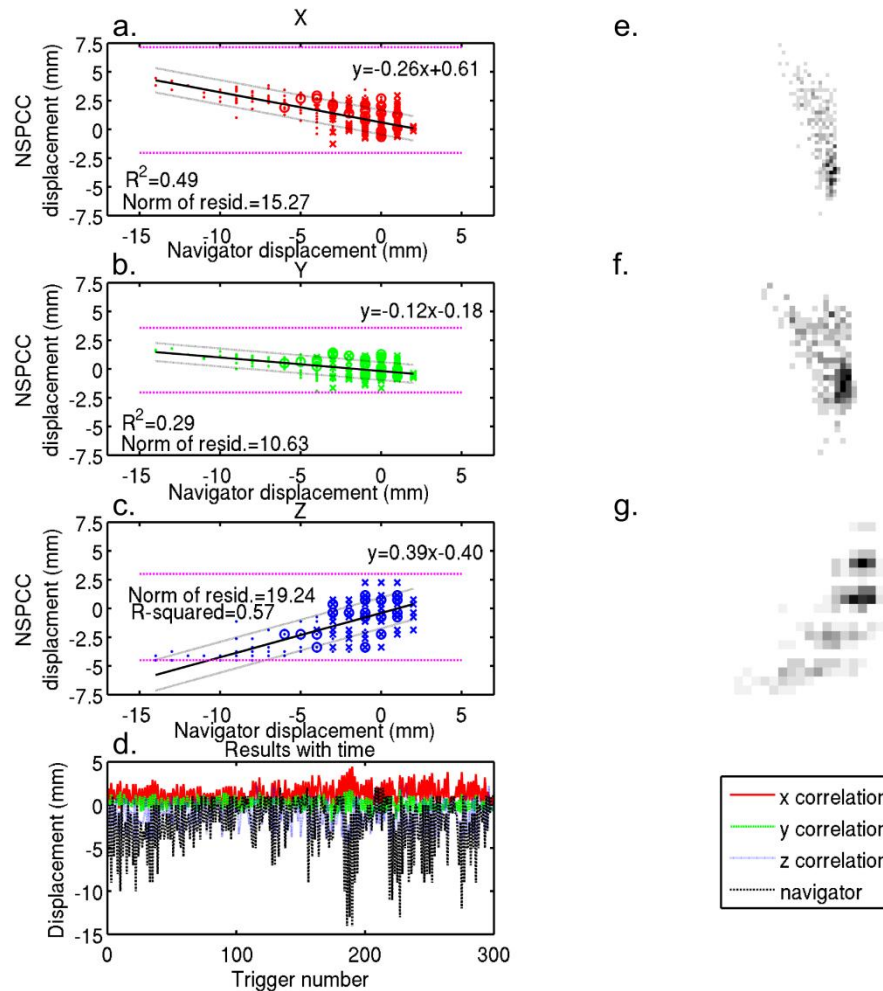
evaluated and adjusted for future NSPCCs. Figure 3.10 demonstrates a case where the search ROI does not extend sufficiently far in the negative through-plane (-z) direction. This is evident from the points which lie on the boundary of the search ROI in the through-plane (z) direction, while the linear least squares fit to the data crosses through the boundary at around $z=-5\text{mm}$, extending to approximately $z=-6\text{mm}$. In this case the search ROI would be extended and the NSPCC repeated.

Figure 3.9: Respiratory displacements obtained using NSPCC plotted against the diaphragmatic navigator displacement in a typical subject



The respiratory displacements obtained from the NSPCC plotted against navigator displacement in the in-plane (a – b) and through-plane (c) directions. Inspiratory points (where the differential of the navigator with time is negative) are plotted as crosses, expiratory points (where the differential is positive) are plotted as dots and stationary points are plotted as empty circles. For each plot, a linear regression (± 2 standard deviations) is superimposed in black. The limits of the NSPCC are indicated by the magenta dotted line. The respiratory displacements from NSPCC and the navigator are also plotted against time (Trigger number) (d), in this case, one measurement was acquired every two RR-intervals (2RR gating). 2D histograms of the NSPCC derived displacement with navigator displacement are shown adjacent to the standard plots (e – g). In this display darker points indicate that a higher number of results were obtained at this combination of NSPCC derived and navigator displacement.

Figure 3.10: Respiratory displacements obtained from NSPCC plotted against diaphragmatic navigator displacement in a case of an insufficient search ROI



Equivalent plots to those shown in figure 3.9 in a case where the search ROI does not extend sufficiently far in the through-plane (z) direction. While the points cluster around end-expiration at $x=y=z=0$, a number of through-plane (z) displacements lie on the search ROI boundary (c), indicated by the dotted magenta line. The linear least squares fit in this direction also passes some way through the search ROI boundary. As a result, this NSPCC was subsequently repeated with an extended search ROI.

3.c.iii Gating data acquired at extreme respiratory displacements

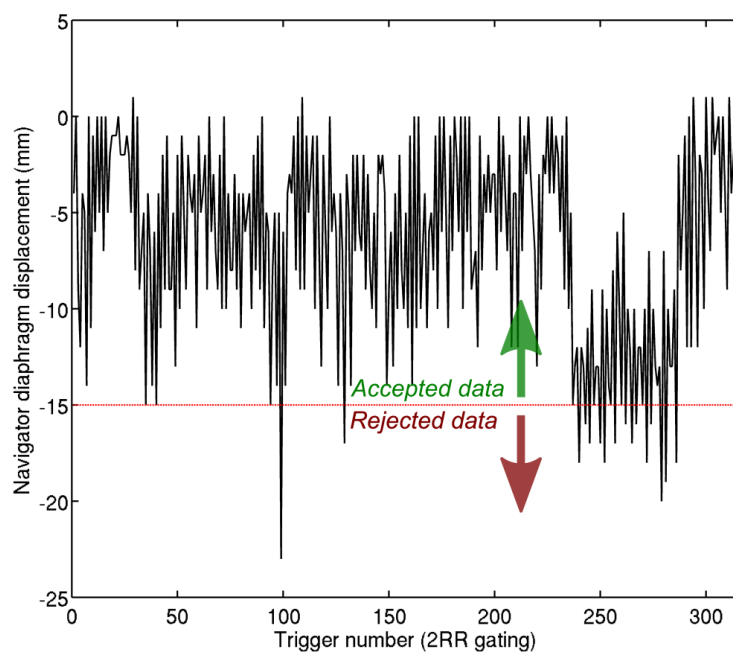
In the initial study (Keegan et al., 2007), the B2B-RMC technique corrected for the full range of normal respiratory motion. However, excessively large breathing motion outside the normal tidal range could result in the anatomy imaged in the reference volume moving completely out of the low resolution imaging slab (24mm thickness). Large respiratory displacements are also more likely to result in substantial rotation or non-rigid deformation of the AV groove and correction of the data using 3D translation alone may be inadequate. For these reasons the sequence and reconstruction code were modified to enable ARA navigator gating of the B2B-RMC acquisitions. As is standard, data acquired outside of a pre-defined gating window was rejected and reacquired

after the immediately subsequent cardiac trigger (i.e. in the next cardiac cycle for 1RR gating). Typically, the gating window was set to accept all data within the normal tidal range (defined during a free breathing navigator scout acquisition of ~30s in duration) $\pm 10\text{mm}$. This gating window size was chosen to exclude large inspirations or expirations (e.g. yawns, coughs and sighs), but not typical respiratory drift. This strategy results in a respiratory efficiency $>99\%$ in almost all cases (see sections 5 and 6).

Figure 3.11 shows an example of the diaphragmatic navigator displacement (a navigator trace) obtained in a healthy subject during a B2B-RMC acquisition using the acquisition parameters described in section 3.f. The navigator gating window was set to reject points acquired $>\pm 15\text{mm}$ from end-expiration. In this case, the usual definition of the navigator gating window of normal tidal range $\pm 10\text{mm}$ would have resulted in the inspiratory boundary (red line on figure 3.11) being positioned at around -25mm with a corresponding respiratory efficiency of 100% . However, because of respiratory drift between the navigator scout acquisition and the B2B-RMC acquisition, the inspiratory boundary was placed closer to end-expiration, producing an abnormally low respiratory efficiency (for B2B-RMC) of 95% (16 of 300 data segments were rejected). Figure 3.12 shows the high resolution B2B-RMC images reconstructed from the data acquired within the gating window (a-c). Equivalent images were also reconstructed to demonstrate the effect of not using navigator gating and are shown in figure 3.12 (d-f, "Ungated"). For these images, all high resolution data segments were accepted for reconstruction the first time they were acquired, regardless of the diaphragmatic navigator displacement at the time of acquisition. There is a clear loss of sharpness in the ungated images due to the inclusion of large inspiratory respiratory displacements that are insufficiently corrected with B2B-RMC.

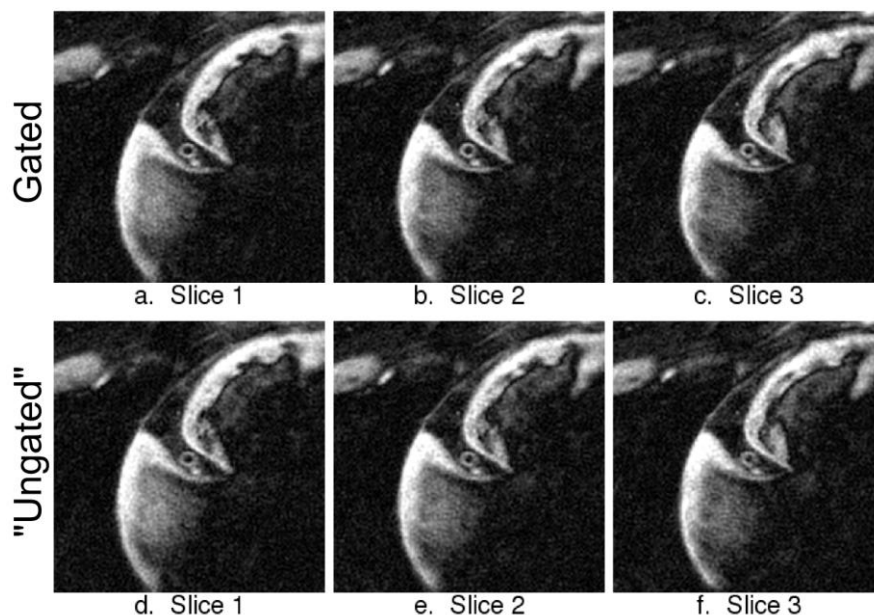
While the example shown here rejects more data than is typical for the acquisitions in this thesis, it demonstrates the improvements in image quality that may be achieved by eliminating a small amount of data acquired at large respiratory displacements at the expense of a small decrease in respiratory efficiency (5% in this case).

Figure 3.11: The diaphragmatic navigator displacement corresponding to the images shown in figure 3.12



The diaphragmatic navigator displacements are plotted (in black) with cardiac trigger number (2RR gating was used in this example). The dotted red line indicates the inspiratory boundary of the navigator gating window.

Figure 3.12: The effect of extreme respiratory displacements on B2B-RMC correction

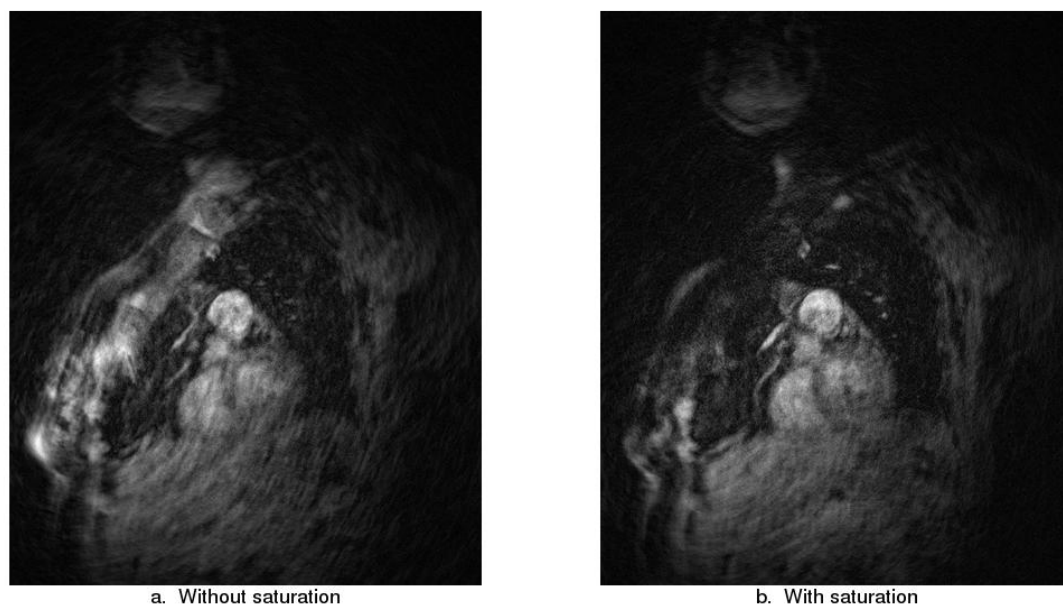


The upper row of images (a-c) are gated as shown in figure 3.11 whereas the lower images (d-f) used data accepted the first time it was acquired irrespective of the navigator displacement ("Ungated"). The ungated images demonstrate a loss of sharpness around the coronary artery vessel wall, particularly in slice 3.

3.c.iv Respiratory motion of the chest wall relative to the heart

B2B-RMC corrects for the rigid 3D translation of the coronary artery, as determined by tracking the in-plane and through-plane displacements of the surrounding epicardial fat. However, respiratory motion of the thorax is not fully described by these 3D translations. In particular, the bright signal from the chest wall can be problematic. Figure 3.13 shows bright blood in-plane 3D spiral coronary MR angiography images of the RCA with B2B-RMC, as performed in chapter 5, without (a) and with (b) a spatial saturation band applied to the chest wall. Without the saturation band, correction of the image for the 3D translation of the proximal RCA results in ghosting artefacts across the image originating from the chest wall. These are much reduced when the chest wall signal is suppressed.

Figure 3.13: The effect of non-rigid motion between the chest wall and coronary arteries in B2B-RMC



The respiratory motion of the chest wall does not correspond rigidly to that of the coronary artery, resulting in ghosting artefacts after correction (a). Such artefacts can be minimised in MR coronary angiography using a spatial saturation applied to the chest wall (b).

This is also a potential problem in coronary vessel wall imaging with B2B-RMC. To demonstrate the effects of chest wall motion relative to the RCA, a numerical simulation was performed. A 2D representation of the chest wall and right AV groove containing the RCA in cross-section of size 900 x 900 pixels was generated, as shown in figure 3.14. The image was separated into two separate 2D images, one of the chest wall and one of the heart. Both images were Fourier transformed and interpolated onto a 2D interleaved spiral k-space path (4096 points per spiral, 75 interleaves, k-space diameter sampled = 815 pixels). For every interleave of the spiral k-space path, the corresponding data from the chest wall image was displaced in the y direction (up-down in figure 3.14) by the in-plane y-displacements obtained using B2B-RMC in a healthy volunteer. This was

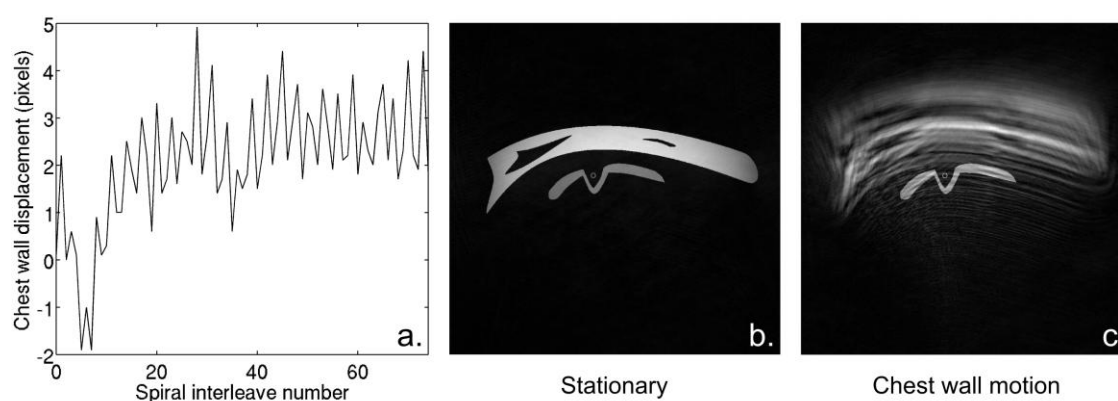
achieved by multiplying the k-space data with a phase factor according to the Fourier shift theorem. The corresponding data for the heart was not displaced. The respiratory displacement of the chest wall, while the heart remains stationary, represents a situation where the data was acquired whilst the heart moved with respiration, whereas the chest wall was completely stationary. Rigidly correcting for the respiratory motion of the heart effectively introduces respiratory motion of the chest wall. After this procedure was performed for every interleave, the data from the heart was summed with that from the chest wall, interpolated back to a Cartesian grid and inversed Fourier transformed back to the image domain. Figure 3.15 shows the resulting image (b), an equivalent image which was processed identically but without any displacements (c) and the respiratory displacements used (a). The relative motion of the chest wall while the heart remains stationary causes ghosting of the chest wall across the anatomy of interest within the heart.

Figure 3.14: A numerical representation of the chest wall and right AV groove containing the RCA



The chest wall is shown in white and the relevant section of the heart and RCA in cross-section are shown in grey. The intensity of the heart and RCA was 50% of the intensity of the chest wall.

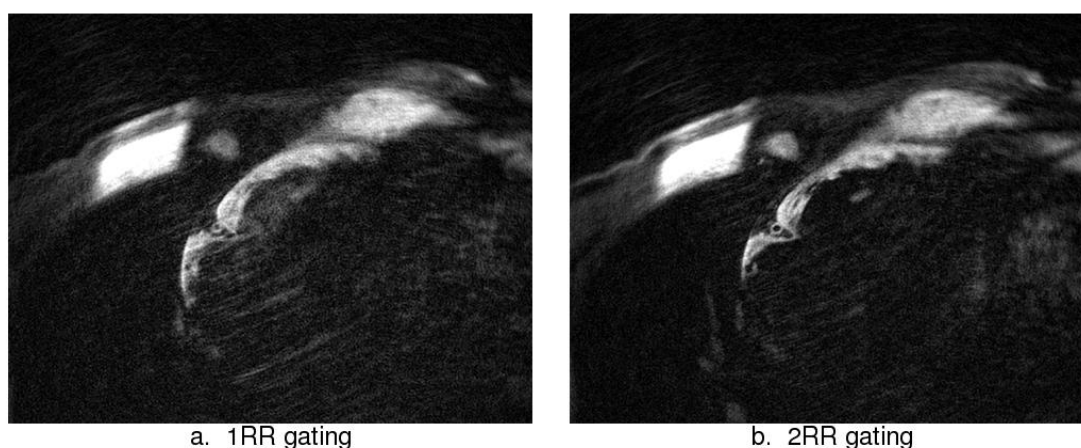
Figure 3.15: The results of the chest wall motion – numerical simulations



For every spiral interleave, the chest wall was displaced in the in-plane y -direction (up-down in the images) by the respiratory displacements shown in (a), while the heart remained stationary. When simulations were performed without motion there were only minor artefacts caused by the rudimentary grid – re-grid algorithm (b), whereas simulations including respiratory motion of the chest wall, resulted in severe ghosting artefacts (c).

In-vivo, chest wall signal in B2B-RMC coronary vessel wall images can be reduced by minimising the intersection of the slab selective reinversion band of the dark blood preparation pulse with the chest wall. This reduces the associated ghosting of the chest wall after respiratory motion correction. Figure 3.16 shows RCA coronary vessel wall images acquired with B2B-RMC in one healthy subject with both 1RR and 2RR gating, using the imaging protocol described in section 3.f. In this case, the reinversion slab avoids reinversion of the chest wall. However, the navigator restore pulse, which is a reinversion pulse applied immediately after the double inversion preparation in the same plane as the 90° navigator pulse in order to improve the SNR of the navigator signal, intersects the chest wall close to the RCA. This results in ghosting of this section of the chest wall across the RCA after B2B-RMC. The ghosting artefact appears similar to that observed in the numerical simulations shown in figure 3.15, confirming the source of the artefact. This effect appears more pronounced in the 1RR gated images, as a result of additional ghosting from this section of chest wall caused by variations in RR-interval. Therefore, wherever possible, reinversion of the chest wall should be avoided by careful positioning of the dark blood reinversion slab and the navigator RF pulses. In future the use of 2D RF pulses should be considered for both the navigator and the selective component of double inversion recovery, as should the possibility of non-rigid respiratory motion correction.

Figure 3.16: Ghosting artefact caused by dark blood preparation and navigator echoes in coronary vessel wall imaging with B2B-RMC



Ghosting of the chest wall is a potential problem in coronary artery vessel wall imaging with B2B-RMC. It can be minimised by positioning the reinversion band of the dark blood preparation to avoid reinversion of the chest wall signal. However, the navigator restore pulse also reinverts a section of chest wall, potentially causing ghosting. The ghosting from this section of chest wall is more evident in 1RR gated images (a) than 2RR gated images (b). This is due to the increased SNR of the 2RR gated images.

3.d Developments to the high resolution acquisition

3.d.i Introduction

As discussed in section 1.e.ii, MR coronary artery vessel wall imaging requires high resolution, rapid imaging techniques with sufficient SNR to image the thin wall of these highly mobile arteries deep within the chest. Insufficient resolution results in over-estimation of coronary vessel wall thickness (Schär et al., 2003) (table 1.10) and an inability to detect small, localised changes in vessel wall thickness caused by disease. The original work by Keegan et al. (2007) was performed at an in-plane resolution of between 0.80mm and 0.94mm. In contrast, IVUS, which is the gold standard for *in-vivo* assessment of the coronary vessel wall, achieves lateral resolutions ~ 0.25 mm, which are currently unachievable in MR coronary imaging. In this work, the aim was to achieve an acquired in-plane spatial resolution of 0.5×0.5 mm while maintaining sufficient SNR for reliable coronary artery vessel wall imaging. This is smaller than the average coronary vessel wall thickness of 0.7 – 0.8mm in healthy subjects over 20 years old (see table 1.2). It is similar to the resolution of ~ 0.5 mm typically achieved with CT coronary angiography and exceeds the in-plane resolutions stated in previously published MR coronary vessel wall imaging studies of between 0.66×0.66 mm (Botnar et al., 2001) and 1.1×1.2 mm (Macedo et al., 2008). Increased resolution may be achieved at the expense of reduced SNR and/or increased acquisition durations, however subject tolerance reduces as the scan duration increases. Acquisition duration should therefore, be limited in order to minimise the possibility of image degradation by motion artefacts. In this section, attempts to increase the in-plane spatial resolution of RCA vessel wall images acquired with B2B-RMC, while maintaining sufficient SNR in order to clearly visualise the vessel wall, are described.

3.d.ii Parameter comparison

The high resolution imaging parameters used in the original sequence (Keegan et al., 2007) are described in table 3.2. In order to increase the resolution of the high resolution coronary artery wall images, four key modifications were made to the original sequence:

1. Increased resolution via modified spiral paths designed to use a greater number of interleaves.
2. Increased FOV using a greater number of spiral interleaves to boost image SNR and reduce the characteristic spiral wrap artefacts.
3. Increased cardiac acquisition window by increasing the number of spiral interleaves acquired per cardiac cycle in order to increase imaging efficiency.
4. Switching from 1RR to 2RR cardiac gating to increase SNR and reduce artefacts caused by variations in RR interval.

Table 3.2: Imaging parameters used for the basic high resolution acquisition

Parameter	Default value
Navigator gating	None - monitoring only
Cardiac gating	1RR
Dark blood inversion time	400ms
Acquisition duration at 100% respiratory efficiency	160 RR
FOV	220mm
Number of spiral interleaves	20
In-plane resolution	0.90 x 0.90mm
Spiral interleaves acquired per trigger	1
Flip angle of binomial water excitation pulse	90°
Through plane phase encode steps acquired (reconstructed)*	8 (16)
Slab thickness*	24mm
Through plane resolution acquired (reconstructed)*	3.0mm (1.5mm)
Spiral readout duration*	10ms
Dwell time per point*	2.5µs
Points per spiral readout*	4096

* - These parameters were not altered in the comparisons described in section 3.d.ii
RR – RR-intervals.

Here, a series of comparisons of *in-vivo* cross-sectional RCA wall acquisitions in healthy subjects are presented with differing high resolution imaging parameters relating to the modifications listed above. In order to provide a quantitative comparison between these pairs of techniques, relative measures of SNR and CNR were obtained from the reconstructed magnitude data via:

$$SNR = 0.655 \cdot \frac{S_v - S_b}{\sigma_b} \quad 3.4$$

$$CNR = 0.655 \cdot \frac{S_v - S_l}{\sigma_b} \quad 3.5$$

where S_v is the mean signal in a freehand ROI drawn around the visible vessel wall, S_b and σ_b are the mean and standard deviation of the signal in an ROI drawn in a background region as close as possible to the vessel wall with minimal visible artefact, S_l is the mean signal in a freehand ROI drawn in the visible lumen and the factor of 0.655 accounts for the expected Rayleigh distribution of background noise in magnitude data, rather than the Gaussian distribution of the acquired complex data. Both SNR and CNR were calculated as the average of the values obtained in 3 contiguous slices from the high resolution volume in each comparison, chosen based on the clarity of the vessel wall. While this method of measurement is unsatisfactory for measurements of

absolute SNR/CNR (Constantinides et al., 1997), it does enable some comparison between the pairs of high resolution datasets and has been used in similar work (Botnar et al., 2001).

All acquisitions presented in this section were acquired with the low resolution acquisition of the B2B-RMC sequence modified to obtain six 15ms spirals with 6/8ths partial Fourier, as described in section 3.c.i and table 3.1, and subsequently retrospectively reconstructed and corrected for respiratory motion as described in section 3.b.ii and 3.c.ii. Respiratory motion compensation was assumed to be equally effective between the acquisitions in each comparison. The comparisons are described below and are summarised in table 3.3.

Table 3.3: Results of the imaging parameter comparisons

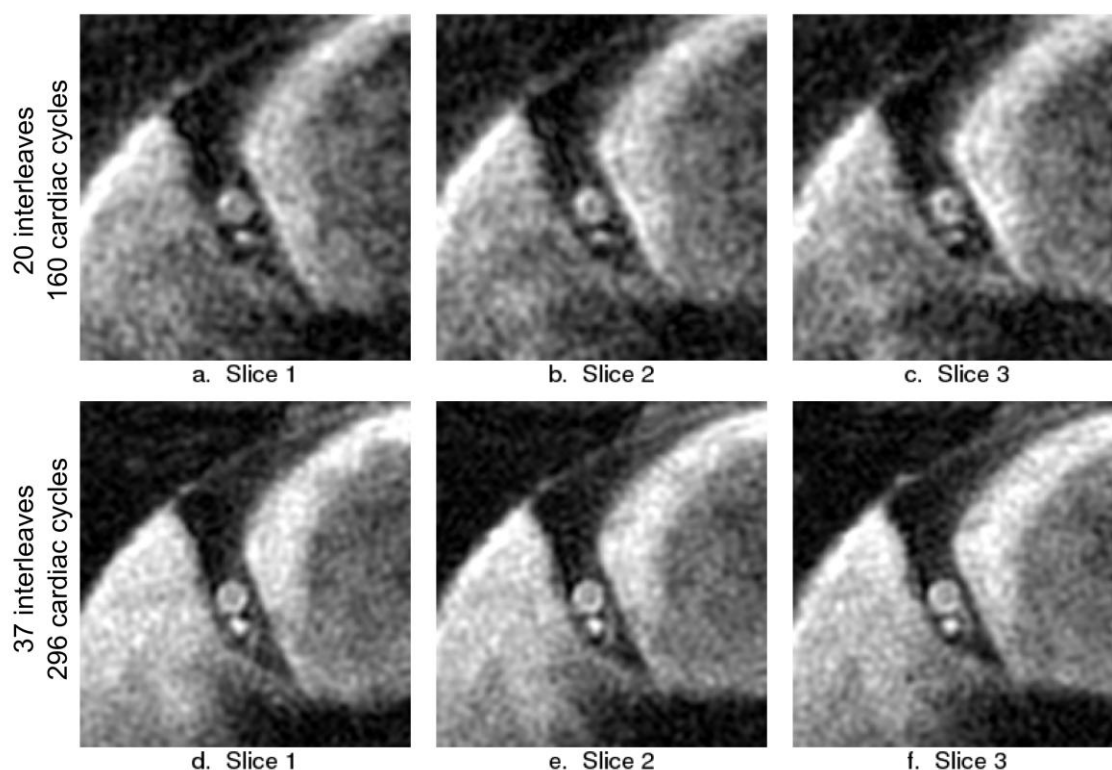
No.	Fig.	Ilvs.	FOV (mm)	Resolution (mm)	Gating	Ilvs./ trigger	Duration (RR)	SNR (range)	CNR (range)
1	3.17	20	220	0.90	1RR	1	160	6.2 (5.7-7.0)	1.9 (1.3-2.6)
		37	390	0.84	1RR	1	296	9.6 (8.7-10.1)	1.7 (1.5-2.0)
2	3.18	37	390	0.84	1RR	1	296	8.4 (7.5-9.1)	2.9 (2.5-3.4)
		37	390	0.84	1RR	2	148	5.3 (5.0-5.7)	2.3 (1.8-2.7)
3	3.19	37	390	0.84	1RR	1	296	14.8 (14.1-15.2)	1.2 (1.2-1.3)
		37	390	0.84	2RR	2	296	10.0 (8.8-11.0)	4.1 (3.2-5.0)
4	3.20	37	390	0.84	1RR	2	148	4.5 (3.8-5.0)	3.6 (3.2-4.1)
		75	390	0.57	1RR	2	300	2.9 (2.7-3.2)	2.8 (2.4-3.2)
5	3.21	75	390	0.57	1RR	2	300	4.1 (3.8-4.7)	2.3 (1.7-2.9)
		75	390	0.57	2RR	2	600	5.1 (4.9-5.2)	3.5 (2.7-3.9)
6	3.22	75	570	0.70	1RR	2	300	9.4 (9.0-9.9)	0.5 (-0.1-1.1)
		75	570	0.70	2RR	2	600	7.5 (7.1-7.8)	5.9 (5.1-6.3)

No. – comparison number**Fig.** – corresponding figure**Ilvs.** – number of interleaves in the spiral trajectory**FOV** – field of view (in both in-plane directions)**Resolution** – in-plane resolution in both directions**Gating** – cardiac gating: either every RR-interval (1RR gating) or every other cardiac cycle (2RR gating).**Ilvs./trigger** – the number of spiral interleaves acquired after every cardiac trigger**Duration** – the total duration of the acquisition without navigator gating**SNR** – measured SNR of the coronary vessel wall, averaged over the 3 contiguous slices shown in the corresponding figure, quoted with the range of SNR values obtained in the 3 slices.**CNR** – measured CNR of the coronary vessel wall – coronary lumen, averaged over the 3 contiguous slices shown in the corresponding figure, quoted with the range of CNR values obtained in the 3 slices.**Comparison 1: 20 interleaves vs. 37 interleaves – increasing the field of view**

Figure 3.17 compares 3 contiguous slices from a 3D volume acquired with the 20 interleave spiral trajectory (as described in table 3.2: in-plane resolution 0.9x0.9mm, FOV 220x220mm, acquisition duration 160 RR-intervals (RR)) with a similar acquisition using redesigned spiral trajectories with

37 interleaves (in-plane resolution 0.84x0.84mm, FOV 390x390mm, acquisition duration 296RR). The CNR is little changed between the acquisitions (mean 1.9 vs. 1.7 for the 20 and 37 interleave trajectories respectively) and the vessel wall/lumen boundary is poorly delineated in both. The average SNR however, was increased by a factor of ~ 1.5 in the 37 interleave acquisition (9.6 vs. 6.2 in the 20 interleave acquisition) and the resulting images appear clearer with visually improved definition of the outer edge of the vessel wall and myocardium.

Figure 3.17: Example images from comparison 1



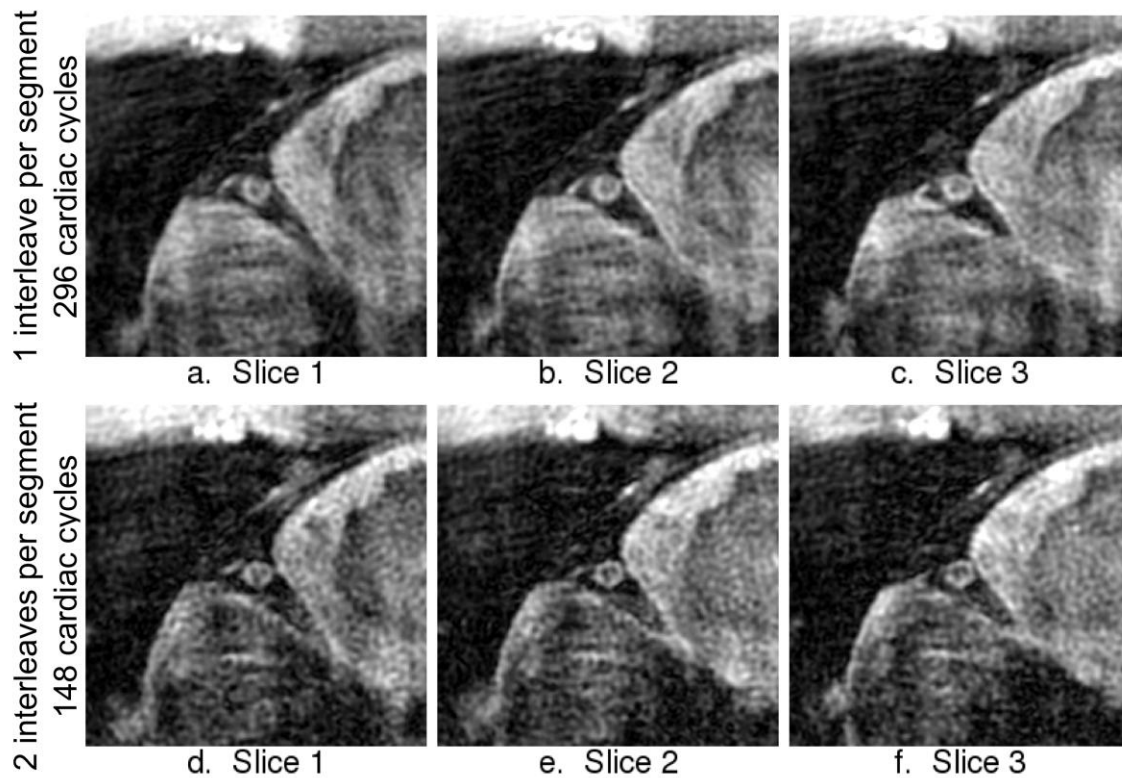
Three contiguous slices from a high resolution volume acquired with the original 20 interleave spiral trajectory (in-plane resolution 0.90x0.90mm, FOV 220x220mm, 1RR gating, 1 spiral interleave per trigger, acquisition duration 160RR – parameters modified between the acquisitions are underlined) (a – c) and from a volume acquired with a 37 interleave spiral trajectory (in-plane resolution 0.84x0.84mm, FOV 390x390mm, 1RR gating, 1 spiral interleave per trigger, acquisition duration 296RR) (d – f). The mean SNR was greater in the 37 interleave acquisition at 9.6, compared to 6.2 in the 20 interleave acquisition. The mean CNR was similar in both acquisitions, at 1.7 and 1.9 for the 37 and 20 interleave acquisition respectively.

Comparison 2: 1 interleave per cardiac cycle vs. 2 interleaves per cardiac cycle – increasing imaging efficiency

In one study of 201 patients, the average rest period of the RCA was 123 ± 60 ms, with a range of 20-396ms (Jahnke et al., 2006). While short acquisition windows, such as those used here (10ms), positioned within the centre of a larger rest period allow for variations in RR-interval, in the vast majority of subjects this results in a large proportion of the rest period being wasted and, hence, a poor imaging efficiency. In this comparison the sequence was modified to acquire two interleaves

of the high resolution spiral trajectory per RR-interval, one immediately after the other (phase encode loop within spiral interleave loop). The flip angle of the first binomial RF pulse was reduced to 45° in order to maintain signal between the first and second interleave (Botnar et al., 2001). This results in an expected reduction in SNR by a factor of 0.71 and an increased high resolution acquisition window of 30ms. Figure 3.18 shows example images from a comparison between two acquisitions, both using the same 37 interleave spiral trajectory (in-plane resolution $0.84 \times 0.84 \text{ mm}$, FOV $390 \times 390 \text{ mm}$), but the first (a – c) acquired one interleave per RR-interval (acquisition duration 296 RR) and the second (d – f) acquired two interleaves per RR-interval (acquisition duration 148 RR). While the images acquired with two interleaves per RR-interval display a loss of SNR (by a factor of 0.63) as expected, visually there are no additional cardiac motion related artefacts in this example (the rest period was 187ms in this subject). However, chest wall ghosting artefacts (as discussed in section 3.c.iv) are present in both images.

Figure 3.18: Example images from comparison 2

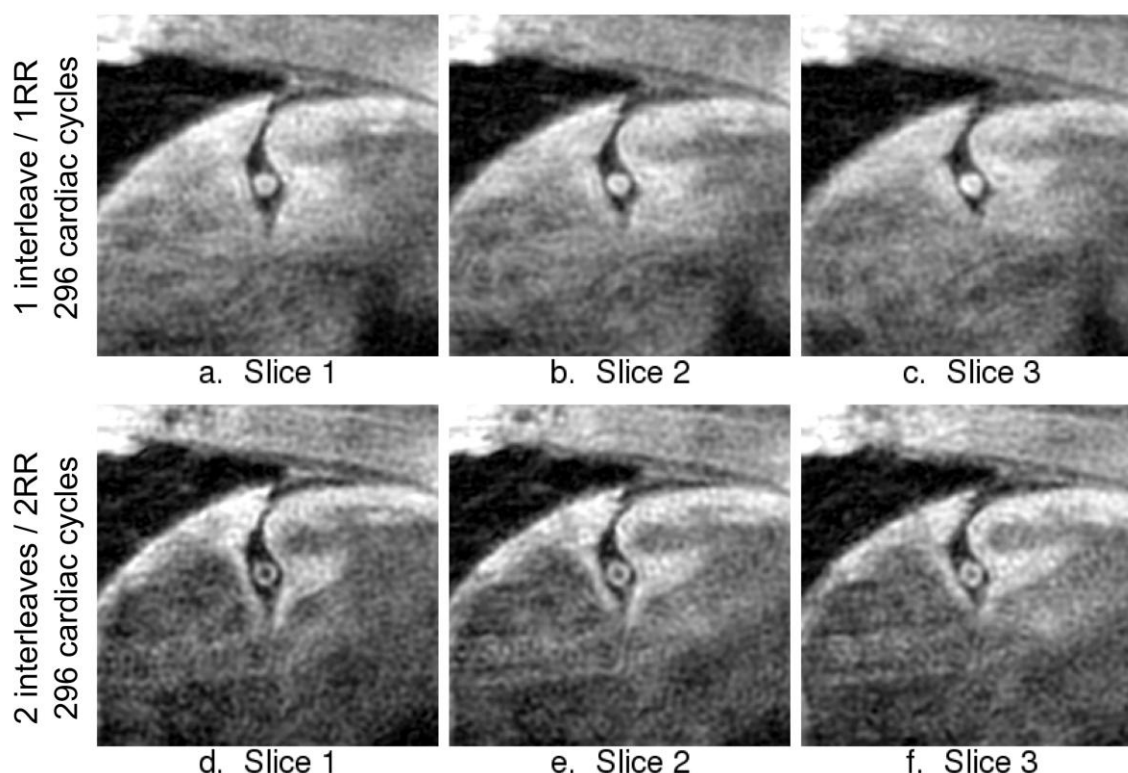


Three contiguous slices from a high resolution volume acquired with the 37 interleave spiral trajectory (in-plane resolution $0.84 \times 0.84 \text{ mm}$, FOV $390 \times 390 \text{ mm}$, 1 RR gating) using one interleave per RR-interval (acquisition duration 296 RR) (a) – (c) and two interleaves per RR-interval (acquisition duration 148 RR) (d) – (f). As expected, the mean SNR was greater in the acquisition with one interleave per RR-interval than in the acquisition with two interleaves per RR-interval (8.4 vs. 5.3 respectively). The mean CNR was 2.9 in the acquisition with one interleave per RR-interval and 2.3 in the acquisition with two interleaves per RR-interval.

Comparison 3: 1 interleave every RR-interval vs. 2 interleaves every 2 RR-intervals – a comparison of acquisitions with equivalent durations

As observed in comparison 2, acquiring a second spiral interleave every RR-interval results in a loss of SNR. Triggering the acquisition on alternate R-waves (2RR gating) results in an increase in SNR, by a factor of approximately 20% (Botnar et al., 2000a), when compared to gating 1RR gating. Hence, acquiring two interleaves every other RR-interval results in a theoretical loss of SNR by a factor of 0.85 relative to acquiring one interleave every RR-interval, compared to a loss of SNR by a factor of 0.71 between acquiring one interleave every RR-interval and acquiring two interleaves every RR-interval. Figure 3.19 shows example images from a comparison of two acquisitions using the 37 interleave acquisition scheme described in comparison 1 and comparison 2 (in-plane resolution 0.84x0.84mm, FOV 390x390mm, acquisition duration 296RR); the first acquisition (a – c) with one interleave acquired every RR-interval (1RR gating) and the second acquisition (d – f) with two interleaves acquired every other RR-interval (2RR gating). The dark blood reinversion time was modified from 400ms for 1RR gating to 625ms for 2RR gating (optimal for a heart rate of 60BPM) to account for the increased recovery of the longitudinal magnetisation between double inversion dark blood preparations (see section 1.e.ii.1). Both acquisitions were obtained in 296 cardiac cycles. As expected, the SNR in the acquisition with two interleaves every other RR-interval was less than that in the acquisition with one interleave every RR-interval. However, the loss of SNR was greater than expected (10.0 vs. 14.8, a factor of 0.68). In contrast, the CNR of the acquisition with two interleaves every other RR-interval was much greater than in the acquisition with one interleave every RR-interval (4.1 vs. 1.2) and the vessel wall is more clearly delineated. The improvements in CNR are the result of improved blood signal suppression when using 2RR gating which is more robust to changes in RR-interval. There were also small inaccuracies in the inversion times used which were more detrimental to the 1RR gated acquisitions; the average RR-interval was 1135ms which results in an optimal inversion time of 438ms for 1RR gating (400ms was used) and 663ms for 2RR gating (625ms was used). No cardiac motion artefacts were observed as a result of acquiring two spiral interleaves during the rest period (196ms in this subject).

Figure 3.19: Example images from comparison 3

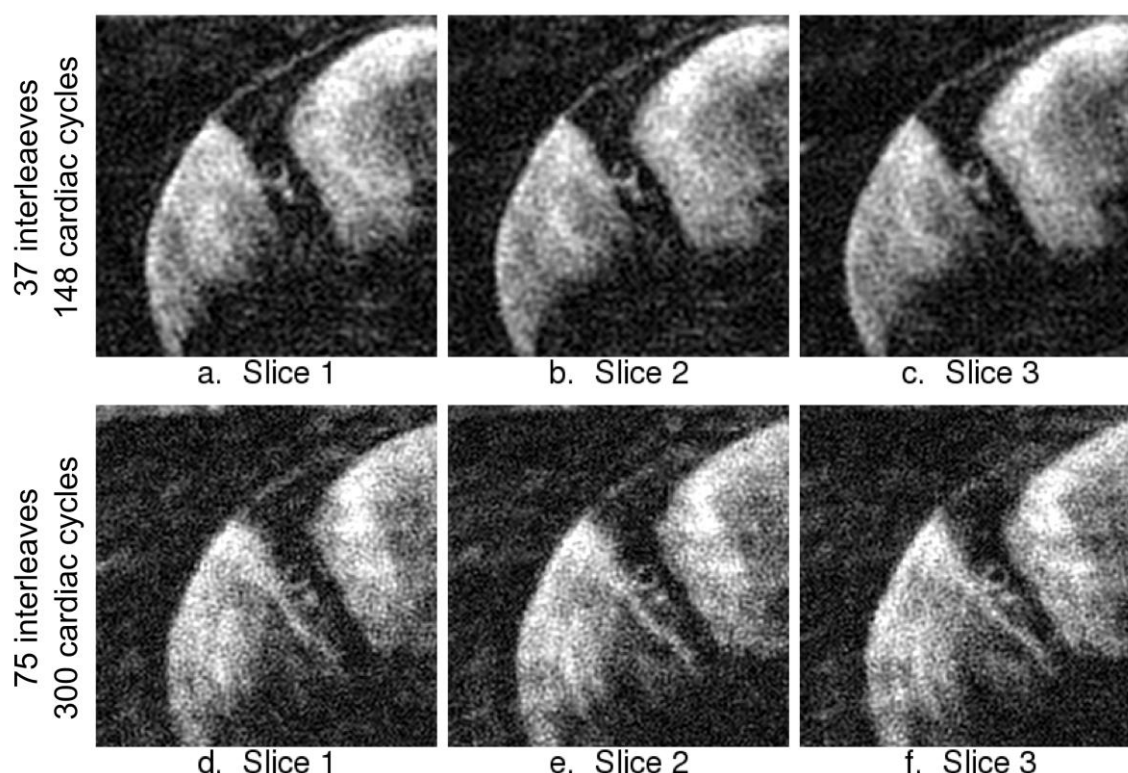


Three contiguous slices from a high resolution volume acquired with the 37 interleave spiral trajectory (in-plane resolution $0.84 \times 0.84 \text{ mm}$, FOV $390 \times 390 \text{ mm}$, acquisition duration 296 RR-intervals) using one interleave every RR-interval (1 interleave per trigger, 1RR gating (a) – (c)) and two interleaves every other RR-interval (2 interleaves per trigger, 2RR gating (d) – (f)). The mean SNR was greater in the acquisition with one interleave every RR-interval than in the acquisition with two interleaves every other RR-interval (14.8 vs. 10.0 respectively). In contrast, the mean CNR was less in the acquisition with one interleave every RR-interval (1.2 vs. 4.1).

Comparison 4: 75 interleaves vs. 37 interleaves – increasing in-plane resolution

The increased SNR that was obtained by increasing the FOV in comparison 1, may be partially exchanged for increased in-plane resolution. Figures 3.20 shows example images from a comparison between the 37 spiral interleave trajectory (a – c) used in the previous three comparisons (in-plane resolution $0.84 \text{ mm} \times 0.84 \text{ mm}$, FOV $390 \times 390 \text{ mm}$, acquisition duration 148RR) and an interleaved spiral trajectory with 75 spiral interleaves (in-plane resolution $0.57 \times 0.57 \text{ mm}$, FOV 390 mm , acquisition duration 300RR) (d – f). In both sequences two spiral interleaves were acquired every RR-interval (1RR gating). The increase in resolution was accompanied by an associated loss of SNR (4.5 vs. 2.9, a factor of 0.64 less) and CNR (3.6 vs. 2.8, a factor of 0.78 less). While blood suppression appears to have been effective for both trajectories and the vessel wall is seen in both images, image quality was poor for the 75 interleave trajectory as a result of the reduced SNR. This example, and others not shown, suggest that at 1.5T with the spiral acquisition and receive coils available for this work, the combination of acquiring two spiral interleaves per RR-interval at $0.57 \times 0.57 \text{ mm}$ in-plane resolution results in insufficient SNR for reliable coronary artery vessel wall imaging.

Figure 3.20: Example images from comparison 4



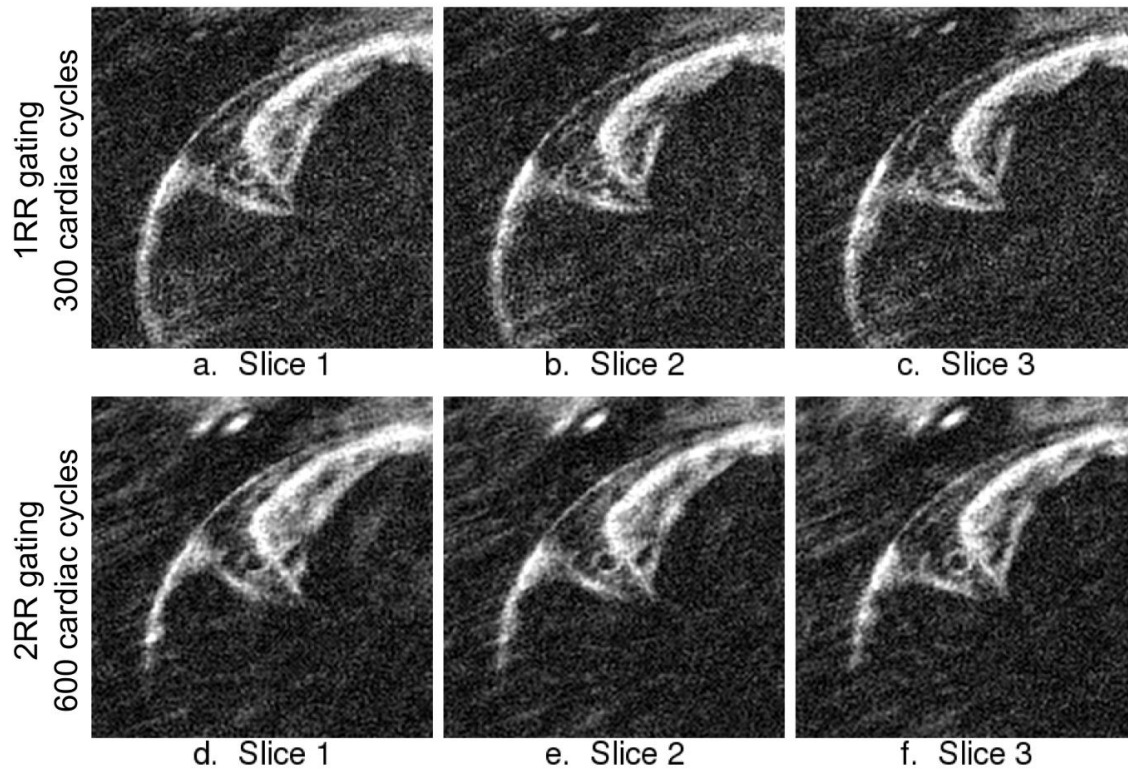
Three contiguous slices from a high resolution volume acquired with the 37 interleaves spiral trajectory (in-plane resolution 0.84x0.84mm, FOV 390x390mm, 1RR gating, 2 spiral interleaves per trigger, acquisition duration 148RR – parameters modified between the acquisitions are underlined) (a – c) and from a volume acquired with a higher resolution 75 interleaves spiral trajectory (in-plane resolution 0.57x0.57mm, FOV 390x390mm, 1RR gating, 2 spiral interleaves per trigger, acquisition duration 300RR) (d – f). The mean SNR was greater in the 37 interleaves acquisition at 4.5, compared to 2.9 in the 75 interleaves acquisition. The mean CNR was 3.6 in the 37 interleaves acquisition compared to 2.8 in the 75 interleaves acquisition.

Comparison 5: 1RR vs. 2RR gating at 0.57mm in-plane resolution – increasing SNR and robustness to heart rate variations

The SNR achieved by imaging at an in-plane resolution of 0.57 x 0.57mm in comparison 4 was insufficient for reliable coronary vessel wall imaging. As discussed in comparison 3, SNR may be improved by using 2RR gating, which also results in increased robustness to variations in RR-interval. Figure 3.21 shows example images acquired using the 75 spiral interleaves acquisition described in comparison 4 (in-plane resolution 0.57 x 0.57mm, FOV 390 x 390mm, two spiral interleaves per cardiac trigger) acquired with 1RR gating (acquisition duration 300RR, (a) – (c)) and with 2RR gating (acquisition duration 600RR, (d) – (f)). As in comparison 3, the dark blood inversion time was increased from 400ms with 1RR gating to 625ms for 2RR gating to compensate for the increased recovery of the longitudinal blood magnetisation between sequence repeats. The use of 2RR gating resulted in the expected 20% increase in SNR over 1RR gating (2RR gating 5.1 vs. 1RR gating 4.1, a factor of 1.24 increase). The CNR was also increased with 2RR gating (from 2.3 to

3.5). While SNR and vessel wall visibility is improved by using 2RR gating, SNR was not sufficient for reliable imaging in either case.

Figure 3.21: Example images from comparison 5



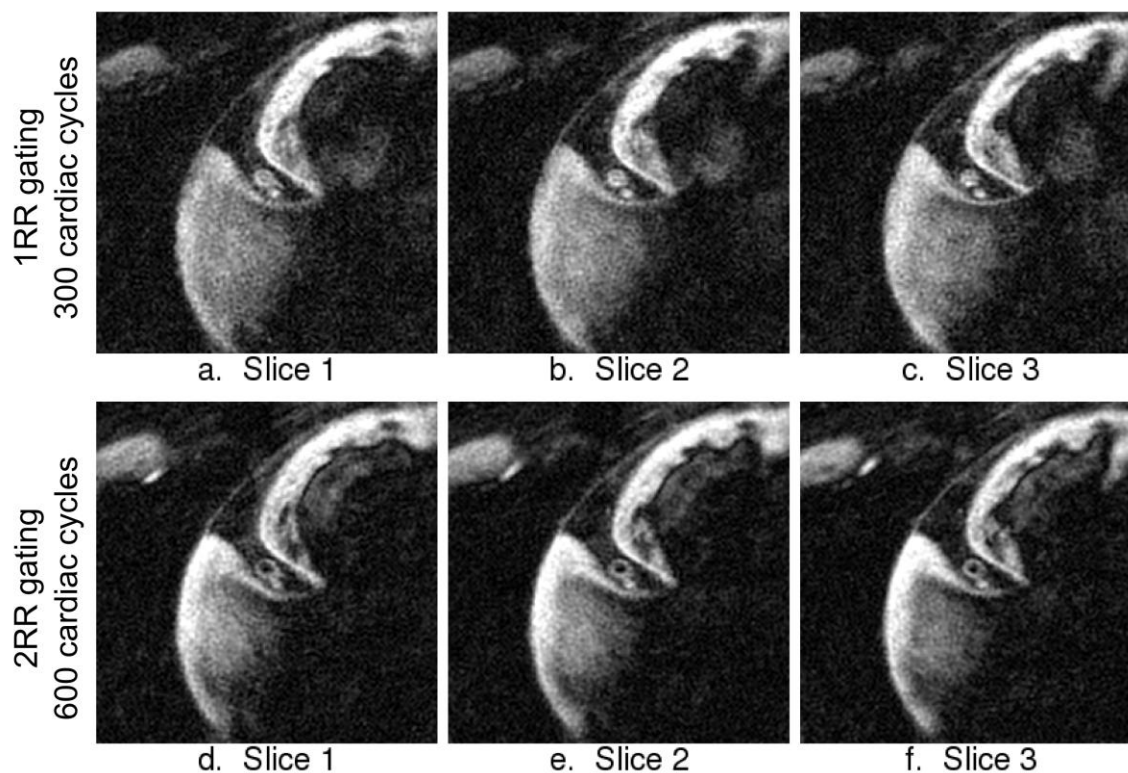
Three contiguous slices from a high resolution volume acquired with the 75 interleave spiral trajectory (in-plane resolution $0.57 \times 0.57 \text{ mm}$, FOV $390 \times 390 \text{ mm}$, 2 spiral interleaves per trigger) using 1RR gating (acquisition duration 300RR, (a) – (c)) and 2RR gating (acquisition duration 600RR (d) – (f)). The mean SNR was greater in the 2RR gated acquisition at 5.1, compared to 4.1 in the 1RR gated acquisition. The mean CNR was also higher in the 2RR gated acquisition at 3.5, compared to 2.3 in the 1RR gated acquisition.

Comparison 6: 1RR vs. 2RR gating at 0.70 mm in-plane resolution – Compromising on image resolution

While imaging at the highest resolution possible is desirable, imaging techniques must be reliable for the routine assessment of coronary artery vessel wall thickness. Throughout these comparisons, images acquired at $0.84 \times 0.84 \text{ mm}$ in-plane resolution with 37 spiral interleaves regularly demonstrated reasonable image quality, while those at $0.57 \times 0.57 \text{ mm}$ with 75 spiral interleaves did not. In this final comparison, images were acquired with the 75 interleave spiral trajectory and 2 interleaves per trigger, but with reduced spatial resolution (in-plane resolution $0.70 \times 0.70 \text{ mm}$, FOV $570 \times 570 \text{ mm}$). Figure 3.22 shows example images (from the same subject imaged in figure 3.17 and 3.20, RR-interval duration 1300ms in this example) acquired using this trajectory with 1RR gating (acquisition duration 300RR, (a) – (c)) and 2RR gating (acquisition duration 600RR, (d) – (f)). The vessel wall is not clearly delineated from the lumen in the 1RR gated images and this is reflected in the poor CNR measurements, whereas the vessel wall is clearly

delineated in the 2RR gated images and the CNR is higher (0.5 in the 1RR gated images vs. 5.9 in the 2RR gated images). Contrary to theory, the measured SNR of the 1RR gated acquisition was higher than that of the 2RR gated acquisition (9.4 vs. 7.5), which may be attributed to the poor blood suppression in the 1RR gated acquisition. This example demonstrates the superior performance of 2RR gating over 1RR gating for MR coronary vessel wall imaging. It also demonstrates the image quality available using the 75 interleave spiral trajectory at an in-plane spatial resolution of $0.7 \times 0.7 \text{ mm}$, which is used throughout the rest of this thesis.

Figure 3.22: Example images from comparison 6



Three contiguous slices from a high resolution volume acquired with the 75 interleave spiral trajectory and reduced resolution (in-plane resolution $0.70 \times 0.70 \text{ mm}$, FOV $570 \times 570 \text{ mm}$, 2 spiral interleaves per trigger) using 1RR gating (acquisition duration 300RR, (a) – (c)) and 2RR gating (acquisition duration 600RR (d) – (f)). The mean SNR was greater in the 1RR gated acquisition at 9.4, compared to 7.5 in the 2RR gated acquisition. The mean CNR was higher in the 2RR gated acquisition at 5.9, compared to 0.5 in the 1RR gated acquisition.

3.d.iii Discussion

The acquisition performed in comparison 6, with the parameters shown in table 3.4, was chosen as a compromise between imaging resolution, SNR and acquisition efficiency. The loss of SNR caused by acquiring two spiral interleaves every cardiac trigger (every RR-interval for 1RR gating and every other RR-interval for 2RR gating) when compared to one spiral interleave every cardiac trigger could have theoretically been exchanged for a reduction in FOV by a factor of 2 and an equivalent reduction in the number of spiral interleaves. However, the large 570mm FOV used in comparison 6 moves the characteristic spiral artefacts away from the anatomy of interest into the surrounding empty part of the FOV. The high number of spiral interleaves is also thought to have

an effect similar to that of the averaging-like properties of radial acquisitions (Spuentrup et al., 2004) – the centre of k-space is sampled repeatedly, resulting in a reduced susceptibility to inter-leaf motion. There is, however, an additional complication of these large FOV spiral acquisitions; in order that the FOV is fully sampled, the spacing between the points on the spiral readout must fulfil the criteria:

$$\Delta t = \frac{2\pi}{\gamma GL} \quad 3.6$$

where Δt is the time between points on the spiral (the dwell time), γ is the gyromagnetic ratio (in rad T⁻¹), G is the gradient strength and L is the size of one edge of the FOV. Therefore, for the peak gradient strength of 33mT m⁻¹ achieved in the high resolution spiral designs, at a FOV of 390mm (used in the 37 interleave spiral acquisitions at 0.84x0.84mm in-plane resolution) or 570mm (used in the 75 interleaves spiral acquisition at 0.70x0.70mm in-plane resolution) the maximum dwell time per point should be 1.8 μ s or 1.2 μ s respectively. The actual dwell time used in this thesis of 2.5 μ s corresponds to a maximum FOV of 285mm. This inadequate sampling of k-space along the spiral readout is only present once the gradient strength exceeds 24mT m⁻¹ or 16.5mT m⁻¹ (for 390mm FOV and 570mm FOV respectively). The expected result of this inadequate sampling rate is high frequency aliasing at the edges of the FOV. Figure 3.23 demonstrates images acquired with the 37 interleave spiral trajectory described in comparison 1 in section 3.d.ii at a FOV of 390x390mm, both with the standard 2.5 μ s dwell time used elsewhere in this thesis and 1.0 μ s sampling, which corresponds to a maximum FOV of 712mm. Additional artefact is observed in the images with 2.5 μ s dwell time, although it is mainly confined to the edges of the FOV and the effect is minimal in images with the intensity windowed to a typical range (figure 3.23 (a) and (b)). However, the reduction in sampling time leads to a proportionate increase in the number of acquired data points and therefore reconstruction time. For this reason, and because of the minimally detrimental effect of the artefact, all other spiral imaging in this thesis was performed with 2.5 μ s sampling. However, future work should investigate this further.

There are a number of limitations to this work. Firstly, these were head-to-head comparisons between sequence parameters in example subjects and not full comparisons in sufficient numbers of subjects to detect significant differences between SNR and CNR values measured. This enabled a larger number of sequence parameters to be investigated in a relatively short timescale. The efficacy of the technique after these developments is further assessed with more subjects in subsequent chapters (see chapter 6 in particular). Secondly, the method of measuring SNR and CNR was not ideal, but was a rapid and simple method of providing some quantitative comparison between sequence parameters. Thirdly, acquisitions were assumed to be identical apart from the modified imaging parameters; changes in heart rate and/or respiratory motion between the acquisitions were possible but were not compared. Finally, while the acquired resolution was increased (from 0.90mm to 0.57mm to 0.70mm), insufficient correction for respiratory motion will

degrade the point spread function and therefore, the effective resolution (Wang et al., 1995b), which was not evaluated.

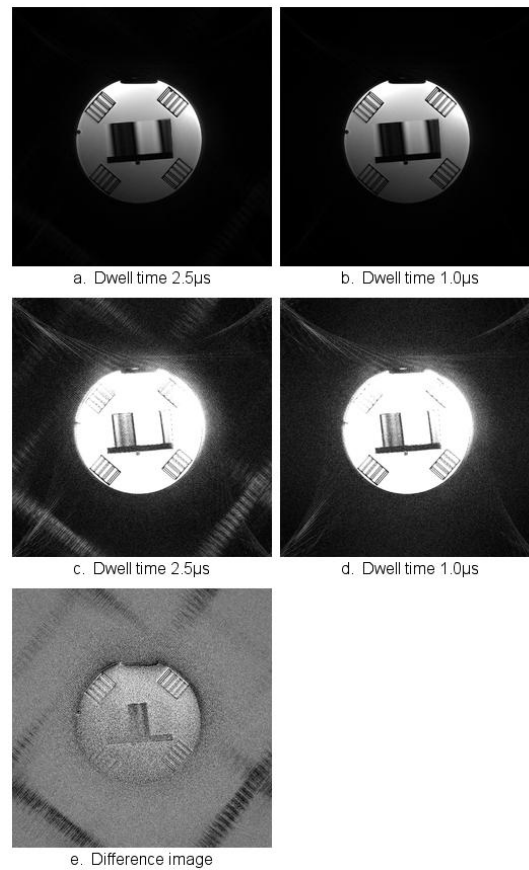
The majority of previous MR coronary vessel wall imaging studies have gated acquisitions to every other cardiac cycle and while several studies have gated every cardiac cycle (Keegan et al., 2007, Abd-Elmoniem et al., 2010) the reduced SNR and increased susceptibility to variations in RR-interval suggest that 2RR gating may be worth the associated factor of two penalty in acquisition duration. A more complete comparison of 1RR vs. 2RR gating is provided in chapter 6 using *in-vivo* coronary vessel wall thickness.

Table 3.4: Imaging parameters used for the basic high resolution acquisition

Parameter	Default value
Navigator gating	Normal tidal range $\pm 10\text{mm}$
Cardiac gating	2RR
Dark blood inversion time	625ms
Acquisition duration at 100% respiratory efficiency	600 RR
FOV	570mm
Number of spiral interleaves	75
In-plane resolution	0.70x0.70mm
Spiral interleaves acquired per trigger	2
Flip angle of binomial water excitation pulse	45°, 90°
Through plane phase encode steps acquired (reconstructed)*	8 (16)
Slab thickness*	24mm
Through plane resolution acquired (reconstructed)*	3.0mm (1.5mm)
Spiral readout duration*	10ms
Dwell time per point*	2.5 μs
Spiral readout points*	4096

* - These parameters were not altered from the original implementation described in table 3.2.

Figure 3.23: The effect of an insufficient sampling rate in the spiral readouts



Images acquired of a water filled resolution phantom with a 37 interleave spiral trajectory at 390x390mm FOV, corresponding to a maximum dwell time of 1.8 μ s. Images acquired at 2.5 μ s dwell time (a and c) demonstrate additional artefacts when compared to those acquired with 1 μ s sampling time (b and d). The additional artefact is more pronounced in the brightened images (c and d). The artefact is mainly restricted to the outside of the FOV, as highlighted in the difference image (d). The edges of the phantom also appear in the difference image (d) due to small differences in timings of the sampling points.

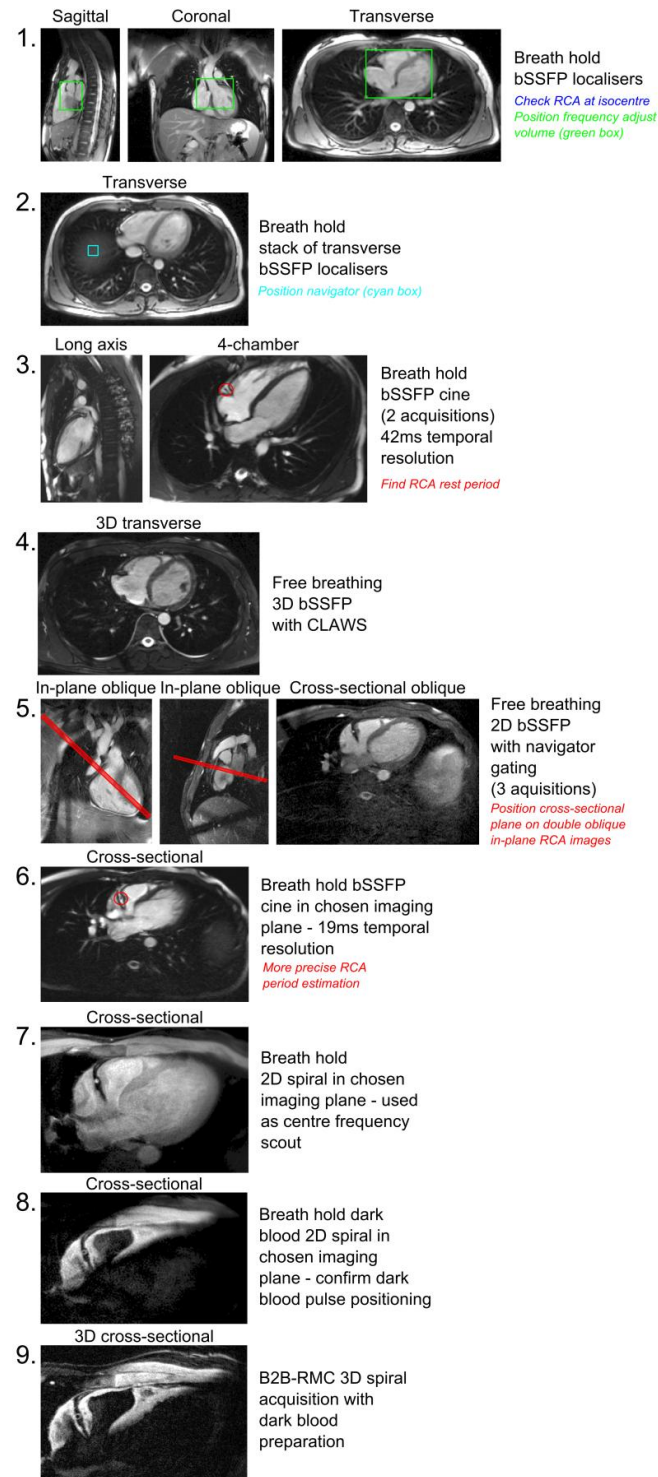
3.e Development of an optimal coronary artery vessel wall imaging protocol

MR coronary vessel wall imaging is challenging. While the improved MR coronary vessel wall imaging sequence with B2B-RMC described in sections 3.c and 3.d has subsequently demonstrated reliable imaging of the coronary artery wall (see chapters 6 and 7), the penalty for a poorly positioned imaging volume or an incorrectly timed acquisition window is a wasted acquisition of up to 600 RR-intervals. In addition, the retrospective reconstruction of these studies means that an acquisition is not known to have failed until the subject is out of the scanner and reacquisition is not possible. Therefore, the need for an efficient and effective imaging protocol is high.

During the work contributing to this thesis, the following 10 stage protocol (also shown in figure 3.24, which is also available in the supplementary material) was developed, for planning 3D spiral coronary artery wall acquisitions with B2B-RMC:

1. Breath-hold bSSFP localiser images to confirm that the target anatomy was located at the region of highest B_0 (the main magnetic field) homogeneity at the centre of the magnet. The subject was repositioned and this step was repeated if necessary.
2. Stack of transverse breath-hold 2D bSSFP images covering the superior part of the liver in order to localise the dome of the right hemi-diaphragm for navigator gating.
3. A breath-hold bSSFP cine acquisition (temporal resolution 42ms, reconstructed to 20 frames per RR-interval) is acquired in the vertical long axis. An identical cine acquisition in the four-chamber view is then planned from the previous one and used to visually determine the approximate start and duration of the RCA rest period. Subsequent acquisitions were performed in this subject specific RCA rest period.
4. Whole heart navigator gated 3D bSSFP coronary angiography study using the CLAWS technique for improved respiratory efficiency. These acquisitions were performed at $1.3 \times 1.3 \times 3.0\text{mm}$ acquired resolution and used to determine the path of the proximal coronary arteries.
5. Navigator gated (5mm ARA window) 2D bSSFP coronary angiography studies planned from the 3D volume acquired in (4). These studies were performed at $1.3 \times 1.3 \times 5\text{mm}$ resolution. Typically 3 such acquisitions were performed: an initial acquisition of the coronary artery in-plane; a second in-plane coronary artery acquisition perpendicular to and planned from the first; and a cross-sectional acquisition in a straight section of the artery, perpendicular to both of the previous two acquisitions, used to confirm the suitability of this plane for subsequent imaging.
6. A breath-hold bSSFP cine acquisition in the selected cross-sectional imaging plane at increased temporal resolution (19ms acquired, 64 frames/RR-interval reconstructed, spatial resolution $1.7 \times 1.7 \times 7.0\text{mm}$), in order to obtain a more accurate assessment of the start and duration of the cardiac rest period for the targeted section of coronary artery. Subsequent imaging was performed in this rest period.
7. A series of breath-hold 2D spiral acquisitions with binomial water selective excitation in the selected imaging plane were performed with a succession of centre frequency offsets (typically at intervals of 20Hz). Typically three such acquisitions were performed and used to accurately determine the optimal centre frequency for the subsequent spiral acquisitions. While all acquisitions from (4) onwards were performed at a centre frequency automatically determined from a shim region carefully defined around the heart, this iterative process was found to be of benefit when acquiring spiral images. Subsequent acquisitions were performed at this optimised centre frequency.
8. A breath-hold 2D spiral acquisition (as in 7) with slab selective dark blood preparation and 1RR gating. This acquisition was used to confirm the performance of the dark blood pulse and, in particular, the location of the user-defined dark blood reinversion pulse which was positioned based on the 2D in plane bSSFP images acquired in (5) and the high resolution cine acquisition (6). The reinversion slab was positioned to avoid the in-flowing blood in the aorta and left ventricle whilst ensuring that the coronary artery in the plane of interest remained within the reinversion slab throughout the cardiac cycle. It is also important to minimise the section of chest wall signal reinverted in order to avoid artefact, as described in section 3.c.iv.
9. Finally, the full 3D coronary artery vessel wall imaging study with B2B-RMC acquisition was performed.

Figure 3.24: The optimised protocol for RCA vessel wall imaging with B2B-RMC

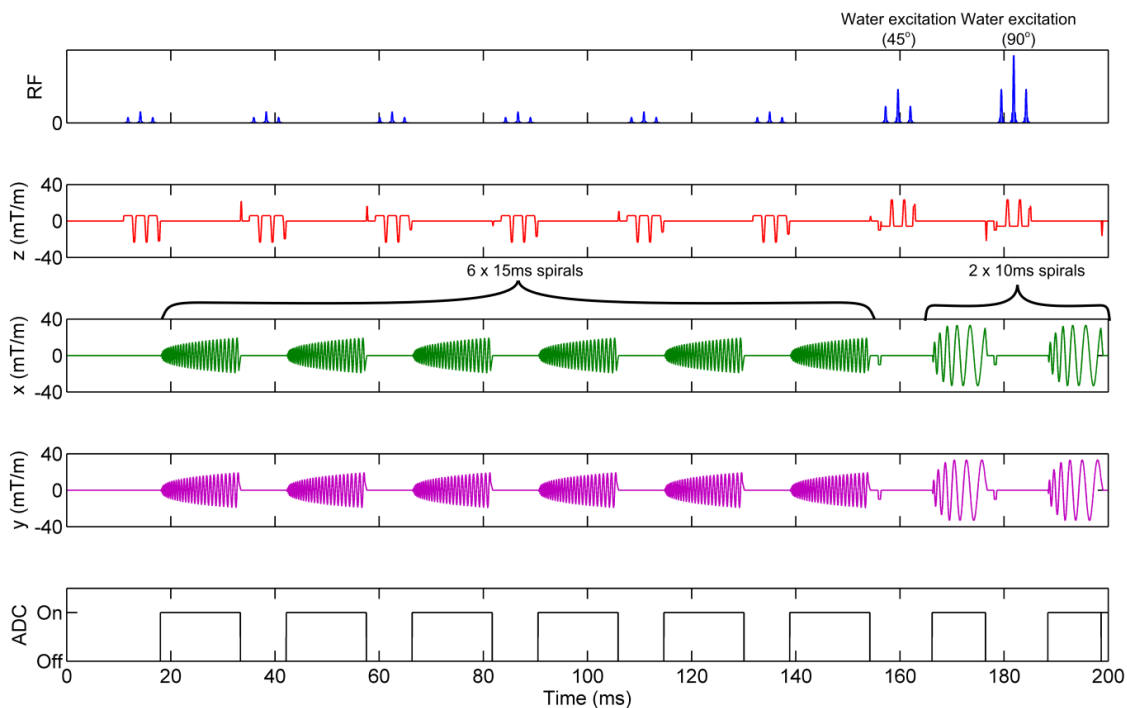


An optimised imaging protocol for planning the B2B-RMC 3D spiral acquisition for cross-sectional coronary artery vessel wall imaging was developed. Key planning stages include: the second breath hold bSSFP cine acquisition (step 6) which is used to obtain a more accurate assessment of the coronary rest period in chosen imaging plane; the multiple breath-hold 2D spiral acquisitions (step 7) used as a centre frequency scout; and the breath hold 2D spiral acquisition with dark blood preparation in order to check the positioning of the slab selective reinversion pulse. This figure is also available electronically in the supplementary material.

3.f The modified B2B-RMC sequence

Following the work in this chapter the original sequence shown in figure 3.1 was modified. This modified sequence is shown in figure 3.25 and the parameters are given in table 3.1 and 3.4. The modified sequence was used for all acquisitions in the remainder of this thesis, except where stated. Acquisitions are typically gated to exclude data acquired at extreme respiratory positions ($>\pm 10\text{mm}$ outside the tidal range) (3.c.iii). Low resolution acquisitions are performed at $4.8 \times 4.8\text{mm}$ in-plane resolution using 15ms spiral readouts with $6/8\text{ths}$ through plane partial Fourier (3.c.i). High resolution acquisitions were performed with 75 spiral interleaves over a FOV of $570 \times 570\text{mm}$ with $0.7 \times 0.7\text{mm}$ in-plane resolution and two spiral interleaves per cardiac trigger (3.d.ii). Dark blood coronary artery vessel wall acquisitions were typically gated to every other R-wave. Images were reconstructed and processed using the tools described in section 3.b.ii.

Figure 3.25: The modified B2B-RMC imaging sequence (imaging section only)



The imaging sequence shown in figure 3.1 was modified to incorporate the longer low resolution spirals (15ms vs. 10ms), the through-plane partial Fourier encoding, the increased high resolution spiral resolution and FOV, and the acquisition of two high resolution spiral interleaves per trigger. The associated imaging parameters are described in table 3.1 (low resolution) and 3.4 (high resolution).

4. An accurate and reproducible respiratory motion phantom for coronary artery imaging

4.a Motivation

An accurate and reproducible respiratory motion phantom enables validation of motion detection and correction algorithms in a controlled environment. It also allows assessment and comparison of new developments applied to the B2B-RMC technique without the added variability and restrictions on acquisition durations that apply when using human subjects. Such a phantom must be capable of following physiological respiratory traces and other user-defined motion profiles accurately over long durations. The complete system consists of a controlled motor, a rotary to linear motion converter and an object to be imaged (a test object). In this chapter, a complete description of the design and construction of this system is detailed. Subsequently, a series of tests performed with the phantom are presented including validation of the phantom itself and an assessment of the performance of B2B-RMC in various situations is described.

4.b Design and construction

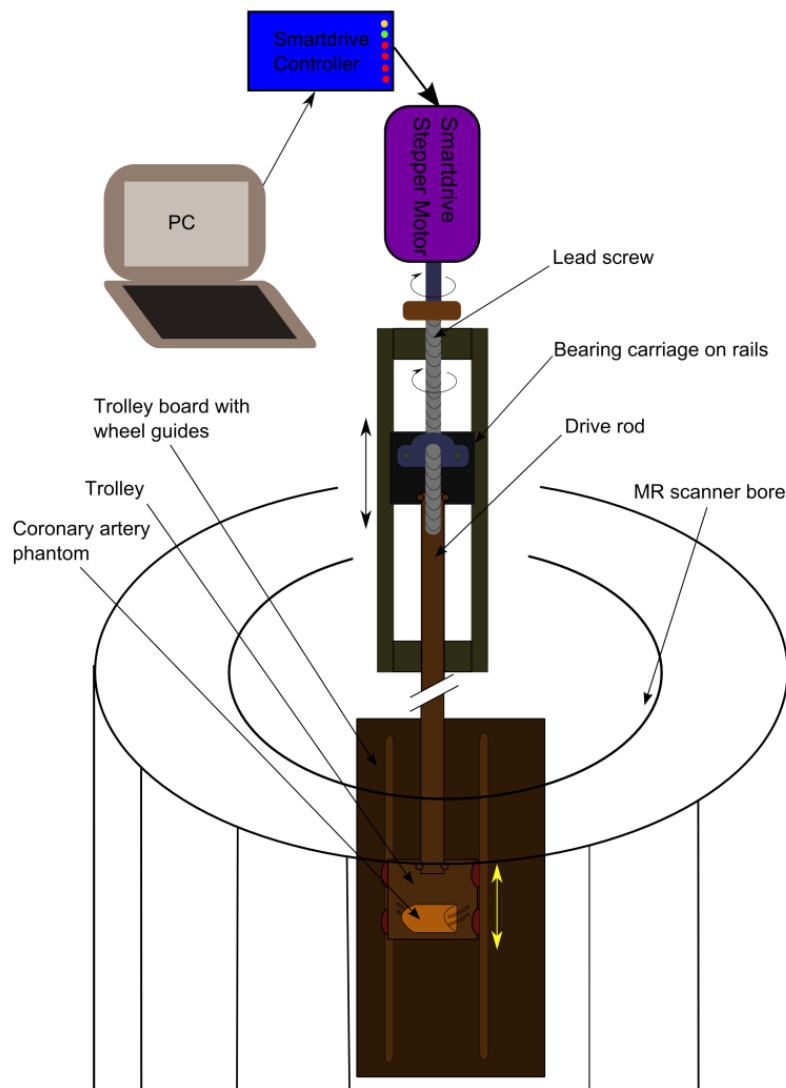
A schematic of the phantom design is presented in figure 4.1 and photographs of the completed phantom are shown in figure 4.2. A stepper motor turns a lead screw which drives a carriage mounted on a rail. In turn the carriage pushes a trolley carrying the test object within the magnet bore. Long drive rods connect the carriage outside the scanner to the trolley within the bore. A discussion of the reasons behind this design is presented here.

A servo motor which is controlled by feedback from a position encoder would be a suitable but costly drive system. Basic stepper motor systems create excessive vibration due to the large rotational step sizes (typically 0.9°) used. Modern microstepping controllers, however, divide each step into a large number of sub-steps, typically 256 (0.004°), enabling smoother motion. Provided they are not used at excessive torque or speed, stepper motors may be used in open loop systems (i.e. without feedback), hence simplifying the design and reducing cost. A SmartDrive Taranis (SmartDrive, Huntingdon, Cambs. UK) microstepping motor was used in this work for its relatively low cost and versatile programming structure.

To convert the rotational motion into linear motion, a lead screw was chosen over a rack and pinion system as the latter would require an additional gearbox which would be more complex and may introduce backlash. Lead screws require mechanical support and introduce more inertia into the system, but are available relatively inexpensively.

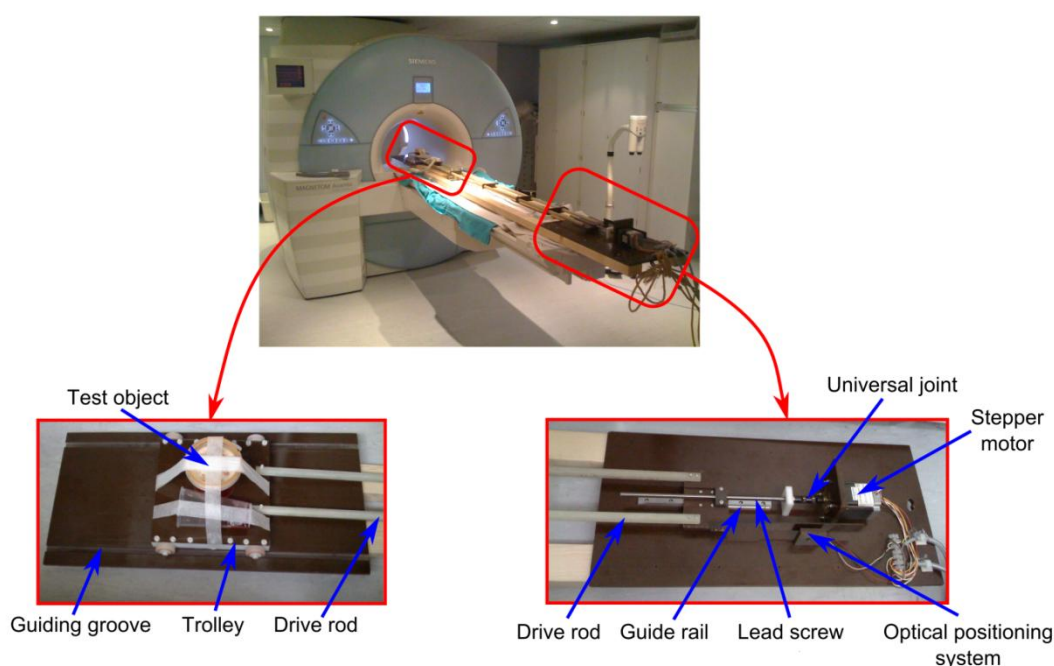
To prevent damage to the system through inadvertent extreme motion, a slotted optical switch was mounted next to the carriage slide and an indicator mounted on the carriage (not shown in figure 4.1). When the carriage is within the normal range of motion the optical beam is broken. The output from the switch is used to stop the carriage moving outside of a safe pre-set range of motion and to set the initial position.

Figure 4.1: A schematic of the basic phantom design



The phantom is driven by a stepper motor which is controlled by a microstepping controller (Smartdrive Taranis) linked to a PC. Rotational motion of the motor is converted into linear motion using a lead screw and a small carriage on rails. Drive rods transfer the linear motion to a trolley holding the test object at the magnet's isocentre. The drive rods are long in order to maintain an adequate distance between the ferromagnetic drive components and the magnet.

Figure 4.2: The completed respiratory motion phantom



The completed phantom set up outside the bore of the magnet (upper) with close ups of: the trolley and basic test objects (left); the drive part of the phantom (right).

The majority of the phantom was constructed from Tufnol, a laminated plastic material which is strong and non-magnetic, but several intricate parts were manufactured in Nylon as it is less brittle. The drive parts were mounted on a sheet of Tufnol. A universal joint was used to couple the motor shaft to the lead screw which was used to drive a ball bearing carriage slide. A pair of Tufnol drive rods were attached to the carriage and brackets were manufactured to maintain constant rod spacing, therefore preventing lateral motion. The drive rods were connected to a trolley sitting in parallel tracks cut into a Tufnol sheet. The rods were of sufficient length to keep the ferromagnetic drive parts out of the magnetic field when the trolley is at the isocentre of the magnet.

Initially, high levels of coherent interference artefacts were observed in the MR images when the phantom was positioned in the scanner with current in the motor windings. This artefact was minimised by earthing the shielding of the phantom's drive and control cables by connecting it to the RF cage of the scanner and by using a small 4 element phased array carotid receive coil placed immediately over the test objects.

4.c Software development

The Taranis microstepping motor controller was programmed via a PC through an RS232 serial port connection using a programming language similar to BASIC. Code was developed to enable the phantom to follow a series of displacements recorded at equal sampling intervals. The code firstly sets the initial phantom position using the optical switch mechanism. It then takes the desired displacements recorded at equal time intervals, which are stored within the program, and

calculates the equivalent velocities. When running, the code updates the velocity at regular time intervals and compares the current displacement to the required displacement at the end of each time interval. Any errors in the displacement are used to update the immediately subsequent velocity accordingly.

The software was written to use displacements recorded at 250ms sampling intervals stored in the controller memory and to use on-the-fly linear interpolation by a factor of 2 and smoothing of the last 6 points using a moving average. At this sampling interval, respiratory traces of around 5min in duration could be stored within the controller. This combination of interpolation and smoothing factors results in smooth motion, which accurately follows the input trace, and may include variations in breathing pattern or respiratory drift.

4.d Construction of realistic test objects

4.d.i Introduction

In order to obtain meaningful results from the respiratory motion phantom, realistic coronary artery and coronary artery wall test objects are required. Such test objects must resemble the anatomy of the RCA and AV groove and be of realistic dimensions in order to demonstrate the loss of image quality due to respiratory motion and to assess the performance of the motion correction technique. Typical coronary artery phantoms previously used in assessing the performance of navigator based techniques (Polzin et al., 1996, Jhooti et al., 1999, Jhooti et al., 2000, Gatehouse et al., 2001, Spuentrup et al., 2002b) consist of curved water filled tubes without the additional surrounding detail that was required in this work. In the only published study describing a coronary vessel wall phantom (Schär et al., 2003), layers of tissue paper soaked in oil or jelly separated by fine adhesive tape, simulating a diseased coronary artery wall (wall thickness 2mm) were wrapped around a hollow plastic tube (diameter 3mm). In this work however, the aim was to replicate a healthy coronary vessel wall and a single layer construction was therefore used.

Spiral acquisitions are particularly prone to artefact related to changes in local magnetic susceptibility, as caused by tissue-air interfaces for example (Delattre et al., 2010). Such susceptibility changes result in a modification of the local resonant frequency and, therefore cause blurring of the image. These local changes in magnetic field also reduce local $T2^*$ values causing signal loss and blurring due to rapid decay of the signal. As a result, the test objects described here were designed to avoid tissue-air interfaces.

4.d.ii Construction materials

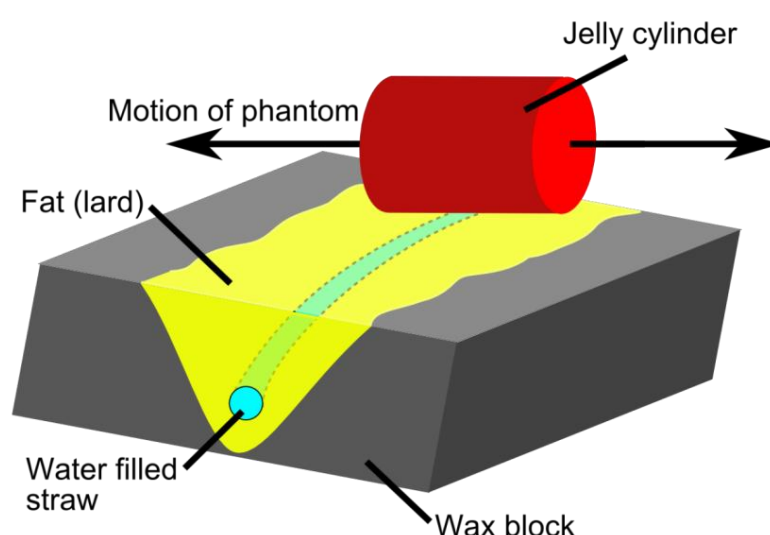
Test objects were primarily constructed from jelly (Hartley's strawberry jelly, The Premier Foods Group, Spalding, UK), lard (Fresh Fields Lard, Matthews Food plc, Ossett, UK) and paraffin wax (Household Candles, Price's Patent Candles Limited, Bedford, UK). Jelly has a high water content and was used with no added water for longevity and stiffness. Lard is made from pure (99.8%) fat, typically extracted from pigs and is solid at room temperature. Paraffin wax is easily moulded or

cast, generates no MR signal and has a magnetic susceptibility similar to that of water (Shmueli et al., 2007).

4.d.iii The coronary artery test object

Figure 4.3 shows the final design of the coronary artery test object. A plastic straw (~3mm diameter) was curved by heating and bending it. The straw was filled with water, plugged at both ends and placed in a V-shaped groove within a wax block. The groove was filled with lard to represent the epicardial fat in the AV groove. A navigator passing through a jelly cylinder on top of the test object was used to monitor the motion. While the straw could have been filled with jelly, the signal from water is higher and the straw's narrow diameter meant that flow within the straw during phantom motion was unlikely.

Figure 4.3: A schematic of the coronary artery test object



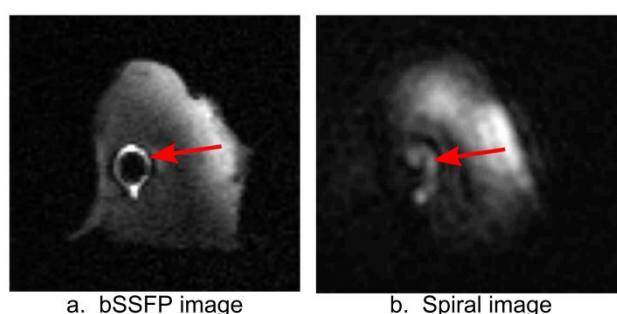
A curved water filled plastic straw of 3mm diameter is placed inside a V-shaped groove in a wax block. The groove is filled with lard to represent epicardial fat. The motion of the test object is monitored with a navigator located on a jelly cylinder positioned parallel to the motion of the phantom.

Upon imaging the finished test object, a number of small air bubbles were found inside the straw. While unintentional, it was decided that this additional spatial detail was beneficial for assessing the performance of respiratory motion correction and the bubbles were, therefore, left in.

4.d.iv The coronary vessel wall test object

Initial test objects were constructed using hollow straws surrounded by jelly soaked paper towels within small mounds of fat surrounded by air. While, as shown in figure 4.4, bSSFP imaging demonstrated a vessel wall like appearance (a), the sensitivity of spiral imaging to susceptibility differences caused by air-jelly interfaces resulted in non-visualisation of the vessel wall (b).

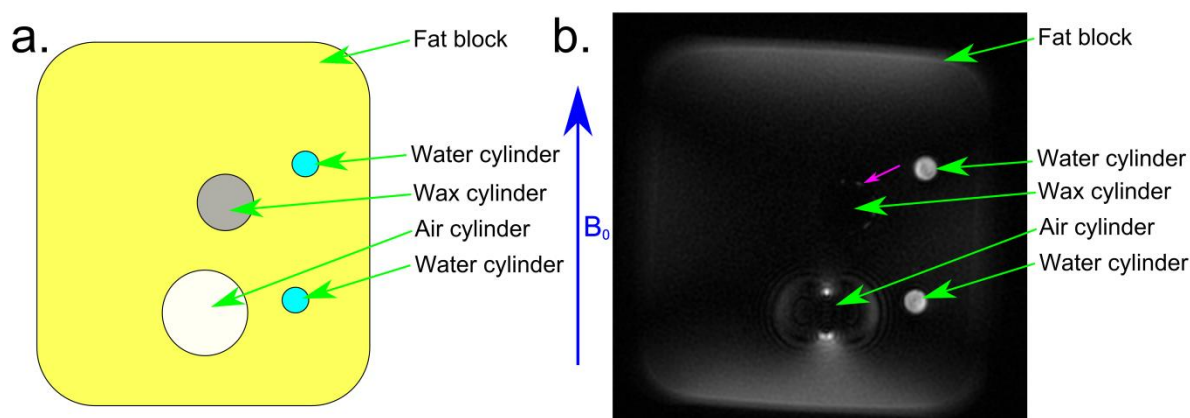
Figure 4.4: The effect of air-tissue boundaries in spiral images



An initial attempt at constructing a coronary artery wall test object consisting of a hollow straw wrapped in jelly soaked paper towels and surrounded by a fat mound. While the vessel wall (red arrow) was visible in the bSSFP images (a), the air-tissue susceptibility differences resulted in severe artefact in the spiral images (b).

The effect of the susceptibility differences at air-tissue interfaces is further highlighted in figure 4.5, which shows a schematic diagram (a) and a 2D coronal spiral image with water selective excitation (b) of another preliminary test object. The test object consisted of a block of fat containing cylinders filled with water, air and wax oriented perpendicular to the imaging plane. The air filled cylinder creates large susceptibility artefacts, while the paraffin wax results in the expected signal void with no artefact. Small pockets of water are trapped between the wax cylinder and the fat, resulting in a bright annulus around part of it (magenta arrow). Fat suppression is poor at the top and bottom of the phantom, also a result of the sharp change in susceptibility at this interface.

Figure 4.5: The susceptibility artefact caused by air vs. wax

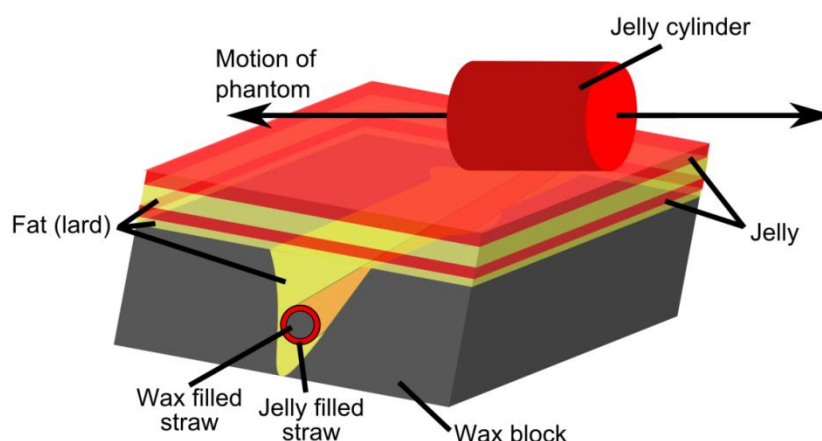


A schematic diagram (a) and a spiral image ($0.7 \times 0.7 \times 3\text{mm}$ resolution) (b) with water selective excitation of a preliminary test object made from block of lard ($\sim 130 \times 130\text{mm}$) containing water, wax and air filled plastic cylinders. Large susceptibility artefacts are observed around the air filled cylinder whereas there are none around the wax or water. There is some signal around the wax cylinder caused by a small amount of water trapped between the wax and lard (magenta arrow).

A schematic of the chosen design of coronary vessel wall test object is shown in figure 4.6. A straight plastic straw of diameter $\sim 3\text{mm}$ was filled with paraffin wax and inserted into a larger straight plastic straw of diameter $\sim 5\text{mm}$. The space between the two concentric straws was filled

with jelly, resulting in a cylindrical layer of jelly of thickness $\sim 1\text{mm}$ representing the vessel wall. The straws were placed inside a V-shaped groove in a wax block which was filled with lard. Layers of fat and jelly were placed on top of the wax block to simulate the overlying anatomy (epicardial fat, chest wall muscle, chest wall fat, chest wall skin). As for the coronary artery test object, a jelly cylinder was placed on top of this test object for monitoring phantom motion with a navigator. The paraffin wax inside the straw and surrounding the fat eliminated the tissue-air interfaces which were in close proximity to the straw.

Figure 4.6: The design of the coronary artery wall test object

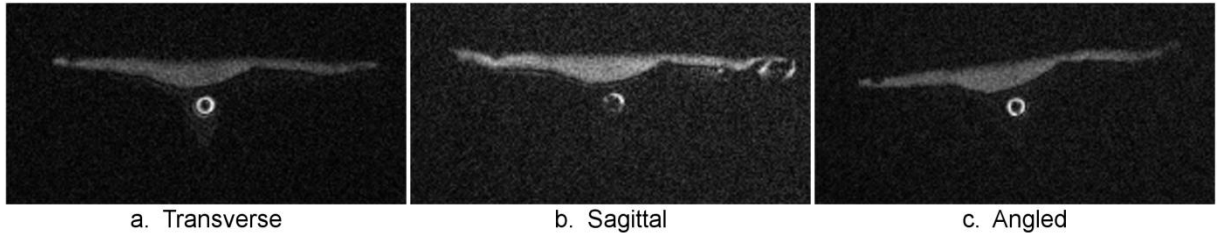


The coronary artery wall test object was constructed from two straight concentric straws $\sim 3\text{mm}$ and $\sim 5\text{mm}$ in diameter. The inner straw was filled with wax and the space between the straws with jelly. The straws were placed in a V-shaped groove in a wax block, filled with lard. Layers of fat and jelly were placed on top of the test object to simulate fat and muscle in the overlying chest wall.

4.d.v Additional complications

Figure 4.7 shows cross-sectional spiral images with water selective excitation acquired of a phantom similar to that depicted in figure 4.6. The image acquired with the vessel parallel to B_0 (a) clearly depicts the full vessel wall, whereas the image acquired with the vessel perpendicular to B_0 (b) is poor quality in the region of the vessel due to susceptibility related B_0 inhomogeneity, despite the use of the wax block. However, with careful angulation of the test object, high quality images can be obtained (c) whilst enabling components of both in and through-plane motion. The same restriction applied to the orientation of the coronary artery test object.

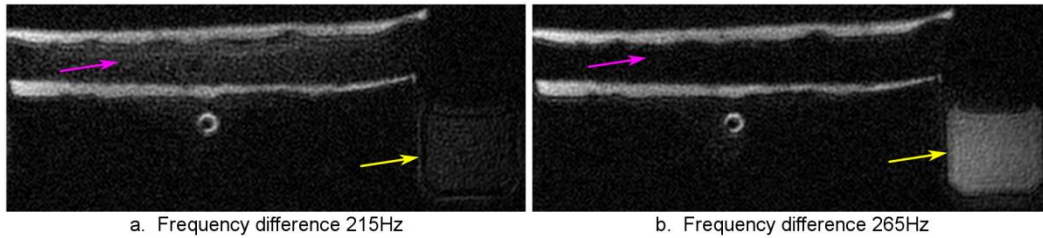
Figure 4.7: Spiral images of a coronary artery vessel wall test object in three orientations



Cross-sectional spiral images of a coronary artery vessel wall test object with the vessel orientated parallel to B_0 (a), perpendicular to B_0 (b) and at an angle of 30° in the left-right plane and 18° in the superior-inferior plane with respect to B_0 (c).

As discussed in section 1.a.i, epicardial fat is liquid at body temperature, whilst the lard used here is solid. Figure 4.8 shows spiral images of a coronary vessel wall test object constructed from jelly, lard and wax with a cuboid shaped container placed to the side of the test object filled with liquid vegetable oil. While the oil is well suppressed in figure 4.8.a, there is still considerable signal from parts of the lard. Figure 4.8.b shows the same image acquired with the timing between the three pulses of the binomial excitation adjusted to suppress frequencies 265Hz off-resonance (rather than the standard 215Hz); as a result, the signal from the lard is well suppressed while there is considerable signal from the oil. The use of lard as a substitute for epicardial fat is convenient as it is solid and malleable. However, as demonstrated here, it does require additional tuning of the binomial excitation pulses.

Figure 4.8: The frequency offset of lard and of oil



Transverse images of a coronary artery wall test object made from lard and jelly with a rectangular bottle of oil placed to one side (yellow arrow). Acquisitions were performed with a binomial water excitation pulse and 2D spiral readouts. Using a standard binomial pulse tuned to null signal 215Hz from resonance (a) results in some residual signal from the lard (magenta arrow) and minimal signal from the oil. Using a modified binomial pulse tuned to null signal 265Hz from resonance (b) results in minimal signal from the lard but increased signal from the oil.

4.e Validation tests

4.e.i Introduction

Initial experiments were designed to validate the accuracy of the motion of the phantom in response to a sinusoidal input trace and then to check that B2B-RMC was able to accurately track the motion of simple objects. Subsequently, tests were performed to validate the performance of

B2B-RMC in tracking and correcting for various physiological respiratory traces in MR coronary angiography type acquisitions using the coronary artery test object described in section 4.c. More advanced tests used the coronary artery vessel wall phantom in combination with a series of sinusoidal and physiological respiratory traces to assess the performance of B2B-RMC in cross-sectional coronary artery vessel wall imaging. Finally, the results obtained with the coronary vessel wall test object were used to determine the effects of varying spatial resolution and noise within the low resolution images on the corrected high resolution image quality.

For each set of tests the phantom was positioned in the scanner so that motion was about the magnet isocentre, parallel to B_0 , except where stated. A 4-channel carotid imaging receive coil was placed directly on the test object, therefore moving rigidly with the phantom and avoiding changes in coil sensitivity with motion. The B2B-RMC imaging sequence was as described in chapter 3 (but without dark blood preparation), triggered every 1000ms using a simulated ECG signal which was unsynchronised with the phantom motion. The component of phantom motion in the direction of B_0 was monitored using a navigator positioned on the flat face of a jelly cylinder perpendicular to B_0 with an acquired resolution of 1mm except where stated.

4.e.ii Validating motion of the phantom

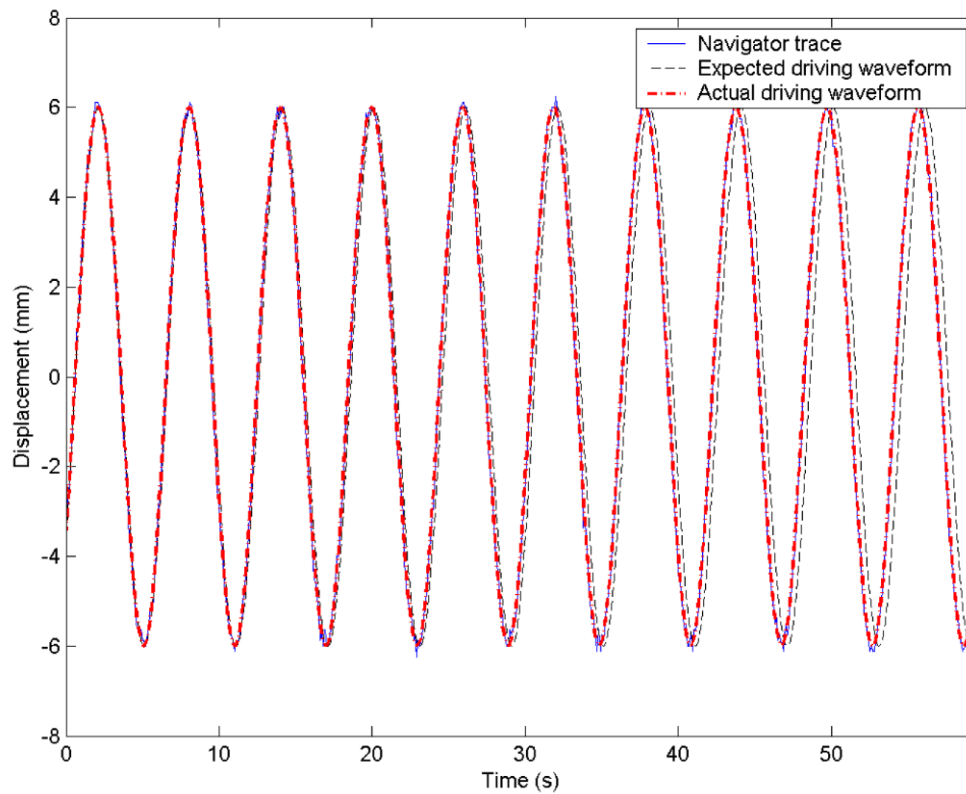
4.e.ii.1 Methods

In order to determine the accuracy of the phantom motion in the scanner, it was programmed to follow a sinusoidal trace with peak to peak amplitude (A_{pp}) 12mm and period (T) 6s. The motion of the phantom was monitored while following the sinusoid trace using a repeated navigator located on a flat face of a jelly cylinder (TR=100ms). Displacement information was obtained using an interpolated least squares fit algorithm applied to the navigator data which was acquired with an increased resolution of 0.5mm.

4.e.ii.2 Results

Figure 4.9 plots the navigator derived displacement of the phantom and the input trace. The measured motion and the input waveform become out of phase with time. Measurements of the accuracy of the controller timing demonstrated an error of 0.8%. The manufacturer of the controller confirmed that an error of this size is possible from the oscillator within the controller, but that the stability is good at constant temperature. The expected displacements were compensated for the timing error (also shown in figure 4.9), which resulted in a root mean square (RMS) error between the measured navigator trace and actual driving trace of 0.12mm.

Figure 4.9: Validation of phantom motion using a navigator



The phantom displacement obtained from a navigator is plotted with time, as is the driving trace for a sinusoidal input ($A_{pp}=12\text{mm}$, $T=5\text{s}$). The expected driving waveform falls out of phase with the navigator trace quickly, but correction for a small timing error in the phantom controller (see Actual driving waveform) results in good agreement.

4.e.ii.3 Discussion

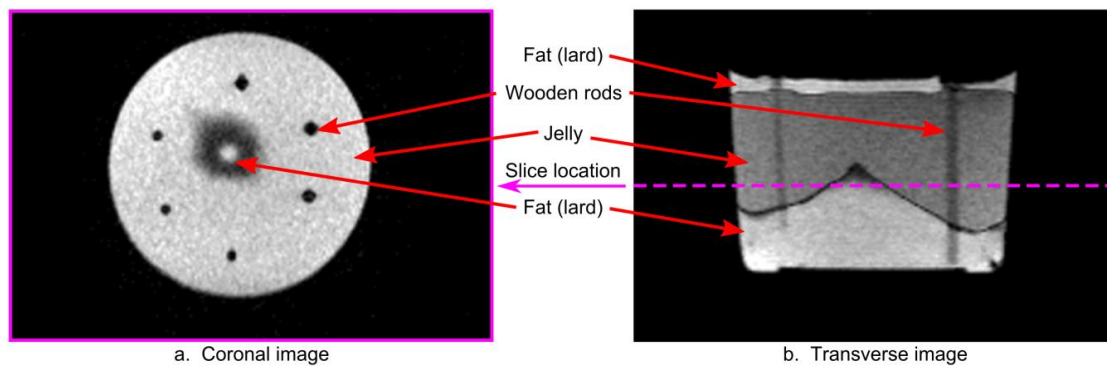
The motion of the phantom was compared to the input trace by measuring the phantom displacement using a navigator. Once a small error in the timing circuits ($<1\%$) of the controller is accounted for, the phantom motion accurately follows input traces of the amplitudes and periods used in this thesis. As the magnitude of this timing error was extremely small it was disregarded in further studies, the success of which did not rely on exact timing of the motion. The RMS error between the navigator derived displacement and the timing corrected input trace was 0.12mm for a sinusoid with $A_{pp}=12\text{mm}$, $T=5\text{s}$. The small mismatch between the corrected input and the measured motion is the combination of actual errors in the motion of the phantom and errors in the navigator measurement of displacement. Errors in the true motion of the phantom are caused by inertia of the lead screw and approximations made in the software used to control the phantom. Errors in the measurement of the displacement are caused by noise and the limited precision of the navigator data. The reduced FOV, which was required for the increased navigator resolution (0.5mm compared to the normally acquired resolution of 1mm), and the short TR of the navigator acquisitions resulted in particularly noisy acquisitions, therefore inflating the RMS error values. In conclusion, the phantom follows the input trace accurately and the RMS error on the phantom displacements is $\sim 0.1\text{mm}$.

4.e.iii Accuracy of NSPCC

4.e.iii.1 Methods

Tests were performed to validate the NSPCC algorithm used in tracking respiratory motion. The phantom was programmed to follow a sinusoid with $A_{pp}=12\text{mm}$ and $T=6\text{s}$. A basic fat based test object (see figure 4.10) was placed on the trolley of the phantom and imaged using the B2B-RMC technique with the imaging plane orientated perpendicular to the motion (transverse plane) and then parallel to the motion (sagittal plane). The displacements in the direction of motion obtained using B2B-RMC were compared to those measured with the navigator.

Figure 4.10: A preliminary phantom used in the tests of NSPCC performance

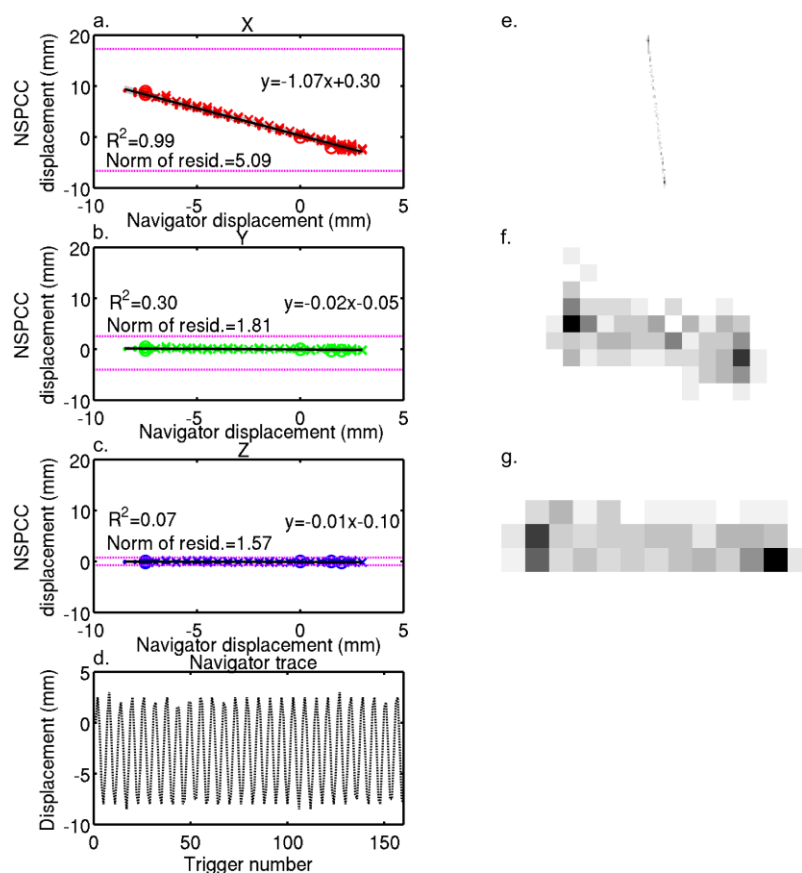


Coronal (a) and transverse (b) 2D bSSFP images of a basic cylindrical test object constructed from lard, jelly and wooden rods.

4.e.iii.2 Results

A movie of one low resolution fat slice of the test object in figure 4.10 moving in-plane sinusoidally is shown in S.11 before and in S.12 after B2B-RMC. The equivalent visualisation of the NSPCC, as discussed in section 3.c.ii is shown in movie S.13. Figure 4.11 and 4.12 plot the B2B-RMC displacements with navigator displacement for in-plane and through-plane motion respectively. In both cases, the slope of the linear fit is close to unity in the expected directions (1.07 in x for in-plane motion, 0.94 in z for through-plane motion) and the R^2 values approach 1 (0.99 in x for in-plane motion, 0.96 in z for through-plane motion). In the directions perpendicular to the motion, a maximum error of 0.6mm in displacement is detected in figure 4.11 and 0.9mm in figure 4.12 (over a total displacement range of 12mm).

Figure 4.11: The performance of the NSPCC for in-plane motion



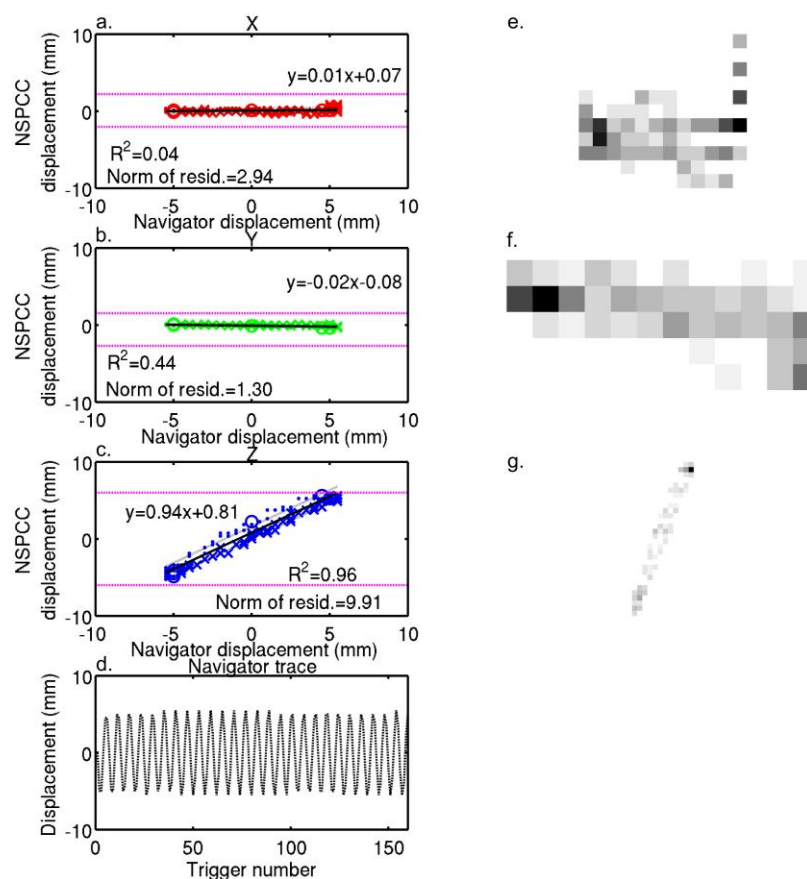
The phantom displacements in-plane (x (a) and y (b)) and through-plane (z (c)) obtained from the B2B-RMC data are plotted against navigator displacement while the phantom follows a sinusoid with $A_{pp}=12\text{mm}$ and $T=6\text{s}$. The navigator trace is shown in (d). The corresponding 2D histograms are shown in (e), (f) and (g) for the plots shown in (a), (b) and (c) respectively. As expected, there is a one to one relationship between displacement in the x direction and that from the navigator, while very little displacement is observed in either of the other directions. Inspiratory points (where the differential of the navigator with time is negative) are plotted as crosses, expiratory points (where the differential is positive) are plotted as dots and stationary points are plotted as empty circles. Mild hysteresis is observed in the in-plane (x) direction due to the 28ms time interval between the low resolution data acquisition and the navigator

4.e.iii.3 Discussion

The phantom was used to demonstrate that when motion is of a typical amplitude and period for respiratory motion ($A_{pp}=12\text{mm}$, $T=6\text{s}$) the displacements obtained using B2B-RMC closely match those obtained with a navigator ($R^2=0.99$, slope=1.07 for in-plane motion (x) and $R^2=0.96$, slope=0.94 for through-plane (z) motion). The 7% and 6% errors in the slope for the in- and through-plane motion respectively correspond to $<1\text{mm}$ over the 12mm amplitude of the sinusoidal trace. These errors may partly be the result of the limited resolution and accuracy of the navigator (acquired resolution 1mm). For the through-plane motion (figure 4.12.c), a greater spread of points is observed around the linear fit, partly due to the larger size of the pixels in the low resolution volumes in this direction (1.5mm reconstructed pixels through-plane compared to

0.5 x 0.5mm reconstructed pixels in-plane). There is a degree of hysteresis between the through-plane B2B-RMC displacements and the navigator (figure 4.12.c), observed as a loop like trend in the data, which is a result of motion between the low resolution data acquisition and the corresponding navigator. This effect is exaggerated in the through-plane direction due to the larger reconstructed pixel size in this direction, but is also present for the in-plane motion (figure 4.11.a). The search ROI appears to have been defined slightly too small in the through-plane direction in figure 4.12, resulting in a grouping of B2B-RMC displacements at the upper boundary. A further consequence of this is that several corresponding displacements have been incorrectly detected by the NSPCC in the in-plane (x) direction (figure 4.12.a and e), highlighting the need to define an adequate search ROI in all three dimensions.

Figure 4.12: The performance of the NSPCC for through-plane motion



The phantom displacements in-plane (x (a) and y (b)) and through-plane (z (c)) obtained from the B2B-RMC data are plotted against navigator displacement while the phantom follows a sinusoid with $A_{pp}=12\text{mm}$ and $T=6\text{s}$. The navigator trace is shown in (d). The corresponding 2D histograms are shown in (e), (f) and (g) for the plots shown in (a), (b) and (c) respectively. As expected, there is a one to one relationship between displacement in the z direction and displacement obtained from the navigator, while very little displacement is observed in either of the other directions. Inspiratory points (where the differential of the navigator with time is negative) are plotted as crosses, expiratory points (where the differential is positive) are plotted as dots and stationary points are plotted as empty circles. Mild hysteresis is observed in the through-plane direction (z) due to the time between the low resolution data acquisition and the navigator.

4.e.iv The performance of B2B-RMC for MR coronary angiography

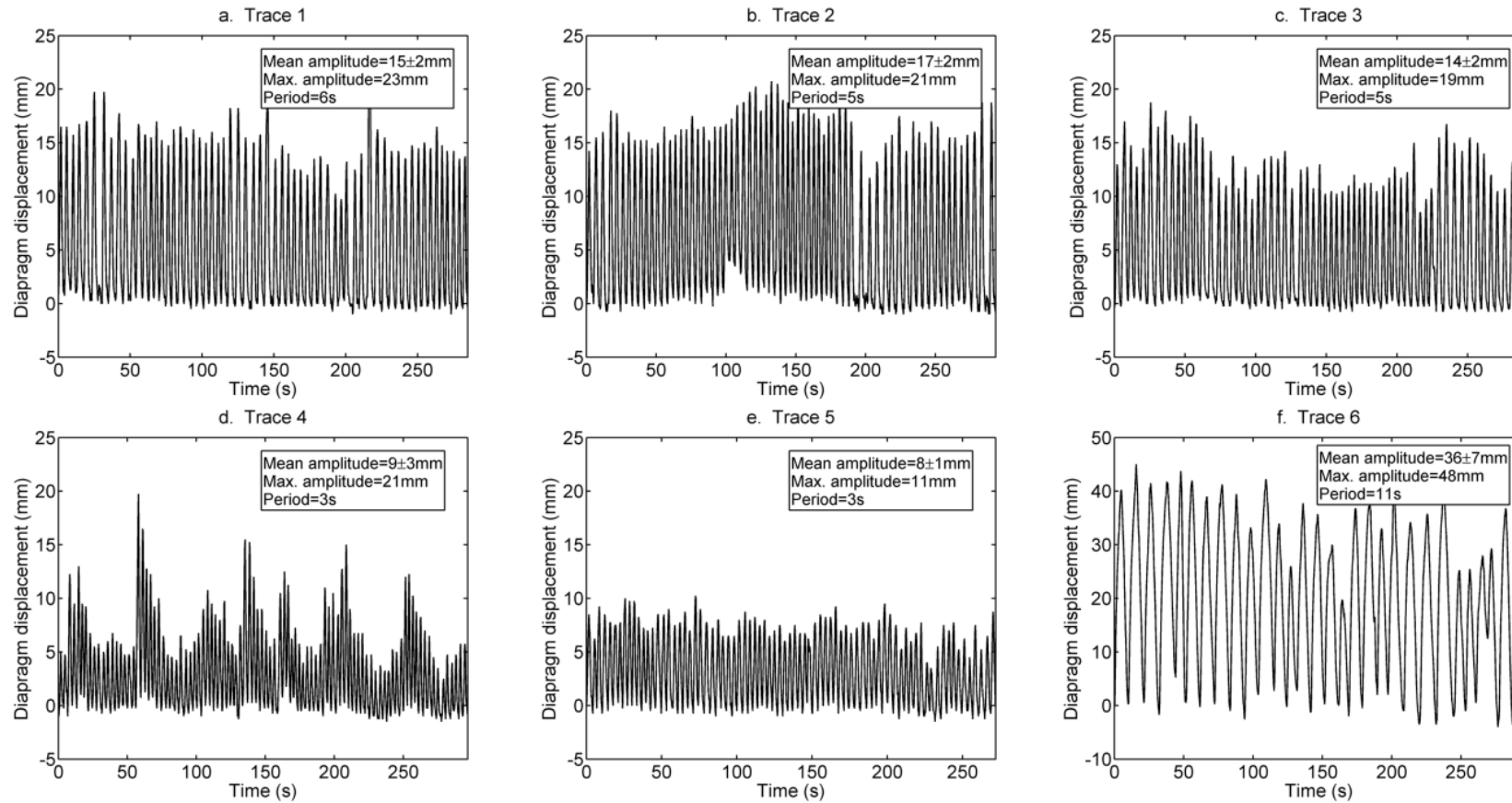
The work presented in this section originally formed part of Scott et al. (2011a).

4.e.iv.1 Methods

A series of tests were performed in order to assess the performance of B2B-RMC compared to navigator gating in MR coronary angiography. The coronary artery test object described in section 4.c and figure 4.3 was placed on the trolley and imaged in a plane showing the length of the vessel (in-plane imaging). The test object was orientated so that motion of the phantom parallel to B_0 produced components of motion in both the in- and through-plane directions. After localisation of the test object, images were acquired using the 3D spiral sequence described in chapter 3 while the phantom was stationary and while following respiratory traces obtained from six healthy subjects using a repeated navigator (TR=250ms), as shown in figure 4.13.

Acquisitions were performed both ungated and gated to a 5mm window around the end-expiratory position using a navigator positioned on a jelly cylinder placed on top of the test object. Apart from the use of navigator gating, acquisitions were identical. The ungated images were corrected using B2B-RMC as described in chapter 3. Ungated, B2B-RMC and navigator gated images were reconstructed and parallel plane maximum intensity projection (MIP) images calculated for each dataset using the tool described in section 3.b.ii.3. Average vessel diameter and average vessel edge sharpness in a 10mm bubble free section of the vessel was measured in the ungated, B2B-RMC and navigator gated MIP images. Vessel diameter was defined as the full width half maximum (FWHM) of intensity profiles drawn perpendicular to the vessel and vessel edge sharpness was defined as the inverse of the distance from 20% to 80% of the maximum intensity averaged over both vessel edges (Shea et al., 2001, Li et al., 2001). Values were compared using repeated measures ANOVA and paired t-tests with Bonferroni correction for multiple comparisons.

Figure 4.13: The physiological respiratory traces used in the respiratory motion phantom tests with the coronary artery and coronary artery vessel wall test objects



Respiratory traces obtained from healthy subjects with a repeated diaphragm navigator ($TR=250$ ms). Note that the large amplitude of trace 6 (f) means that the scale on the y-axis is different from the previous plots (a – e).

4.e.iv.2 Results

Figure 4.14 shows the MIP images obtained for the stationary acquisition (a) and for each of the six physiological respiratory traces (b – r) shown in figure 4.13. For each physiological respiratory trace, the corresponding MIP image is shown for the uncorrected acquisition (b, e, h, k, n and q), the acquisition corrected using B2B-RMC (c, f, i, l, o and r) and the acquisition gated to a 5mm window using a navigator (d, g, h, m and p). The gated acquisition failed for respiratory trace 6 (see figure 4.13.f) due to the unusually large tidal range of respiratory motion in this subject which resulted in a very long navigator trace which could not be written to file due to restrictions within the sequence code. The mean respiratory efficiency for the remaining navigator gated acquisitions was $53 \pm 8\%$ (range 47 – 66%). Some residual fat signal is observed in the MIP images, but this does not affect the appearance of the vessel. There is residual blurring of the vessel present in the navigator gated images while blurring is minimal in those corrected with B2B-RMC. The corresponding vessel sharpness and diameter for each of the images is shown in figure 4.14 and presented in table 4.1. The extremely poor quality of the images reconstructed without correction for respiratory trace 6 meant that diameter and sharpness could not be measured in this case. For the stationary acquisition the vessel diameter was 2.60mm and the sharpness was 1.35mm^{-1} . The average vessel diameter was greater for the uncorrected images ($3.06 \pm 0.52\text{mm}$) than for the B2B-RMC images ($2.60 \pm 0.02\text{mm}$) or for the gated images ($2.74 \pm 0.12\text{mm}$), although the difference is not significant. The average vessel sharpness was significantly greater in the B2B-RMC images ($1.01 \pm 0.02\text{mm}^{-1}$) than in the gated images ($0.86 \pm 0.08\text{mm}^{-1}$, $p < 0.05$) or the uncorrected images ($0.71 \pm 0.10\text{mm}^{-1}$, $p < 0.01$).

4.e.iv.3 Discussion

B2B-RMC was effective in correcting a range of physiological respiratory traces and performed better than navigator gating with a 5mm window when compared using average vessel diameter and sharpness. Even in the case of extreme respiratory motion (trace 6, figure 4.14.r), the B2B-RMC technique performed well with 100% respiratory efficiency. In this instance, the respiratory efficiency using navigator gating was so low (13%) that the acquisition failed.

Vessel diameter measurements obtained from the B2B-RMC images were very similar to those obtained from the equivalent stationary images ($2.60 \pm 0.02\text{mm}$ B2B-RMC vs. 2.60mm stationary). The under estimation of the vessel diameter obtained in these experiments (2.60mm in the stationary phantom compared to the 3.0mm actual diameter) is a result of using the FWHM of a 2D projection of a 3D image of a cylindrical object and demonstrates a limitation of this method of measurement.

Average vessel sharpness was significantly better using B2B-RMC than when images were navigator gated. However, vessel sharpness was greater in the stationary images than in the B2B-RMC images (1.35mm^{-1} vs. $1.01 \pm 0.02\text{mm}^{-1}$). This is due to a number of factors including: motion during the acquisition of the high resolution data; the limited precision of B2B-RMC displacements obtained from NSPCC; motion during the acquisition of the low resolution data; and the limited resolution and SNR of the low resolution data (see section 4.e.vi and 4.e.vii).

The coronary artery test object designed specifically for these tests performed well. B2B-RMC was able to track the fat surrounding the vessel and adequate suppression of fat signal was achieved in order to clearly visualise the vessel. While air bubbles were inadvertently introduced into the water within the straw (the vessel), they were found to add useful detail and any signal loss due to susceptibility artefacts was localised to the very immediate surroundings.

In this comparison, the phantom followed the respiratory traces obtained from the diaphragms of healthy subjects and there was no compensation for the difference between the motion of the diaphragm and that of the coronary arteries. This suggests that *in-vivo*, the respiratory motion to be corrected would be less (for both navigator gating and B2B-RMC). While typical factors of 0.6 are often used to relate respiratory motion of the diaphragm to that of the proximal coronary arteries for many *in-vivo* studies (Wang et al., 1995c, Oshinski et al., 1998, Botnar et al., 2000a, Bornert et al., 2001a, Stuber et al., 2001, Weber et al., 2003), factors vary widely between subjects and along the length of the vessel.

Table 4.1: Results of the phantom tests using the coronary artery test object

Trace	Mean Amplitude (mm)	Mean Period (s)	Sharpness			Diameter		
			Uncorrected (mm ⁻¹)	B2B-RMC (mm ⁻¹)	Nav-Gated (mm ⁻¹)	Uncorrected (mm)	B2B-RMC (mm)	Nav-Gated (mm)
1	15	6	0.69	1.01	0.96	2.84	2.64	2.60
2	17	5	0.75	1.02	0.79	2.64	2.58	2.73
3	14	5	0.86	1.02	0.91	2.72	2.59	2.76
4	9	3	0.60	0.97	0.76	3.91	2.60	2.94
5	8	3	0.63	1.02	0.88	3.20	2.60	2.68
6	36	11	*	0.86	†	*	2.70	†
Mean (SD)	17	6	0.71 (0.10)	1.01 [‡] (0.02)	0.86 (0.08)	3.06 (0.52)	2.60 (0.02)	2.74 (0.12)

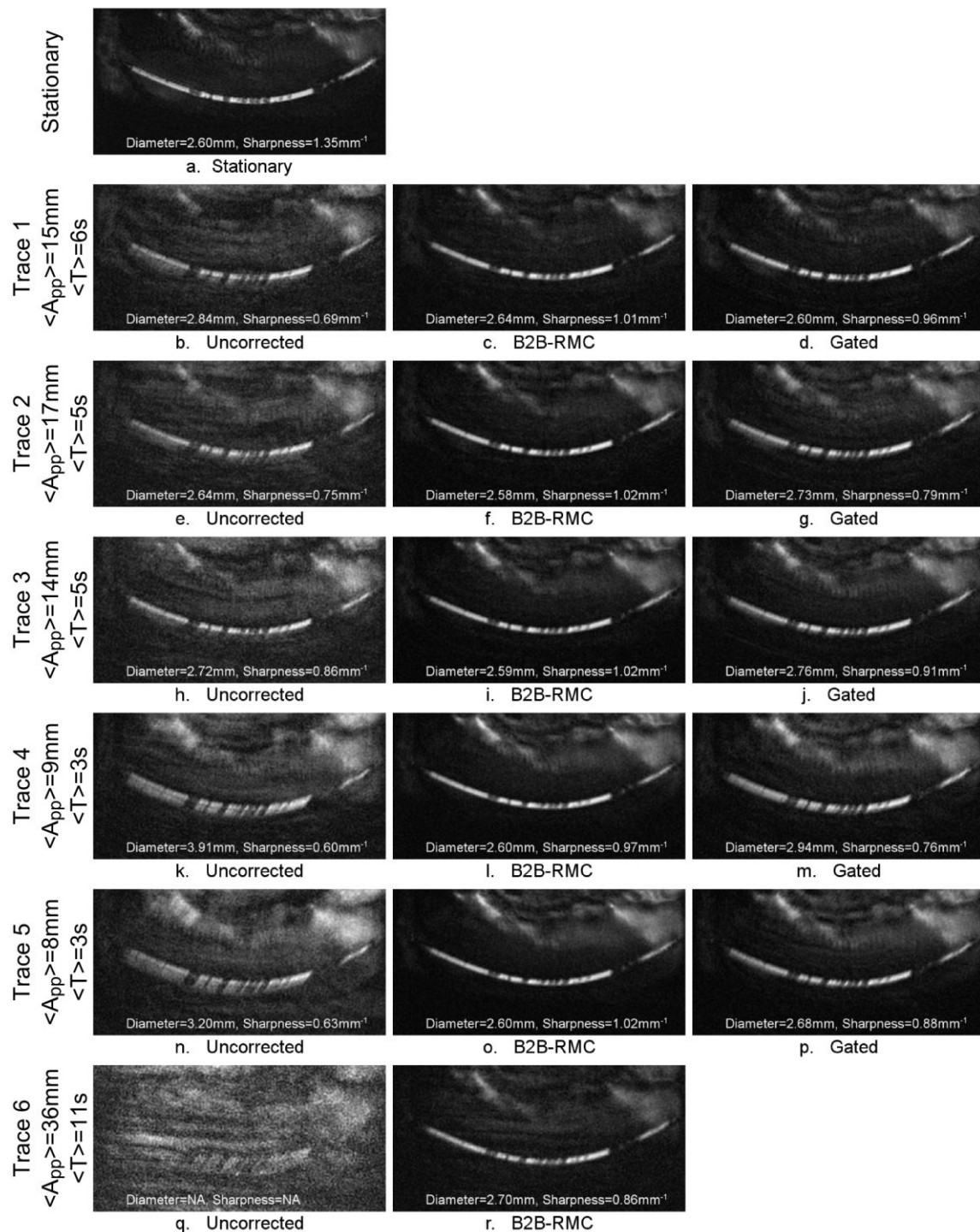
Sharpness and diameter measurements in the coronary artery test object acquired while following respiratory traces obtained from six healthy subjects. For reference, the measured vessel sharpness in the stationary phantom was 1.35mm⁻¹ and the measured vessel diameter was 2.60mm.

* not measurable

† acquisition failed

[‡] $p < 0.01$ compared to uncorrected and $p < 0.05$ compared to navigator gated

Figure 4.14: Results of the phantom tests comparing navigator gating and B2B-RMC in a coronary artery test object



Parallel plane MIP images of a coronary artery test object acquired while the phantom was stationary (a) and while following 6 respiratory traces obtained from healthy subjects (b – r) as shown in figure 4.13. Images were reconstructed uncorrected and ungated (left column), corrected using B2B-RMC (central column) and gated to a 5mm window around end-expiration. For each image the diameter (in mm) and sharpness (in mm⁻¹) is given. In each case some residual fat signal is also present.

4.e.v The performance of B2B-RMC for coronary artery vessel wall imaging

4.e.v.1 Methods

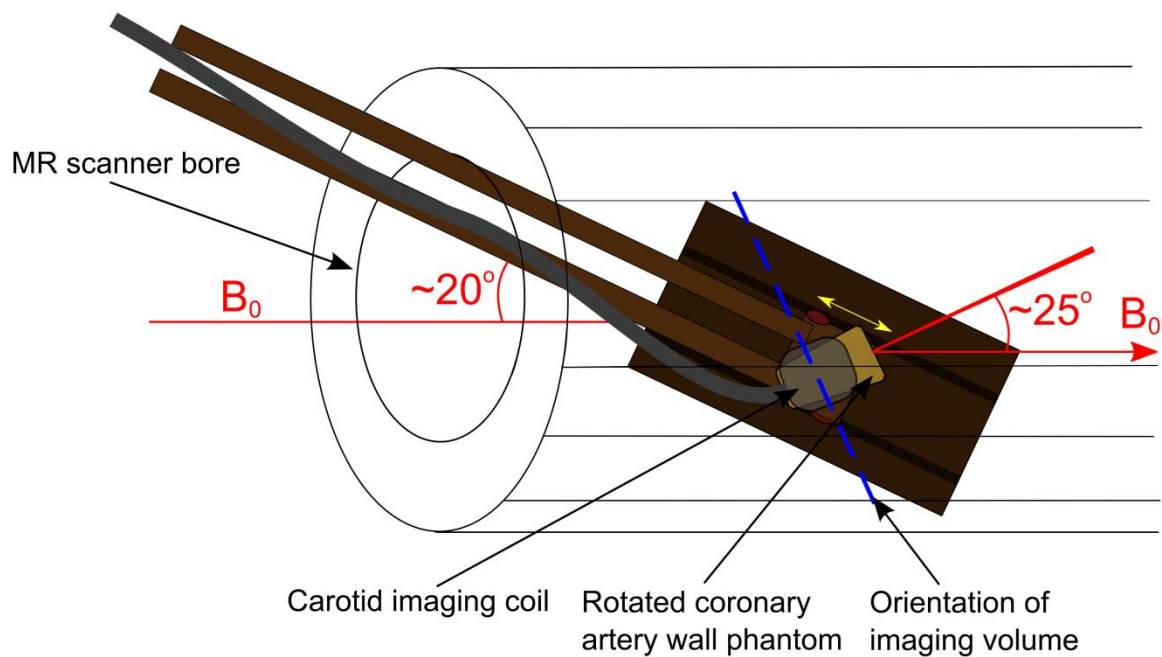
A series of tests were performed to assess the performance of B2B-RMC in MR coronary vessel wall imaging. The phantom was orientated (see figure 4.15) at the greatest angle permitted by the geometry of the scanner whilst positioning the test object at the magnet isocenter ($\sim 20^\circ$), by rotating the drive end of the phantom in the coronal plane. The test object was then rotated, as shown in figure 4.15, in order to produce the largest component of phantom motion in-plane for cross-sectional imaging. Very large displacements in the through-plane direction were avoided as they could result in the desired section of the test object moving out of the imaging volume and can be difficult to correct when the test object is a similar cross-sectional shape along its length. This setup also minimised the rotation of the test object with respect to B_0 ($\sim 25^\circ$), thus minimising the susceptibility artefacts generated when the vessel is not parallel to B_0 (see section 4.e and figure 4.6). The imaging plane was aligned to produce cross-sectional images of the vessel wall test object. Images were acquired while the phantom was stationary and while following four sinusoidal traces and the six physiological respiratory traces shown in figure 4.13. The sinusoidal traces had peak to peak amplitudes (A_{pp}) and periods (T) as follows:

1. $A_{pp}=15\text{mm}$, $T=5\text{s}$
2. $A_{pp}=15\text{mm}$, $T=3\text{s}$
3. $A_{pp}=25\text{mm}$, $T=5\text{s}$
4. $A_{pp}=25\text{mm}$, $T=3\text{s}$.

While the physiological respiratory traces are examples of actual free-breathing diaphragm motion, the sinusoids have constant period and amplitude, therefore allowing separate assessment of the effects of these parameters on the final image quality. Images were reconstructed from the data acquired during sinusoidal motion both uncorrected and corrected using B2B-RMC, whereas the data acquired with physiological respiratory traces were reconstructed uncorrected, corrected using B2B-RMC and from data gated to a 5mm window around end expiration using a navigator. Apart from navigator gating, the sequence was identical for all acquisitions. Due to a limitation of the scanner software the readout direction for the navigator is fixed in the direction of B_0 (SI *in-vivo*). As the phantom was orientated at an angle to B_0 , the navigator measured the component of motion in the direction of B_0 and not the full magnitude of the motion. Therefore, the navigator gating window of 5mm corresponded to 5.3mm of phantom motion at the typical phantom angle of 20° .

A single representative slice of each high resolution acquisition was selected for analysis and horizontal intensity profiles were drawn through the right hand edge of the vessel wall (at the 3 o'clock position) to qualitatively compare the efficacy of the respiratory motion correction. The FWHM of the profiles was also calculated as a quantitative indicator of performance.

Figure 4.15: The phantom setup used in the coronary artery wall imaging tests



For the coronary artery wall phantom tests, the test object was located at the magnet isocenter and the phantom was rotated in the coronal plane as far as the geometry of the bore will allow ($\sim 20^\circ$). The test object was rotated in the opposite direction to create the largest component of motion in the imaging plane, whilst minimizing the angle between the phantom and B_0 ($\sim 25^\circ$). There was also a component of the rotation of the test object out of the coronal plane.

4.e.v.2 Results

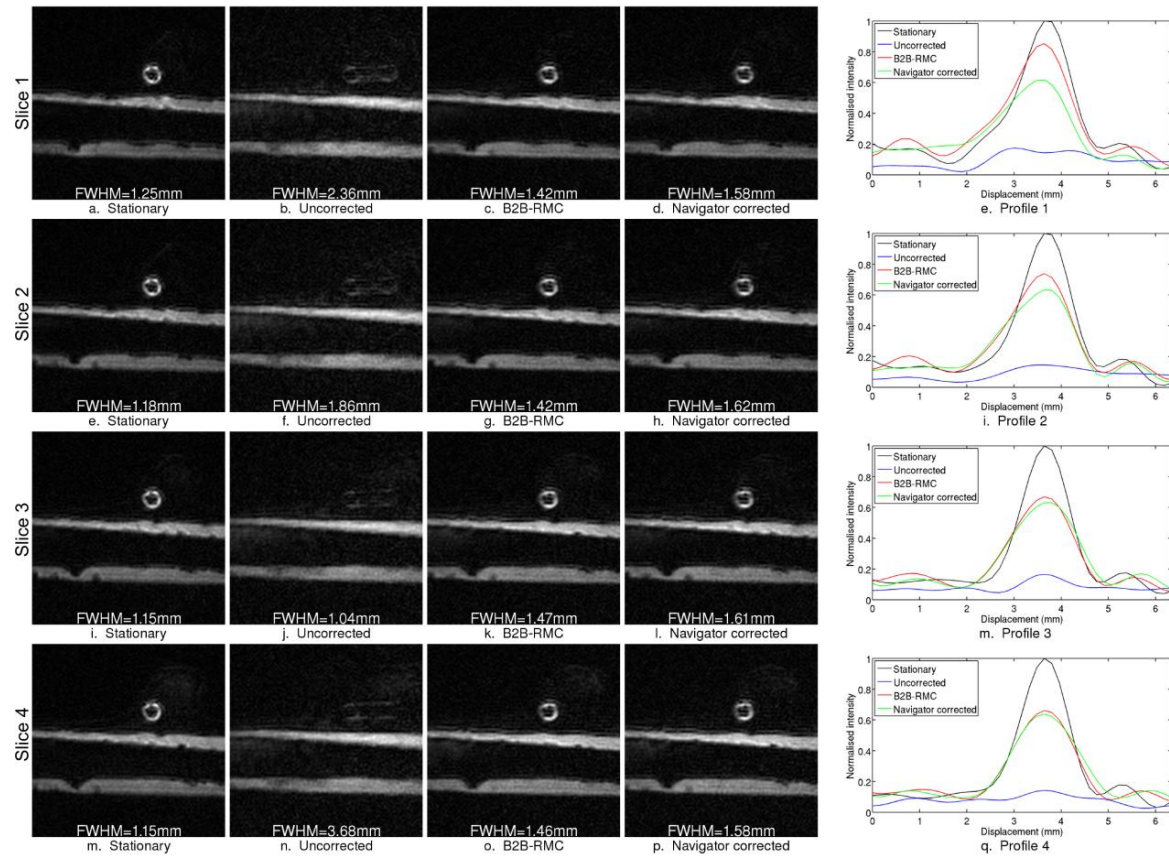
Sinusoidal respiratory Traces

Figure 4.16 shows four consecutive slices of images obtained of the coronary vessel wall test object while stationary (a, e, i and m) and while following a sinusoid with $A_{pp}=15\text{mm}$ and $T=5\text{s}$. In addition, navigator corrected images were reconstructed from the ungated data by using the navigator displacements and the imaging plane orientation to calculate the corresponding 3D displacement. The images corrected with B2B-RMC (c, g, k and o) and the FWHM of the corresponding intensity profiles (mean $\text{FWHM}=1.44\pm 0.03\text{mm}$) were substantially improved over the uncorrected images (b, f, j and n) (mean $\text{FWHM}=2.24\pm 1.10\text{mm}$) and also improved over the images corrected using the navigator information (d, h, l and p) (mean $\text{FWHM}=1.60\pm 0.02\text{mm}$). The stationary images and the corresponding FWHM values were, however, best (mean $\text{FWHM}=1.18\pm 0.05\text{mm}$). The corresponding displacements obtained from B2B-RMC are plotted in figure 4.17. Excellent R^2 values were obtained when linearly fitting B2B-RMC to navigator displacements in all directions (0.98, 0.89 and 0.92 in in-plane x, in-plane y and through-plane z respectively). From the orientation of the imaging plane and the direction of the phantom motion, the expected slopes of the linear fit were 0.97, 0.02 and 0.43 in in-plane (x), in-plane (y) and through-plane (z) respectively, which compare well to the observed slopes of 0.91, 0.04 and 0.31. Figure 4.18 shows the equivalent plots of the B2B-RMC results obtained when the phantom was programmed to follow a sinusoid with $A_{pp}=25\text{mm}$ and $T=5\text{s}$. Once again, excellent R^2 values were obtained in all directions (0.89,

0.93 and 0.93 in in-plane (x), in-plane (y) and through-plane (z) respectively) and the slopes of the linear fits (0.89, 0.02 and 0.28) remained similar to the expected values. However at the extremes of motion the linear relationship between the B2B-RMC displacement in the through-plane direction and the navigator broke down, resulting in a sigmoid like curve. Figure 4.19 plots the respiratory displacements obtained from B2B-RMC for the sinusoid with $A_{pp}=15\text{mm}$ and $T=3\text{s}$. When compared to figure 4.17, the reduced period of the sinusoid is seen to result in an increase in the loop like hysteretic trend in the plots of B2B-RMC displacements verses navigator displacements (see parts (a) and (c) in particular), which is further highlighted by the 2D histograms (see parts (e) and (g) in particular). Despite this R^2 values are high (0.95, 0.85 and 0.83) and the accuracy of the slope of the linear fit was maintained (0.90, 0.04 and 0.30). The equivalent results for the sinusoid with $A_{pp}=25\text{mm}$ and $T=3\text{s}$ (not shown) demonstrated a combination of the increased hysteresis due to the reduced period and the sigmoid like curve related to the increased amplitude. The corresponding R^2 values for this sinusoid are (0.96, 0.90 and 0.94) and the slopes are (0.89, 0.02 and 0.26).

Figure 4.20 shows one example slice from all of the acquisitions performed with sinusoidal input traces both before and after correction. The equivalent slice from the stationary acquisition (a) is shown for reference. For each sinusoidal trace, B2B-RMC (c, f, i and l) resulted in substantial improvement of the images over the uncorrected equivalent (b, e, h and k) and, in the case of the sinusoid with $A_{pp}=15\text{mm}$ and $T=5\text{s}$, the B2B-RMC image appears very similar to the stationary reference. For each sinusoidal input trace, the intensity profiles are also shown (d, g, j and m) with the equivalent profile through the stationary image given for reference in each case. The FWHM of the intensity profile is provided on the corresponding image. While the intensity profile of the B2B-RMC image was improved over the uncorrected image for each sinusoid, none of the B2B-RMC profiles matched the stationary profile and this is reflected in the poorer FWHM values (FWHM median= 1.92mm, range=1.42mm – 3.12mm for B2B-RMC vs. FWHM=1.19mm for the stationary image). With increased A_{pp} or decreased T there was a loss of image quality in the B2B-RMC image which is reflected in the FWHM of the corresponding intensity profile. The uncorrected images show reduced vessel wall signal and considerable artefact. As a result, the signal intensity profiles have multiple low amplitude peaks and measurement of the FWHM is difficult.

Figure 4.16: Images from the tests using a coronary vessel wall test object

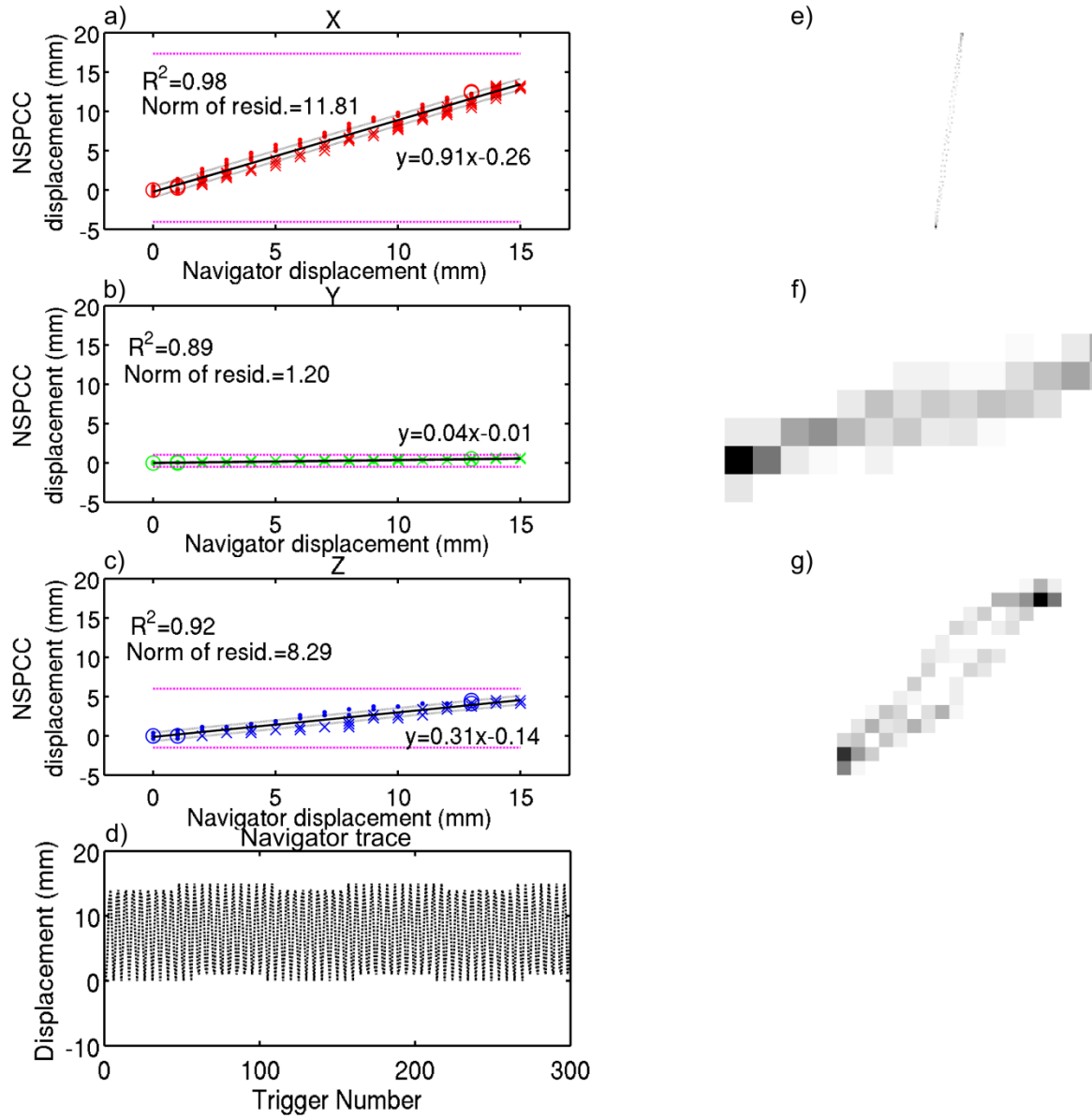


Four slices from images acquired of a coronary artery wall test object performed while stationary (a, e, i and m) and while moving sinusoidally ($A_{pp}=15\text{mm}$, $T=5\text{s}$). Images corrected with B2B-RMC (c, g, k and o) are greatly improved when compared to the uncorrected images (b, f, j and n), and similar to those images corrected with the navigator displacements (d, h, i and p). The quality of the corrections is highlighted by horizontal intensity profiles drawn through the right hand edge of the vessel wall (e, i, m and q) and the corresponding FWHM values given on the images.

Physiological respiratory traces

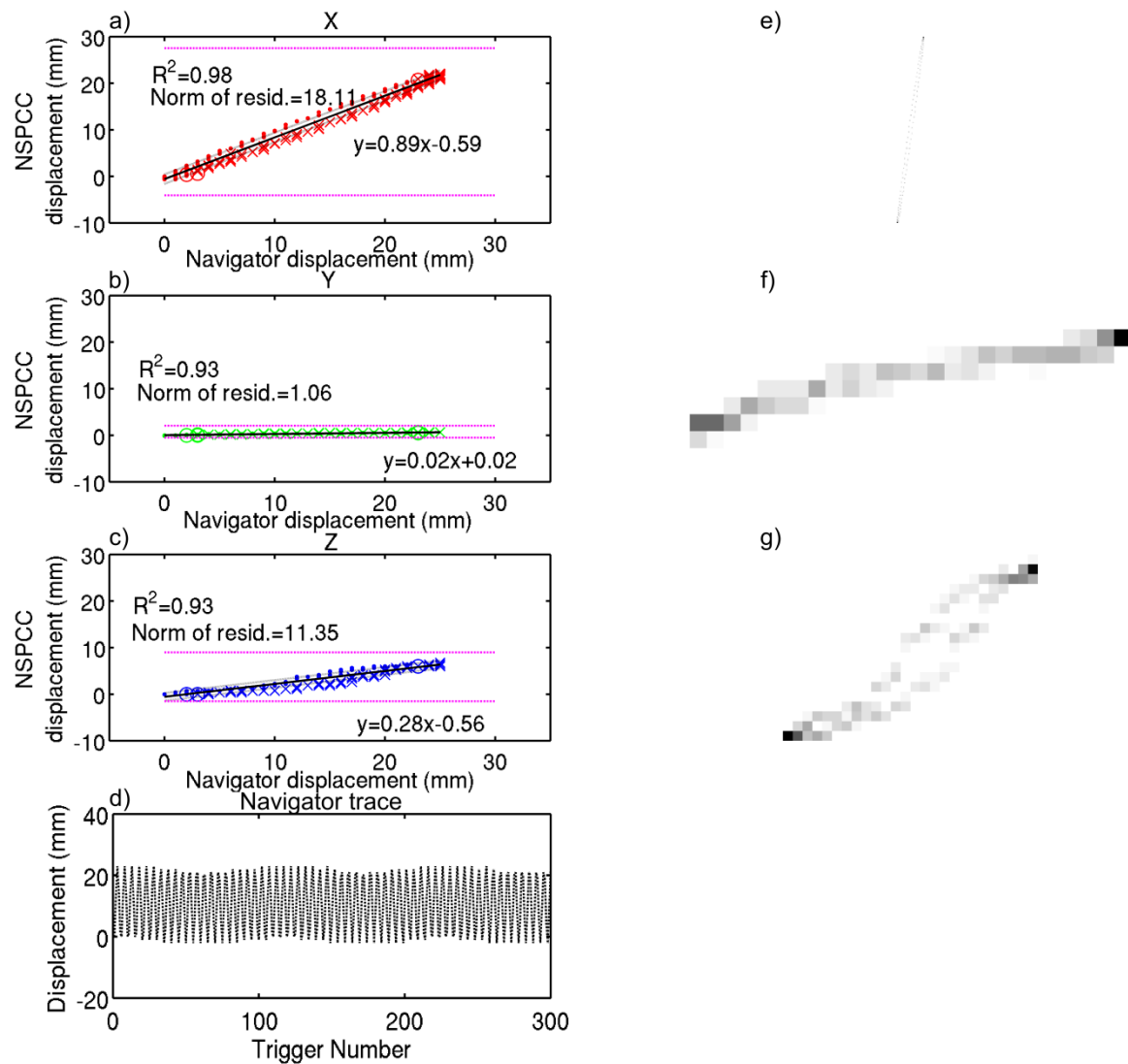
Ungated images for B2B-RMC were acquired for all six physiological respiratory traces and navigator gated images were acquired for traces 1-5 (traces shown in figure 4.13). As in section 4.e.iv navigator gating failed for trace 6 due to the unusually large range of respiratory motion exhibited by this subject. Figures 4.21 (stationary and traces 1-3) and 4.22 (stationary and traces 4-6) show one example slice from the stationary acquisition (a) and from the uncorrected (b, f and j) B2B-RMC (c, g and k) and navigator gated images (d, h and l) for each physiological respiratory trace. While navigator gating resulted in improvements in image quality over the uncorrected images, B2B-RMC images were superior. This is reflected in the FWHM of the corresponding intensity profiles (e, i and m), although it did not achieve statistical significance (mean FWHM= $1.38 \pm 0.10\text{mm}$ for B2B-RMC vs. $1.70 \pm 0.25\text{mm}$ for navigator gating, $p=0.08$). Even in the case of trace 6, with mean peak to peak amplitude ($\langle A_{pp} \rangle$) 36mm, B2B-RMC resulted in well corrected images with only a relatively small increase in the FWHM compared to the stationary reference (1.53mm vs. 1.19mm).

Figure 4.17: B2B-RMC displacements plotted with navigator displacements for the phantom tests using the coronary artery wall test object (sinusoidal input, $A_{pp}=15\text{mm}$, $T=5\text{s}$)



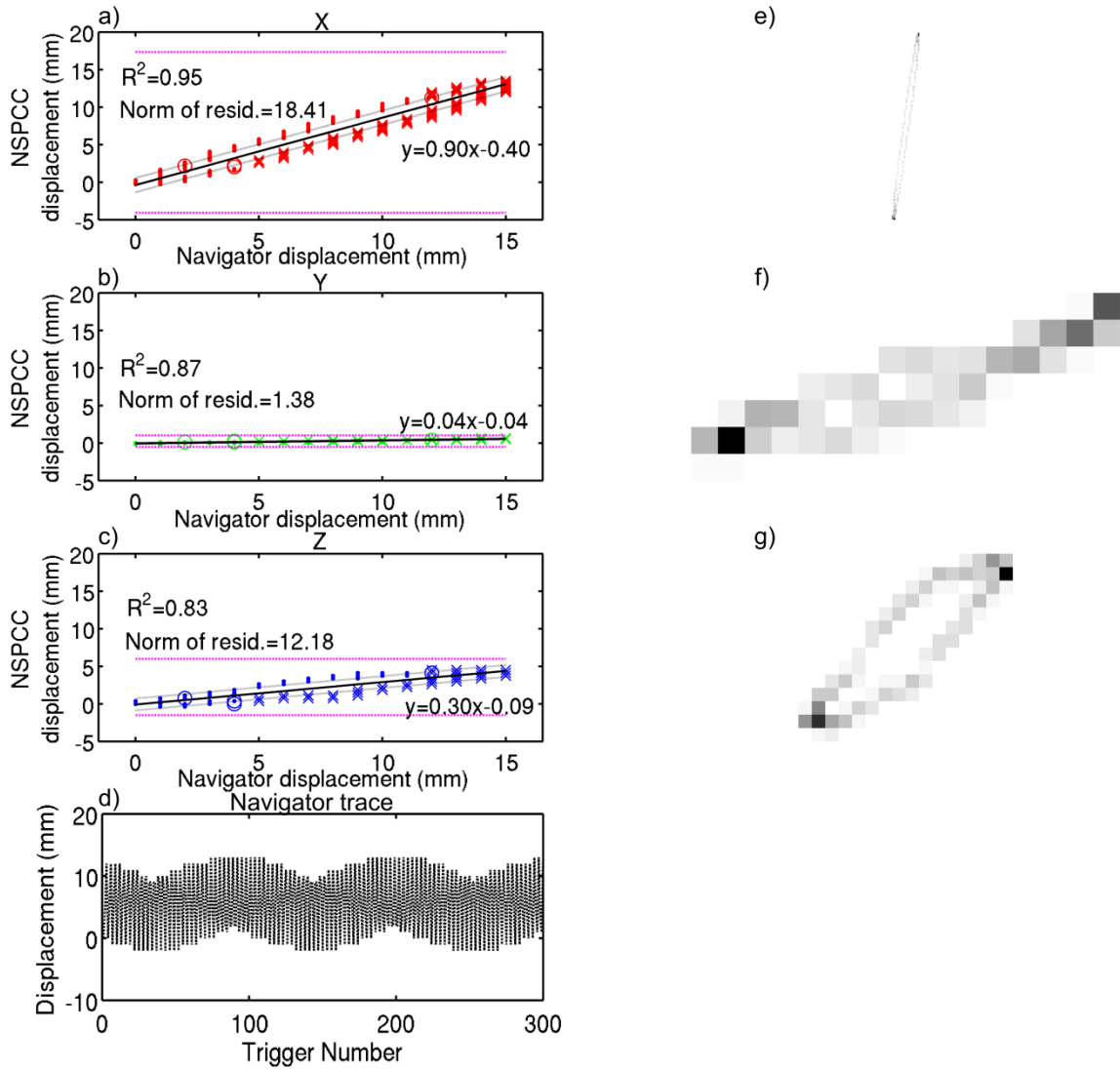
The in-plane (x (a) and y (b)) and through-plane (z (c)) B2B-RMC displacements plotted with navigator displacement for the tests performed with a coronary artery wall test object and an input sinusoid with $A_{pp}=15\text{mm}$ and $T=5\text{s}$. The navigator trace is shown in (d). The corresponding 2D histograms are shown in (e), (f) and (g) for the plots shown in (a), (b) and (c) respectively. B2B-RMC accurately tracked the motion of the phantom in all three directions. Some hysteresis between B2B-RMC displacements and the navigator is evident. Inspiratory points (positive differential of the navigator displacement) are plotted as points, whereas expiratory points (negative differential of the navigator displacement) are plotted as crosses and stationary points (zero differential of the navigator displacement) are plotted as empty circles. Inspiratory points lie on the top of the loops and expiratory points on the bottom (see (a) and (c)).

Figure 4.18: B2B-RMC displacements plotted with navigator displacements for the phantom tests using the coronary artery wall test object (sinusoidal input, $A_{pp}=25\text{mm}$, $T=5\text{s}$)



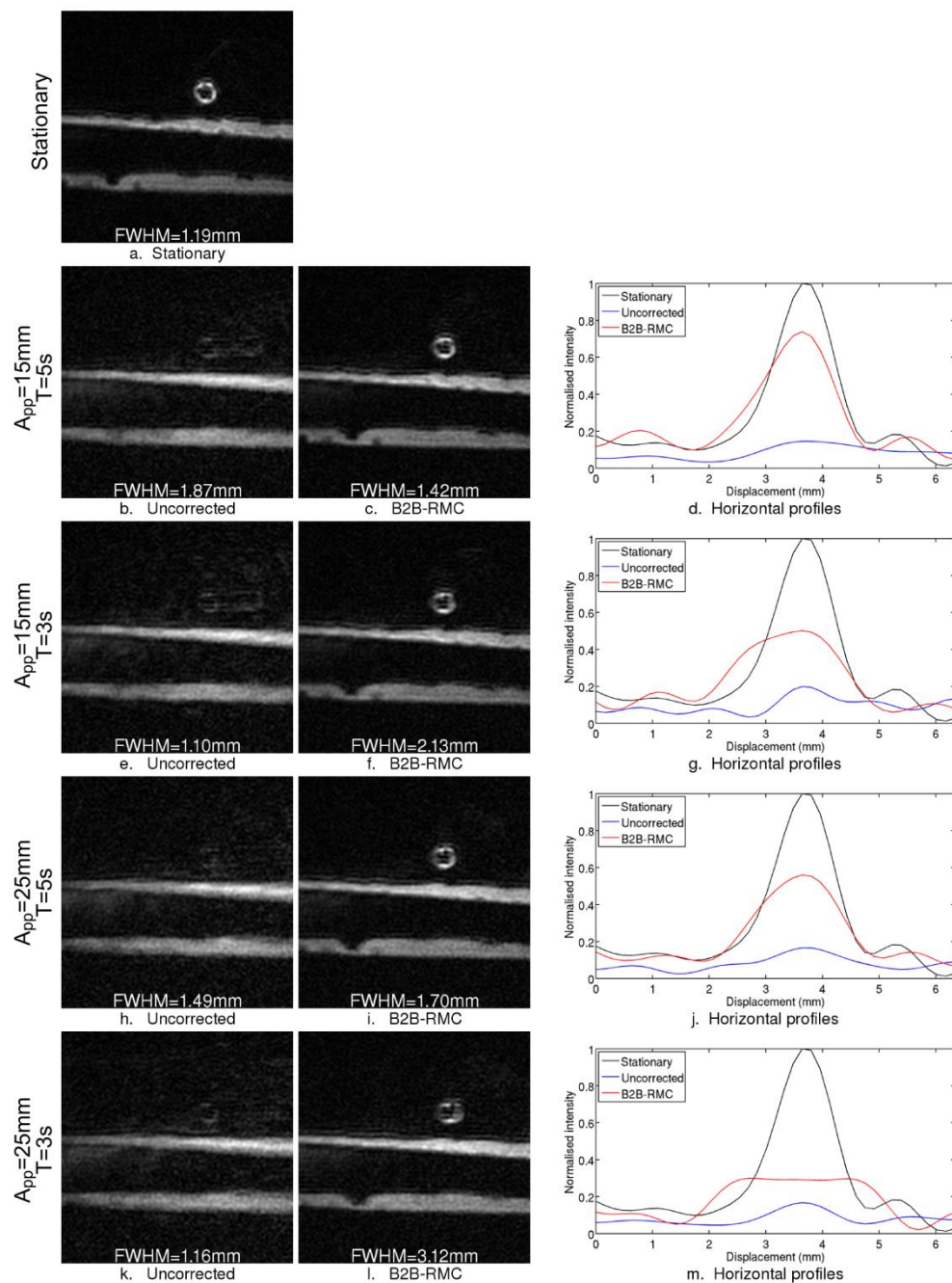
The in-plane (x (a) and y (b)) and through-plane (z (c)) B2B-RMC displacements plotted with navigator displacement for the tests performed with a coronary artery wall test object and an input sinusoid with $A_{pp}=25\text{mm}$ and $T=5\text{s}$. The navigator trace is shown in (d). The corresponding 2D histograms are shown in (e), (f) and (g) for the plots shown in (a), (b) and (c) respectively. B2B-RMC was unable to fully track the large through-plane displacements, resulting in a sigmoid like curve in the through-plane direction (c). Inspiratory points (positive differential of the navigator displacement) are plotted as points, whereas expiratory points (negative differential of the navigator displacement) are plotted as crosses and stationary points (zero differential of the navigator displacement) are plotted as empty circles.

Figure 4.19: B2B-RMC displacements plotted with navigator displacements for the phantom tests using the coronary artery wall test object (sinusoidal input, $A_{pp}=15\text{mm}$, $T=3\text{s}$)



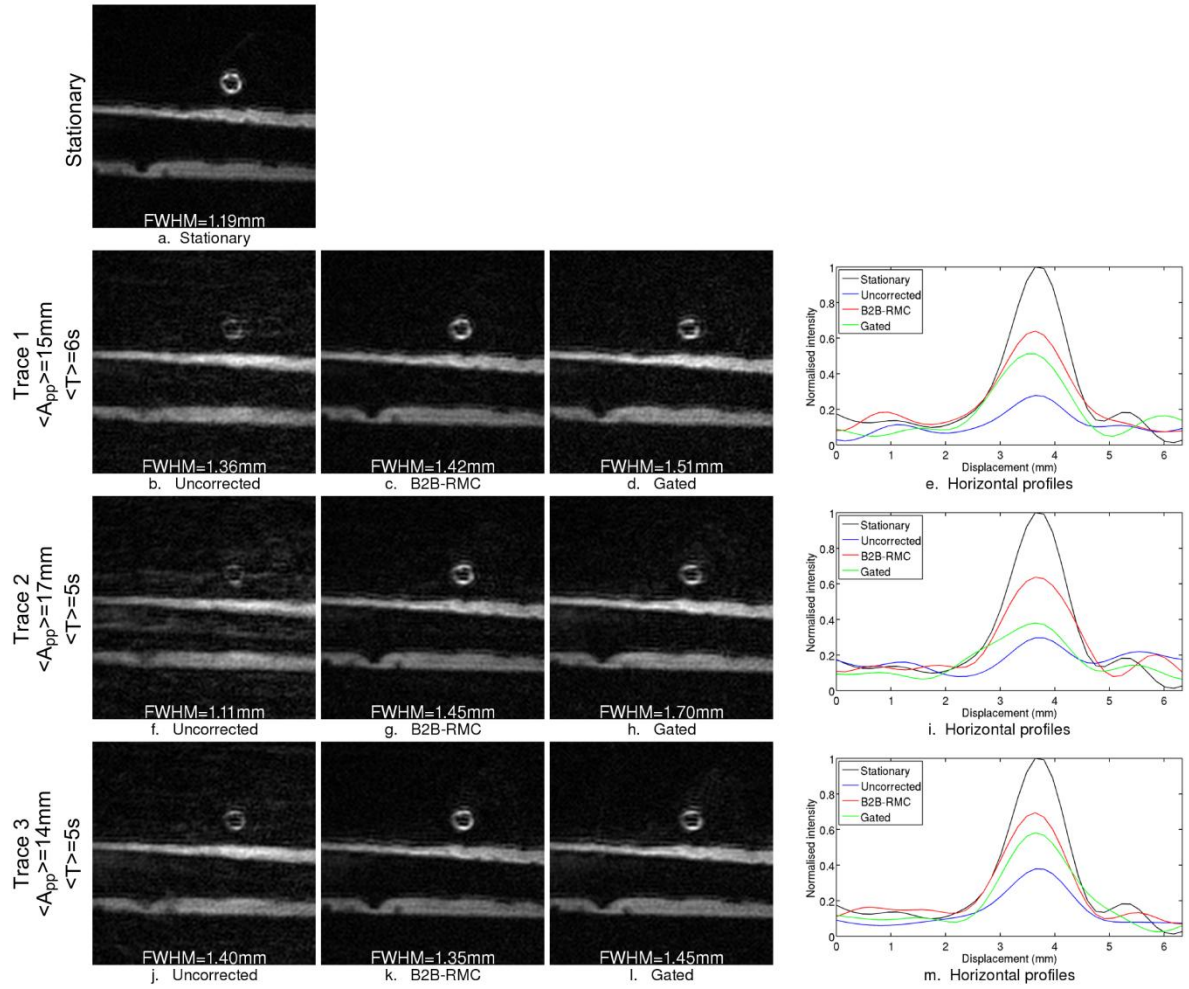
The in-plane (x (a) and y (b)) and through-plane (z (c)) B2B-RMC displacements plotted with navigator displacement for the tests performed with a coronary artery wall test object and an input sinusoid with $A_{pp}=15\text{mm}$ and $T=3\text{s}$. The navigator trace is shown in (d). The corresponding 2D histograms are shown in (e), (f) and (g) for the plots shown in (a), (b) and (c) respectively. The increased velocity of the phantom resulted in an increase in the loop like trend of the data when compared to figure 4.17 caused by motion between the low resolution data acquisition and the navigator. Inspiratory points (positive differential of the navigator displacement) are plotted as points, whereas expiratory points (negative differential of the navigator displacement) are plotted as crosses and stationary points (zero differential of the navigator displacement) are plotted as empty circles. Inspiratory points lie on the top of the loops and expiratory points on the bottom (see a and c).

Figure 4.20: The performance of B2B-RMC in correcting sinusoidal motion in images of a coronary artery wall test object



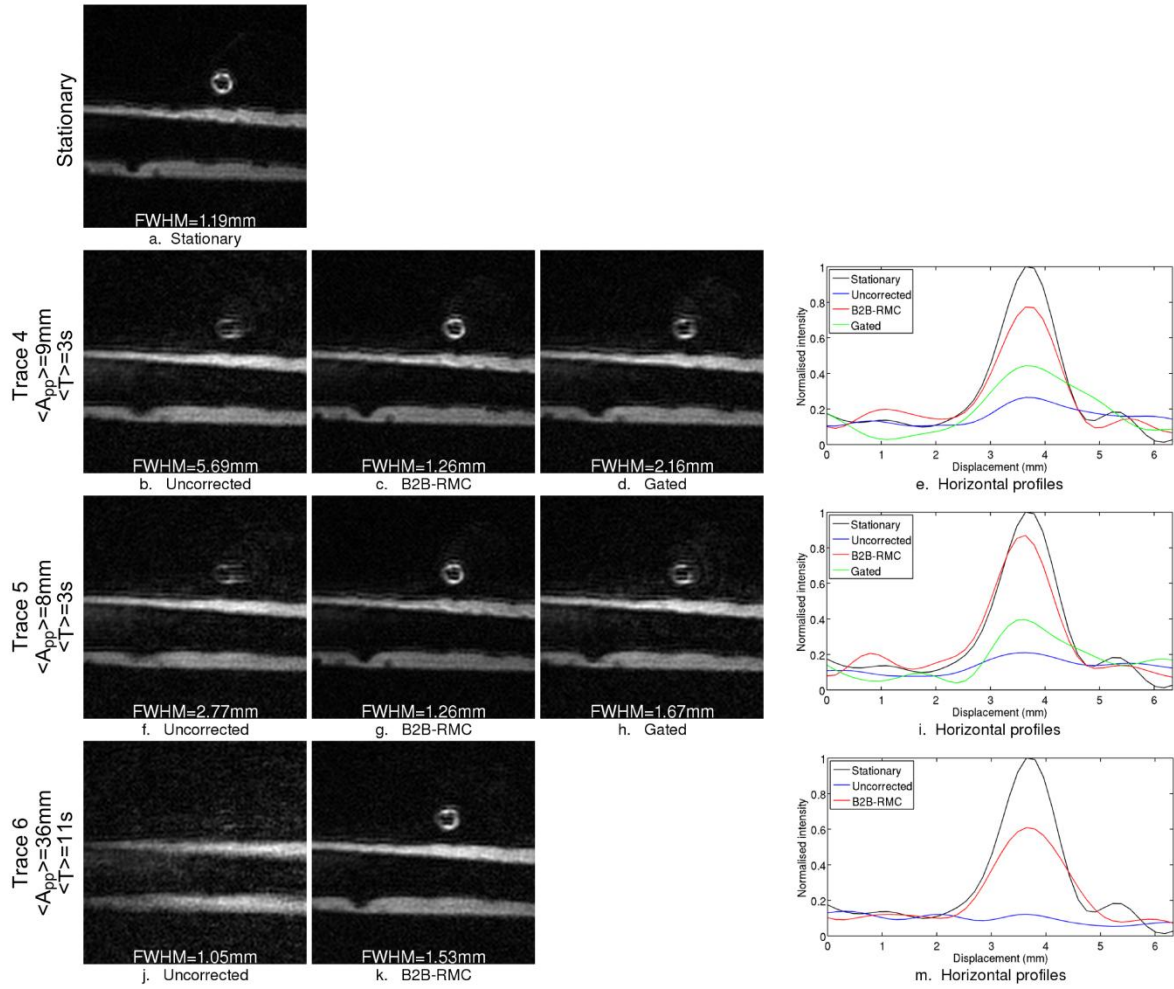
Images of a coronary artery wall test object acquired while stationary (a) and while moving with sinusoidal motion of amplitude A_{pp} and period T . B2B-RMC results in substantial image improvement (c, f, i and l) when compared to the uncorrected images (b, e, h and k). Horizontal intensity profiles through the right hand edge of the vessel wall (d, g, j and m) are provided and the corresponding FWHM is provided on the respective image.

Figure 4.21: Example uncorrected, B2B-RMC and gated images acquired with a coronary artery test object following physiological respiratory traces 1-3



Images of a coronary artery wall test object acquired while stationary (a) and while following respiratory traces obtained from three healthy volunteers (see figure 4.13) with mean peak to peak amplitude $\langle A_{pp} \rangle$ and mean period $\langle T \rangle$. Images are shown uncorrected and ungated for motion (b, f and j), corrected using B2B-RMC (c, g and k) and gated to a 5mm window around the end-expiratory position using a navigator (d, h and l). Horizontal intensity profiles through the right hand edge of the vessel wall (e, i and m) are provided and the corresponding FWHM is given on the respective image. While the gated images demonstrate a substantial improvement in image quality over the uncorrected images, the B2B-RMC images are better still, which is highlighted by the smaller FWHM of the horizontal intensity profiles (e, i and m, red line).

Figure 4.22: Example uncorrected, B2B-RMC and gated images acquired with a coronary artery test object following respiratory traces 4-6



Images of a coronary artery wall test object acquired while stationary (a) and while following respiratory traces obtained from three healthy volunteers (see figure 4.13) with mean peak to peak amplitude $\langle A_{pp} \rangle$ and mean period $\langle T \rangle$. Images are shown uncorrected and ungated for motion (b, f and j), corrected using B2B-RMC (c, g and k) and gated to a 5mm window around the end-expiratory position using a navigator (d, h and l). Horizontal intensity profiles through the right hand edge of the vessel wall (e, i and m) are provided and the corresponding FWHM is given on the respective image. While the gated images demonstrate a substantial improvement in image quality over the uncorrected images, the B2B-RMC images are better still, which is highlighted by the smaller FWHM of the horizontal intensity profiles (e, i and m, red line).

4.e.v.3 Discussion

B2B-RMC is able to successfully correct for a range of motion in coronary artery vessel wall test objects. When compared to images corrected using the navigator displacements (see figure 4.16), B2B-RMC images appeared similar and measurements of the FWHM of an intensity profile drawn through the right hand edge of the vessel wall suggest that B2B-RMC was more effective (mean FWHM $1.18 \pm 0.05\text{mm}$, $1.44 \pm 0.03\text{mm}$ and $1.60 \pm 0.02\text{mm}$ for stationary, B2B-RMC and navigator based correction respectively). The poorer performance of the navigator based correction was caused by the lower precision of the navigator information.

Images acquired during sinusoidal motion were substantially improved after B2B-RMC. However, when the horizontal intensity profiles and corresponding FWHMs are compared to those from the stationary images, it is apparent that B2B-RMC is unable to completely compensate for sinusoidal motion. Furthermore, degradation of the B2B-RMC images and the corresponding FWHM values was observed when both the period was reduced and the amplitude was increased. There are three clear reasons for this reduced performance: firstly there is more motion during the acquisition of the low resolution data with reduced periods or increased amplitude; secondly the FOV is small in the through-plane direction and the SNR rapidly reduces towards the edges of the volume, limiting the amount of motion that can be corrected in this direction; finally there is more motion during the acquisition of the high resolution data which will degrade the images and cannot be corrected using this technique. In cases where the amplitude of motion is too large in the through-plane direction, a sigmoid like curve may be observed when the B2B-RMC displacements are plotted with the actual displacement, due to the decrease in SNR at the edges of the volume and the limited change in shape of the test object in this direction. While this results in underestimation of the motion at extreme displacements (see figure 4.18), it is preferable to the NSPCC matching to an incorrect region, possibly within the image noise, which would produce random erroneous displacements. A consequence of more rapid motion (see figure 4.19) is an increase in the loop like trend of the B2B-RMC displacements when plotted with navigator displacement. Points obtained when the differential of the navigator displacement was positive (expiratory points, dots in the figures) are located on the top of the loop and those from when the differential of the navigator displacement was negative (inspiratory points, crosses on the figures) are located on the bottom of the loop. This hysteresis like trend is the result of motion between the low resolution acquisition and the navigator echo. Assuming a typical time from the low resolution data (central kz line) to the navigator echo of 50ms in B2B-RMC, with sinusoidal motion, $A_{pp}=15\text{mm}$, $T=3\text{s}$, the expected maximum displacement between the inspiratory and expiratory curves is approximately 3mm, which corresponds to the results in figure 4.19. However, the reverse centric through-plane phase ordering of the low resolution data means that the time between the centre of k-space of the low resolution data and the high resolution data is minimised (28ms), thus maintaining the temporal relevance of the B2B-RMC displacements.

B2B-RMC was more effective in correcting physiological respiratory motion than sinusoids and the FWHMs measured in the B2B-RMC images acquired during respiratory traces 4 and 5 (both, $\text{FWHM}=1.26\text{mm}$) are close to the FWHM obtained from the stationary image ($\text{FWHM}=1.19\text{mm}$). This is partly due to the skewed distribution of displacements in the physiological respiratory traces which spend more time at end-expiration when compared to the sinusoids. Furthermore, while some of the respiratory traces had short mean periods ($\langle T \rangle=3\text{s}$ for both traces 4 and 5) these were traces with smaller mean amplitudes ($\langle A_{pp} \rangle=9\text{mm}$ for trace 4 and $\langle A_{pp} \rangle=8\text{mm}$ for trace 5). Respiratory trace 6, which had a very large amplitude ($\langle A_{pp} \rangle=36\text{mm}$), had a very long period ($\langle T \rangle=11\text{s}$). As a result, the combination of short periods and large amplitudes, which caused problems in the sinusoidal acquisitions, was not present in these physiological respiratory traces.

Navigator gating with a 5mm window was found to substantially improve image quality over the uncorrected images, but using B2B-RMC, image quality improved further and, although the difference is not statistically significant, the FWHM was reduced (mean FWHM 1.38 ± 0.10 mm vs. 1.70 ± 0.25 mm for B2B-RMC vs. navigator gating, $p=0.08$). This further supports the earlier findings (section 4.e.iv) that for the physiological respiratory traces used in these tests, B2B-RMC outperforms navigator gating with a 5mm window. However, it should be noted that respiratory motion of the coronary arteries is less than that of the diaphragm and the differences in image quality *in-vivo* are expected to be less as a result.

4.e.vi The dependence of high resolution image quality on the spatial resolution of the low resolution images used in B2B-RMC for coronary artery vessel wall imaging

4.e.vi.1 Methods

As discussed in section 3.c.i, the fidelity of the motion correction is expected to depend on the resolution of the low resolution images used in B2B-RMC. However, should the performance of B2B-RMC be sufficient following a reduction in resolution, the spiral readouts could be shortened, thus reducing the acquisition window. Alternatively, the acquisition window could be maintained which would permit an increase in the number of slices acquired. In order to test this, the corrections performed in section 4.e.v were repeated after degrading the in-plane resolution of the low resolution fat images. The reduction in in-plane resolution was achieved by applying a circular mask to the gridded low resolution k-space data in the k_x - k_y plane. Otherwise images were reconstructed and corrected using B2B-RMC in the normal way. For each of the four sinusoids and six physiological respiratory traces the correction was performed for in-plane resolutions (with the approximate equivalent spiral readout duration in brackets) of:

1. 4.8x4.8mm (15ms – original data)
2. 7.6x7.6mm (10ms)
3. 11.8x11.8mm (6ms)
4. 16.2x16.2mm (4ms)
5. 21.6x21.6mm (3ms)

The reconstructed images were compared as in section 4.e.v.

4.e.vi.2 Results

Figure 4.23 shows images of the coronary artery wall test object moving with sinusoidal motion and corrected with B2B-RMC for decreasing in-plane resolution of the low resolution images. The quality of the correction degrades with reduced in-plane resolution, resulting in increased FWHM values. The loss of image quality with reduced resolution is greater with increasing amplitude or decreasing period of the sinusoid. While the visual loss of image quality between (b – 4.8x4.8mm) and (f – 21.6x21.6mm) (acquired with $A_{pp}=15$ mm and $T=5$ s) is small (the FWHM increases from 1.42mm to 1.71mm), the degradation between (t – 4.8x4.8mm) and (x – 21.6x21.6mm) (acquired with $A_{pp}=25$ mm and $T=3$ s) is large (the FWHM increases from 3.12mm to 4.43mm). Figure 4.24 shows the B2B-RMC respiratory displacement plots for the correction of the sinusoid with $A_{pp}=25$ mm and $T=5$ s for the low resolution images with in-plane resolution of 21.6x21.6mm. When compared to the equivalent plots in figure 4.18,

the linear fit in the in-plane (x) direction is very similar (slope=0.89 at full resolution vs. slope=0.88 at 21.6x21.6mm resolution). In the through-plane (z) direction, despite an excellent R^2 value (0.94) of the linear fit, the NSPCC does not track the motion of the phantom (slope=0.28 at full resolution vs. slope=0.07 at 21.6x21.6mm).

For the physiological respiratory traces a similar pattern was observed (see figure 4.25 for traces 1-3 and figure 4.26 for traces 4-6). For traces with small amplitudes (traces 4 and 5), only small changes in the image quality, the shape of the intensity profile and the FWHM values are observed with reducing resolution but for the respiratory traces with larger amplitudes (traces 1, 2 and 6) the degradation is more marked.

Figure 4.27 plots the FWHM for each sinusoid and physiological respiratory trace with the in-plane resolution of the low resolution data used in B2B-RMC. For all four sinusoids and five of the six respiratory traces, FWHM significantly correlates with in-plane resolution ($p < 0.05$ in each case using Pearson's correlation coefficient).

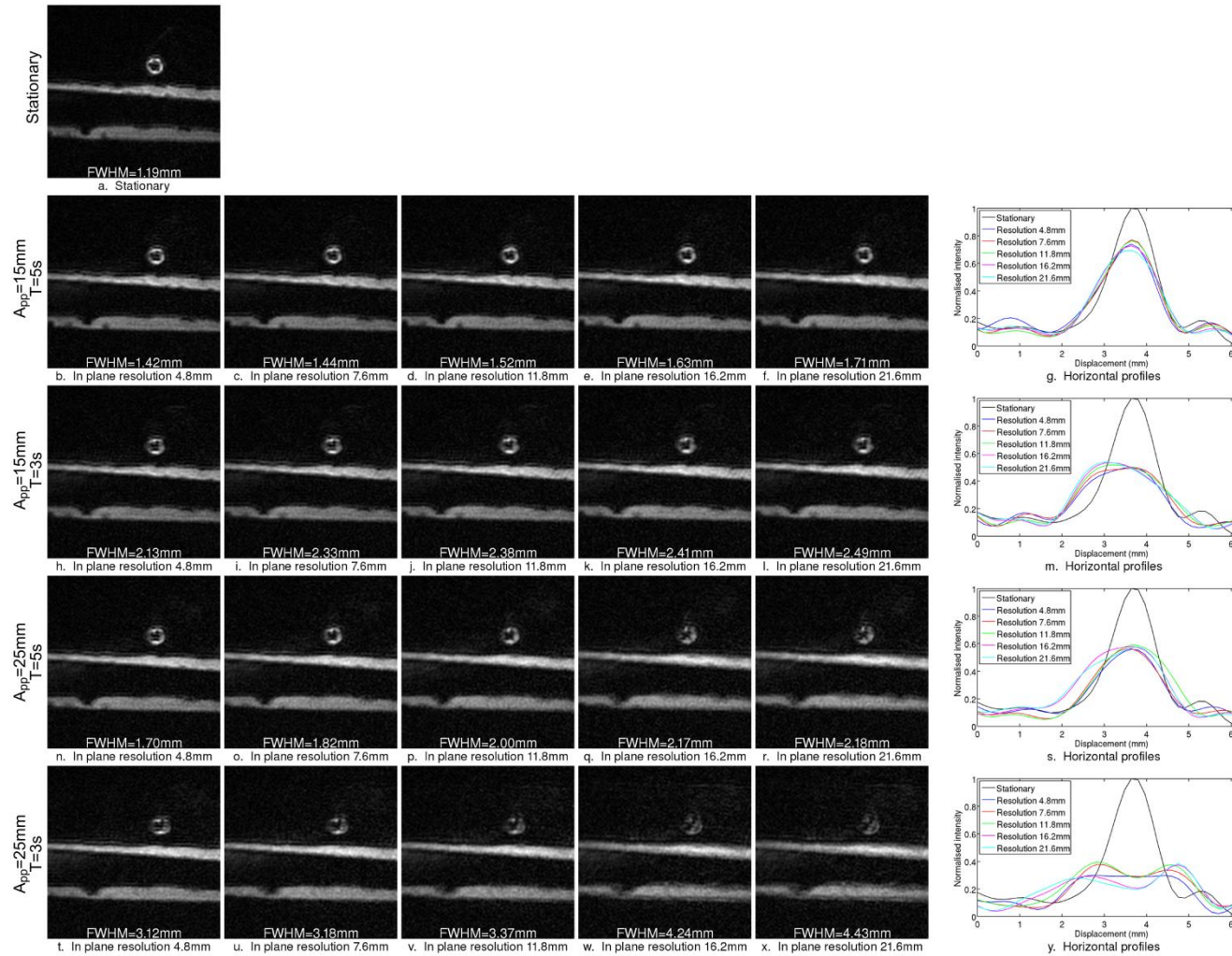
4.e.vi.3 Discussion

Filtering the low resolution images to reduce the in-plane resolution reduces noise but also removes higher resolution information. As a result, the low resolution images acquired at different displacements become more similar. This is particularly a problem in the through-plane direction where there is only a small change in the appearance of the tracked object between slices within the search and reference ROIs, so the NSPCC is less able to track its motion.

The loss of image quality with in-plane resolution is reflected in the FWHM of the horizontal intensity profiles which demonstrated an approximately linear relationship with in-plane resolution. Furthermore, the effect of the loss of in-plane resolution is greater for traces with larger amplitudes and shorter periods due to the more detrimental effect of the uncorrected motion during these acquisitions. *In-vivo*, reduced resolution of the low resolution images could also result in the NSPCC matching the reference ROI to an incorrect region in the nearby fatty anatomy, resulting in erroneous displacements and hence reducing the accuracy of B2B-RMC. However, the possibility of this was minimised in the phantom studies by using a single test object moving rigidly with the phantom without the surrounding anatomy that is present *in-vivo*,

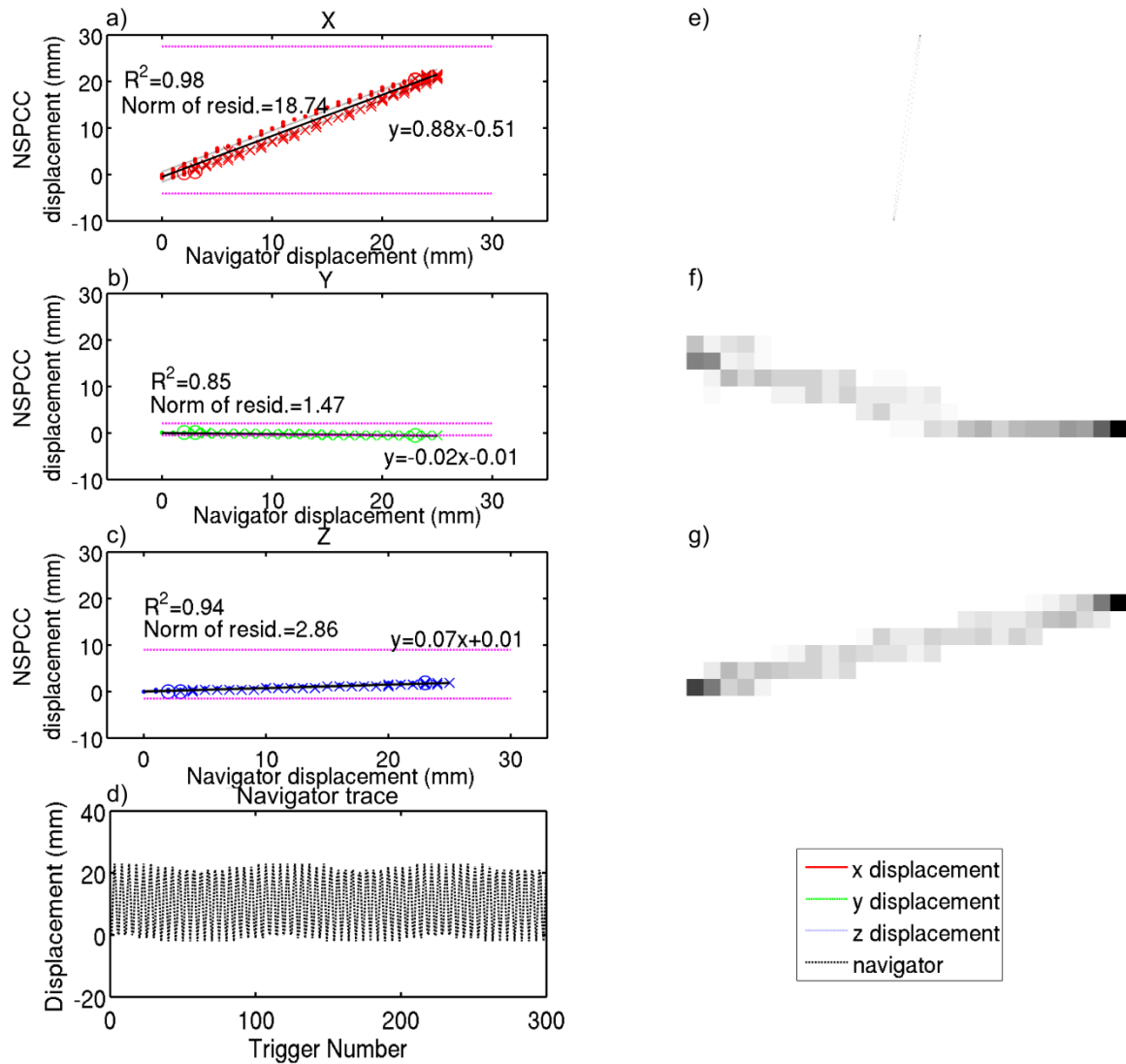
In section 3.c.i the in-plane resolution of the low resolution images was increased (from 6.0mm to 4.8mm) in an attempt to improve the performance of B2B-RMC. The results obtained here using a respiratory motion phantom, suggest that increases in in-plane resolution can improve the performance of B2B-RMC.

Figure 4.23: The effect of in-plane resolution on the performance of B2B-RMC in correcting sinusoidal motion of a coronary artery wall test object



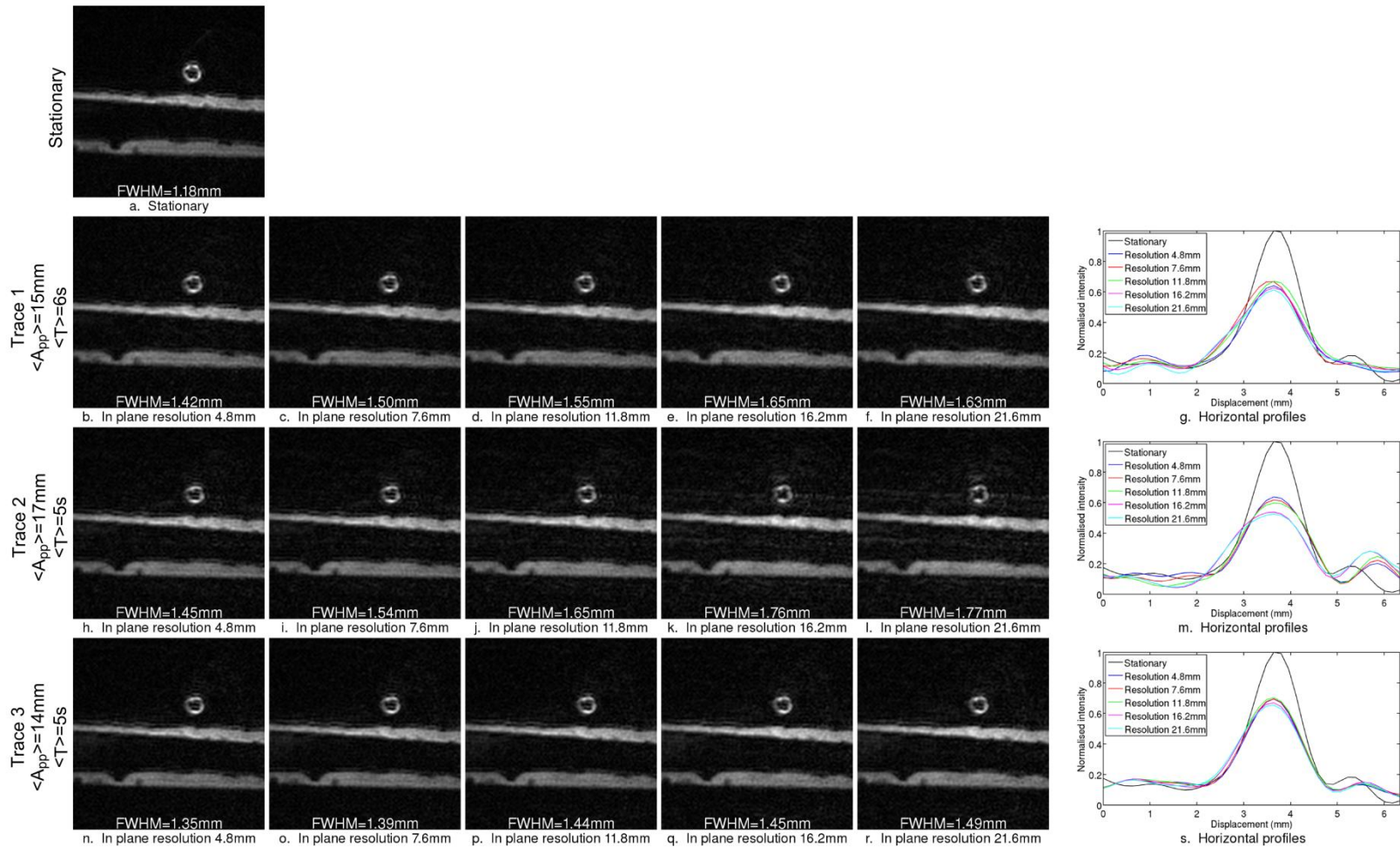
Images of a coronary artery wall test object moving with sinusoidal motion of amplitude A_{pp} and period T , motion corrected using B2B-RMC. Corresponding horizontal intensity profiles through the right hand edge of the vessel wall are also shown (g, m, s, y) and the FWHM of these profiles is given on the images. Prior to correction the low resolution images used for B2B-RMC were filtered to reduce in-plane resolution. Lower resolution images result in poorer B2B-RMC performance and this is reflected in the corresponding increasing FWHM values. The equivalent stationary image is also shown for reference (a).

Figure 4.24: B2B-RMC displacements plotted with navigator displacements for the sinusoid with $A_{pp}=25\text{mm}$ and $T=5\text{s}$ after degrading the low resolution images to $21.6\times 21.6\text{mm}$ in-plane resolution



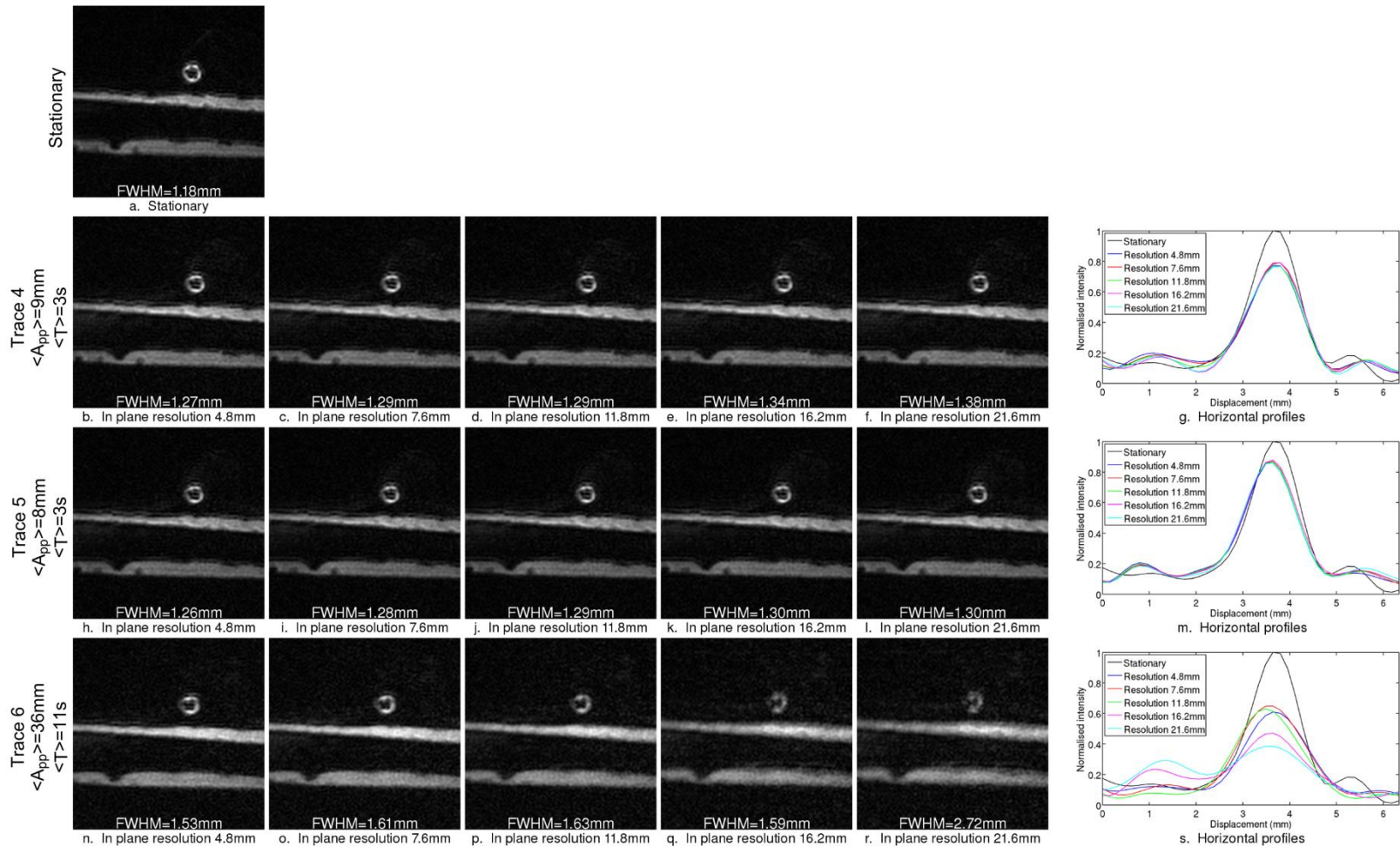
The in-plane (x (a) and y (b)) and through-plane (z (c)) B2B-RMC displacements plotted with navigator displacement for a coronary artery wall test object and an input sinusoid with $A_{pp}=25\text{mm}$ and $T=5\text{s}$ after degradation of the in-plane resolution of the low resolution images to $21.6\times 21.6\text{mm}$. The navigator trace is shown in (d). The corresponding 2D histograms are shown in (e), (f) and (g) for the plots shown in (a), (b) and (c) respectively. While a linear relationship between the B2B-RMC and navigator displacements is observed in all directions the loss of detail in the low resolution images results in a failure to track the through-plane (z) motion (c).

Figure 4.25: The effect of in-plane resolution on the performance of B2B-RMC in correcting respiratory motion of a coronary artery wall test object (traces 1-3)



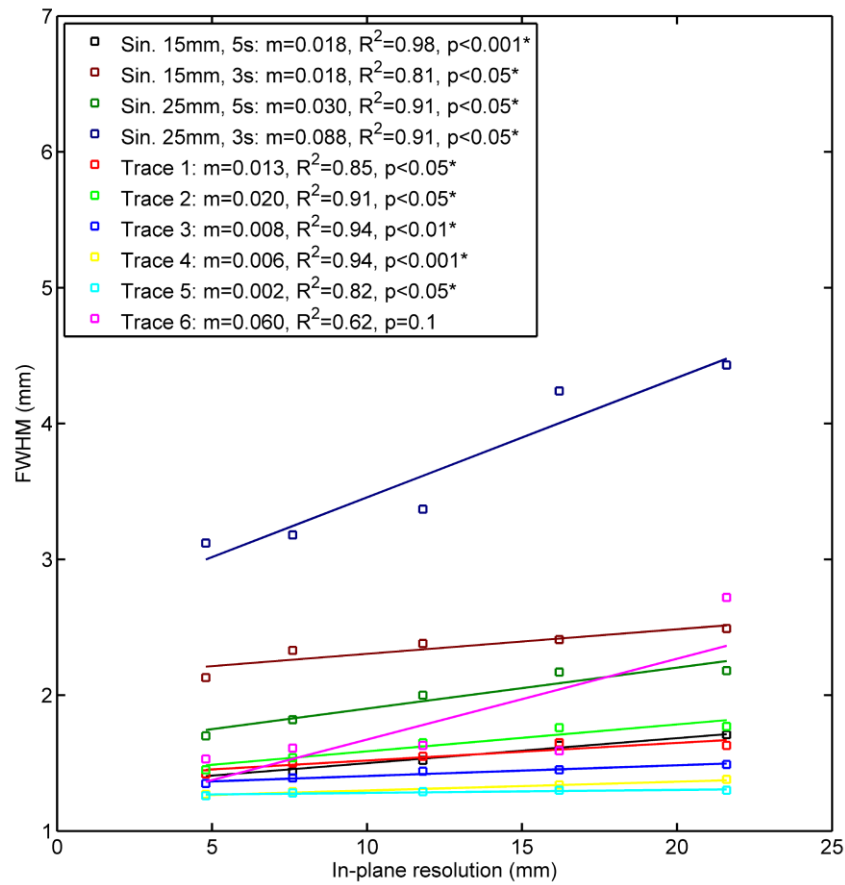
Images of a coronary artery wall test object moving with respiratory traces 1-3 (shown in figure 4.13) of mean peak to peak amplitude $\langle A_{pp} \rangle$ and period $\langle T \rangle$, motion corrected using B2B-RMC. Prior to correction the low resolution images used for B2B-RMC were filtered to reduce in-plane resolution. Lower resolution images generally result in poorer B2B-RMC performance and this is reflected in the FWHM of the corresponding intensity profiles (g, m and s) which is given on the images. The equivalent stationary image is also shown for reference (a).

Figure 4.26: The effect of in-plane resolution on the performance of B2B-RMC in correcting respiratory motion of a coronary artery wall test object (traces 4-6)



Images of a coronary artery wall test object moving with respiratory traces 4-6 (shown in figure 4.13) of mean peak to peak amplitude $\langle A_{pp} \rangle$ and period $\langle T \rangle$, motion corrected using B2B-RMC. Prior to correction the low resolution images used for B2B-RMC were filtered to reduce in-plane resolution. Lower resolution images generally result in poorer B2B-RMC performance and this is reflected in the FWHM of the corresponding intensity profiles (g, m and s) which is given on the images. The equivalent stationary image is also shown for reference (a).

Figure 4.27: The variation of the FWHM of the intensity profiles with noise in the low resolution images



The FWHM of the horizontal intensity profile through the right hand edge of the vessel wall after B2B-RMC increases with decreasing in-plane resolution. The amplitude and period of the sinusoids (labelled as "sin.") with the slope of the linear fit to the data (m), Pearson's correlation coefficient (R^2) and the associated p-value are given in the legend. Cases where R^2 of the linear fit reached significance ($p < 0.05$) are highlighted with *.

4.e.vii The dependence of high resolution image quality on the SNR of the low resolution images used in B2B-RMC for coronary artery vessel wall imaging

4.e.vii.1 Methods

In MR imaging, SNR may be traded for increased image resolution or decreased imaging time. However, it is expected that a loss of SNR in the low resolution images is likely to result in an increased error in the B2B-RMC displacements. In extreme cases, the NSPCC could incorrectly identify a region of noise instead of the region of fat to be tracked. In order to test the dependence of the performance of B2B-RMC on noise in the low resolution images, the corrections performed in section 4.e.v were repeated after degrading the SNR.

A similar acquisition to the B2B-RMC acquisition performed in section 4.e.v was performed with the same test object and receive coil, but with all of the RF pulses switched off, resulting in an equivalent, noise only acquisition. Noise was added to the low resolution data used in the corrections by modifying the ungridded raw low resolution data according to:

$$s'(l, m, n) = s(l, m, n) + f \cdot \eta(l, m, n) \quad 4.1$$

where $s(l, m, n)$ is the original complex low resolution data acquired at spiral point l , kz step m and low resolution dataset n ; $\eta(l, m, n)$ is the complex noise only data acquired at the same point; $s'(l, m, n)$ is the new data at the same point; and f is a multiplying factor. Assuming that the noise in the original data ($s(l, m, n)$) is normally distributed with standard deviation σ and that the noise only data ($\eta(l, m, n)$) is purely noise with the same distribution and standard deviation σ , the standard deviation of the noise in $s'(l, m, n)$ is:

$$\sigma' = \sqrt{f^2 + 1} \cdot \sigma \quad 4.2.$$

The SNR in the reconstructed images, should therefore, be reduced by a factor of $\sqrt{f^2 + 1}$. Low resolution images were reconstructed with values of $f=0, 4, 9, 16$ and 25 , corresponding to σ' of $1.0\sigma, 4.1\sigma, 9.1\sigma, 16.0\sigma$ and 25.0σ for use in the corrections. All other reconstruction and processing was performed in the usual way. The reconstructed images were compared in the same way as those in sections 4.e.v.

4.e.vii.2 Results

Figure 4.28 shows images of the coronary artery wall test object moving with sinusoidal motion corrected using B2B-RMC with increasingly noisy low resolution images. In general, increased noise within the low resolution images results in a poorer correction and, therefore an increased FWHM of the horizontal intensity profile. The effect of noise within the low resolution images increases with increasing A_{pp} and decreasing T . Figure 4.29 shows the B2B-RMC displacements for the sinusoidal correction with $A_{pp}=15\text{mm}$, $T=5\text{s}$ and a noise increase of 25.0 . Comparing these plots to the equivalent plots shown in figure 4.17 with no added noise, the effect of the increased noise is evident. There is little change in the slope of the linear fit to the navigator displacement in each direction: $0.91, 0.04$ and 0.31 in in-plane (x), in-plane (y) and through-plane (z) respectively for the original data vs. $0.92, 0.04$ and 0.27 for the data with a noise increase of 25.0 . However, there is a greater spread of results around the linear fit, which is reflected in the reduced R^2 values in the in-plane (y) and through-plane (z) directions in figure 4.29 when compared to figure 4.17 ($R^2=0.89$ and 0.92 in in-plane (y) and through-plane (z) respectively for the original data vs. $R^2=0.37$ and 0.58 for the data with a noise increase of 25.0).

For the physiological respiratory traces (see figure 4.30 and figure 4.31) a slight loss in image quality and an associated increase in the FWHM is observed with increased noise in the low resolution images. The loss in image quality is greatest for respiratory trace 6 which has the largest amplitude.

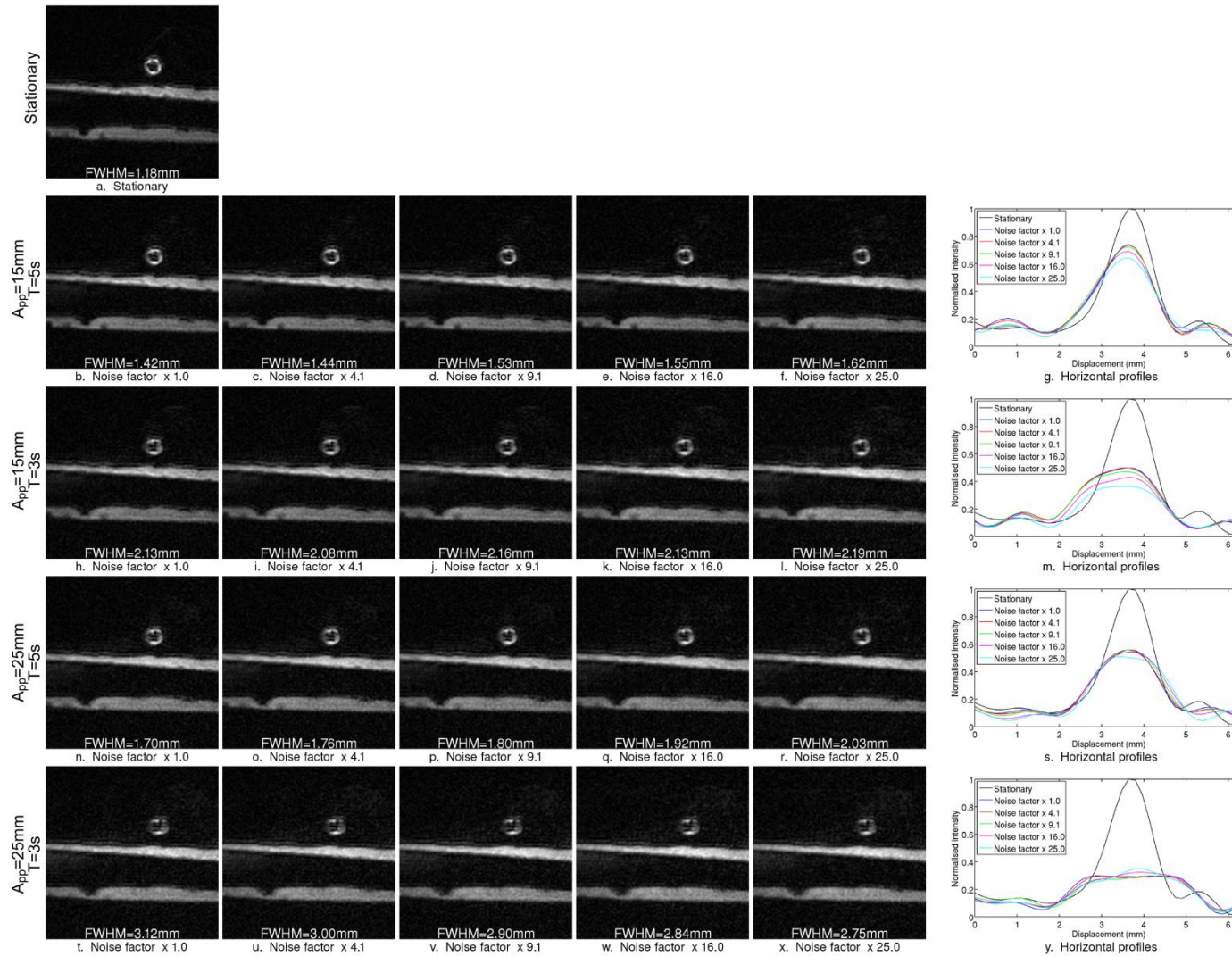
Figure 4.32 plots the FWHM for each sinusoid and physiological respiratory trace with the noise in the low resolution images relative to the original data. For six of the ten traces (four sinusoids and six

respiratory traces) a significant linear relationship ($p < 0.05$) was observed between FWHM and the relative noise level. In the case of the sinusoid with $A_{pp} = 25\text{mm}$ and $T = 3\text{s}$, FWHM was found to significantly decrease with increasing noise (slope = -0.014mm , $R^2 = 0.96$, $p < 0.01$). However, visually, there is a degradation of image quality with increasing noise in this case (figure 4.28), and this aberrant result is thought to be due to the limitations of using FWHM as a measure of image quality. For the remaining three traces no significant relationship was found between FWHM and the relative noise level. However, this is thought to be the result of the low number of noise levels (5) used and the small magnitude of the effect of SNR on FWHM.

4.e.vii.3 Discussion

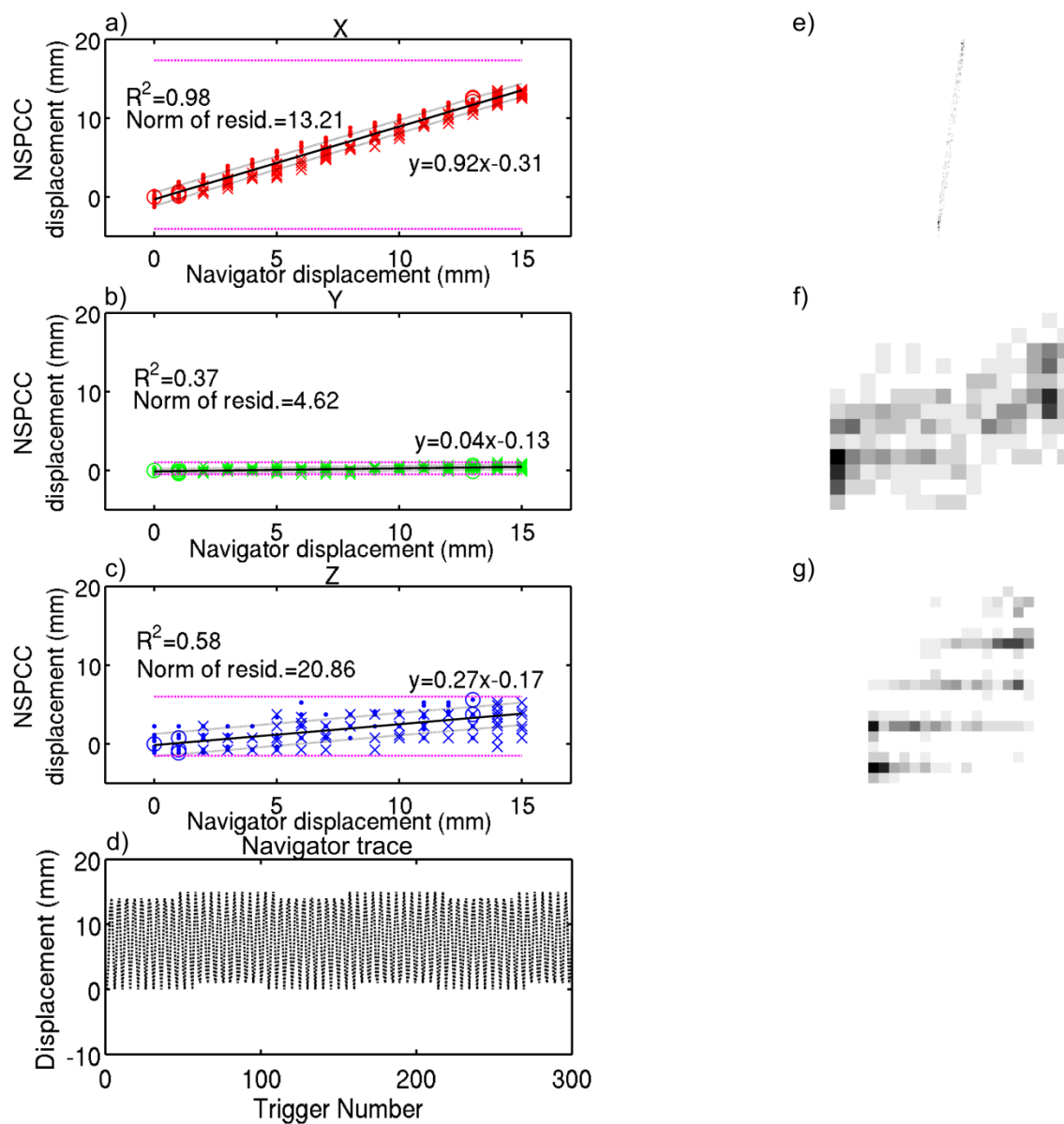
Increasing noise within the low resolution acquisitions degrades the B2B-RMC images via a spread of the B2B-RMC displacements around the true values (see figure 4.28 compared to figure 4.17). Overall, there was an increase in FWHM of the horizontal intensity profiles as the noise level increased and this reached statistical significance in six of the ten traces used in these tests. Even though the final result of this degradation is similar to the result of reducing the in-plane resolution, the magnitude of the degradation was much less for the noise increases applied here. For a noise increase by a factor of 4.1 there was no visible loss in image quality for any of the traces and the maximum increase in FWHM was 0.06mm . This suggests that the low resolution data may be acquired more rapidly in future by sacrificing some of the SNR, which may be achieved via parallel imaging techniques or reductions in the FOV. As for the resolution tests, it is yet to be determined whether such decreases in SNR can be achieved *in-vivo* with similar results.

Figure 4.28: The effect of noise on the performance of B2B-RMC in correcting sinusoidal motion of a coronary artery wall test object



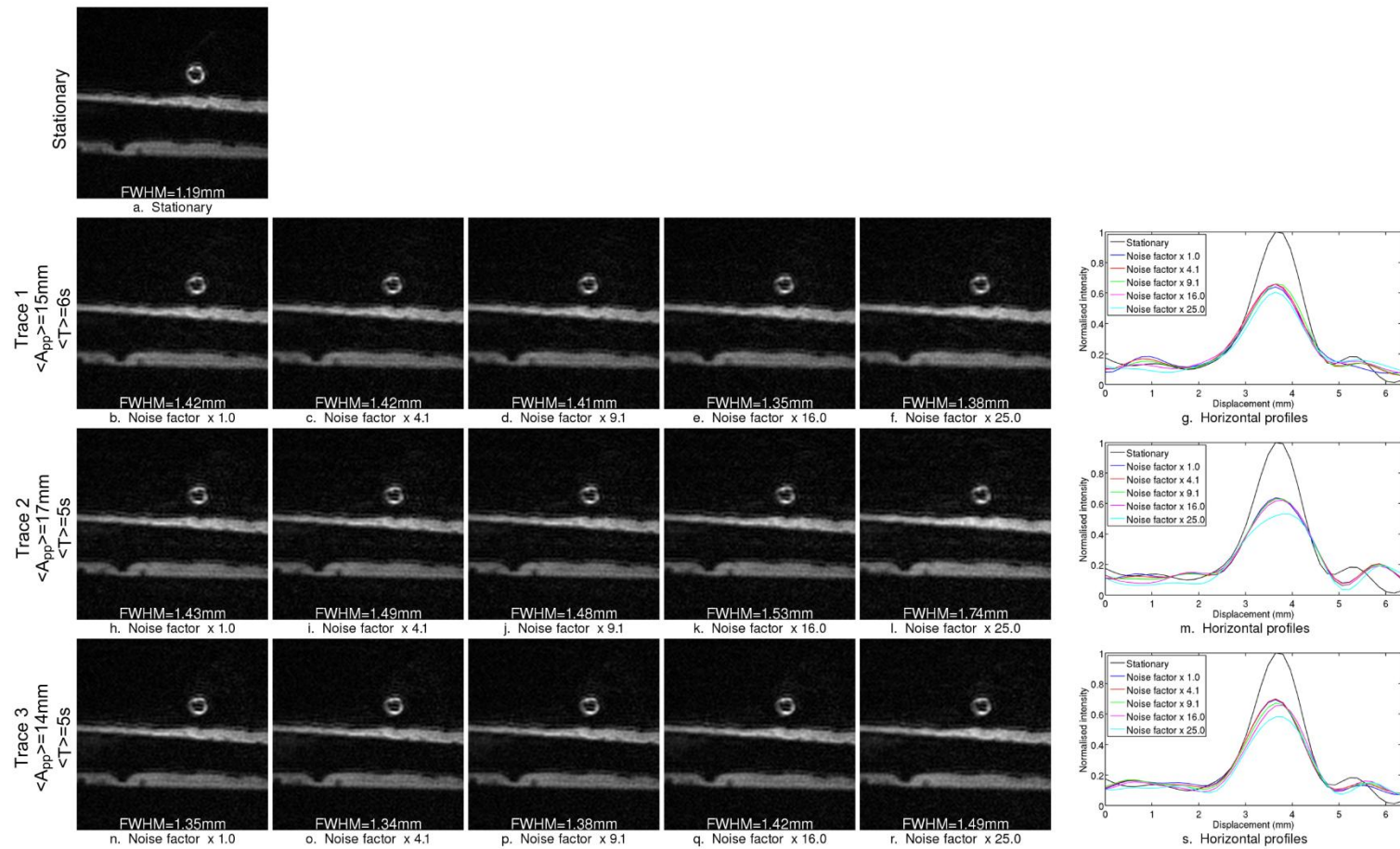
Images of a coronary artery wall test object moving with sinusoidal motion of amplitude A_{pp} and period T , motion corrected using B2B-RMC. Prior to correction additional noise was added to the low resolution images used for B2B-RMC. More noisy images result in poorer B2B-RMC performance. This is reflected in the horizontal intensity profiles through the right hand side of the vessel wall (g, m, s and y) and the corresponding FWHM which is given on the images. The equivalent stationary image is also shown for reference (a).

Figure 4.29: B2B-RMC displacements plotted with navigator displacements for the sinusoid with $A_{pp}=15\text{mm}$ and $T=5\text{s}$ after increasing the noise in the low resolution images by a factor of 25



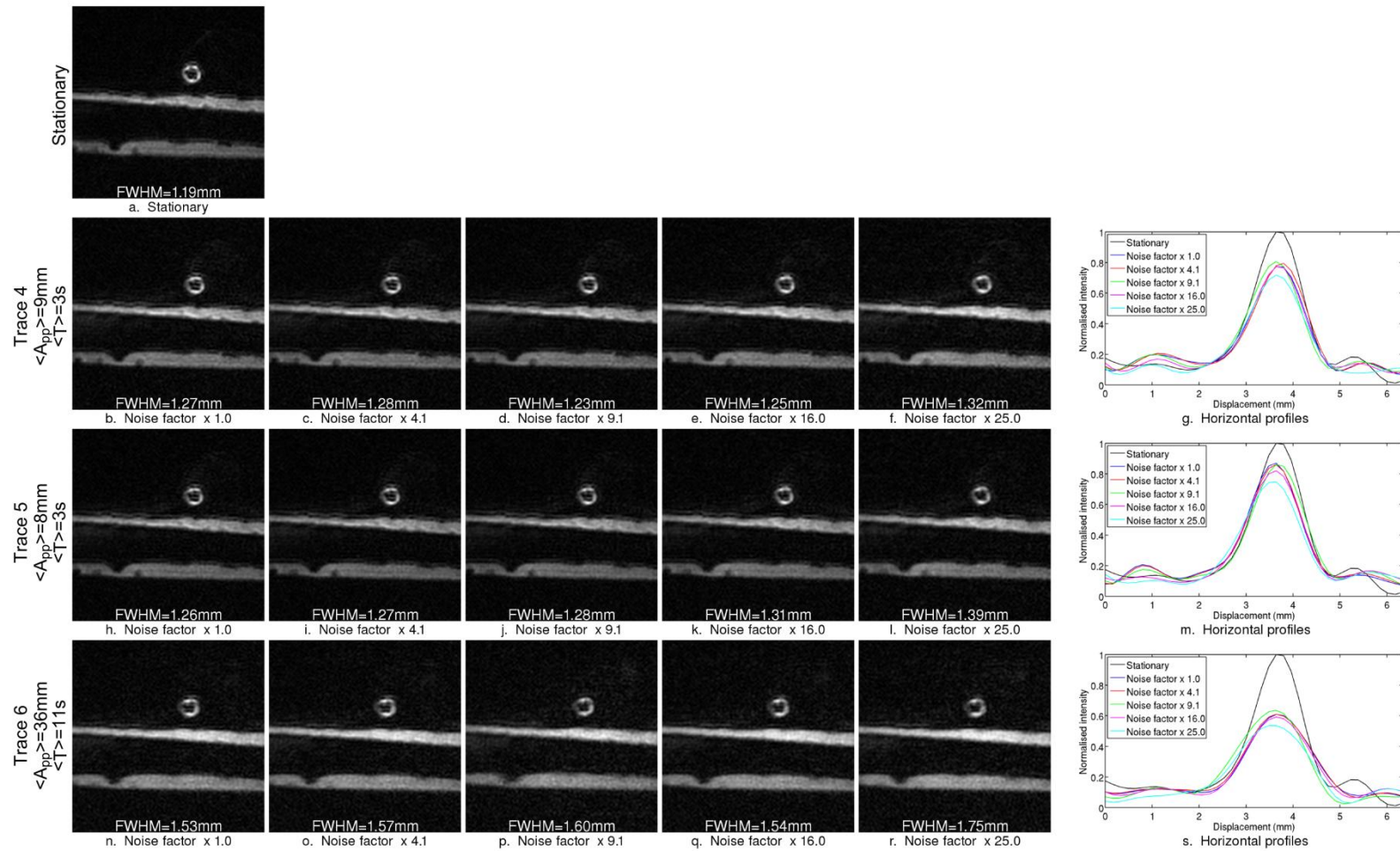
The phantom displacements in-plane (x (a) and y (b)) and through-plane (z (c)) obtained from the B2B-RMC data are plotted against navigator displacement for a coronary artery wall test object and an input sinusoid with $A_{pp}=15\text{mm}$ and $T=5\text{s}$ after increasing the noise in the low resolution images by a factor of 25.0. The navigator trace is shown in (d). The corresponding 2D histograms are shown in (e), (f) and (g) for the plots shown in (a), (b) and (c) respectively. While there is greater spread of the B2B-RMC displacements around the linear fit, the slope of the linear relationship is maintained (compare to figure 4.17).

Figure 4.30: The effect of noise on the performance of B2B-RMC in correcting respiratory motion of a coronary artery wall test object (traces 1-3)



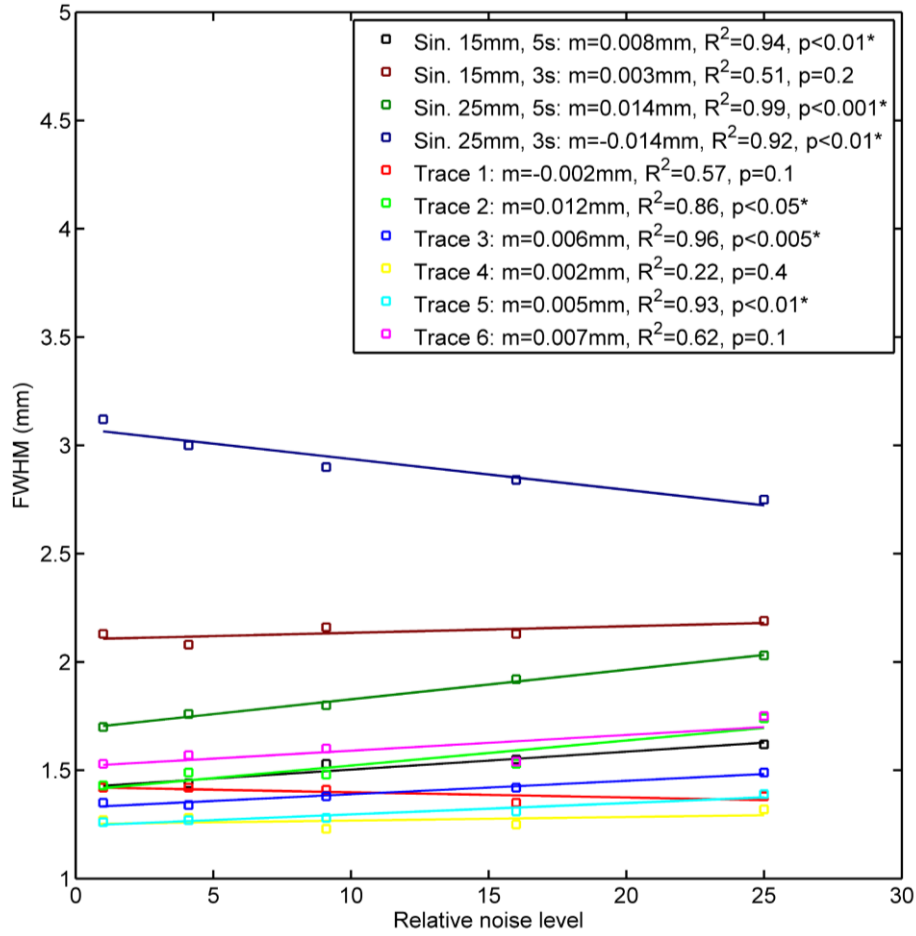
Images of a coronary artery wall test object moving with respiratory traces 1-3 (shown in figure 4.13) of mean peak to peak amplitude $\langle A_{pp} \rangle$ and period $\langle T \rangle$, motion corrected using B2B-RMC. Prior to correction additional noise was added to the low resolution images used for B2B-RMC. Noisier images result in poorer B2B-RMC performance which is generally reflected in the corresponding intensity profiles (g, m and s) and their FWHM values (given on the images). The equivalent stationary image is also shown for reference (a).

Figure 4.31: The effect of noise on the performance of B2B-RMC in correcting respiratory motion of a coronary artery wall test object (traces 4-6)



Images of a coronary artery wall test object moving with respiratory traces 4-6 (shown in figure 4.13) of mean peak to peak amplitude $\langle A_{pp} \rangle$ and period $\langle T \rangle$, motion corrected using B2B-RMC. Prior to correction additional noise was added to the low resolution images used for B2B-RMC. Noisier images result in poorer B2B-RMC performance which is generally reflected in the corresponding intensity profiles (g, m and s) and their FWHM values (given on the images). The equivalent stationary image is also shown for reference (a).

Figure 4.32: The variation of the FWHM of the intensity profiles with noise in the low resolution images



The FWHM of the horizontal intensity profile through the right hand edge of the vessel wall is plotted with the relative noise level in the low resolution images used in B2B-RMC. The amplitude and period of the sinusoids (labelled as “sin.”) with the slope of the linear fit to the data (m), Pearson’s correlation coefficient (R^2) and the associated p -value are given in the legend. Cases where R^2 of the linear fit reached significance ($p < 0.05$) are highlighted with *.

4.f Discussion

Careful design and construction of a respiratory motion phantom and the associated realistic coronary test objects has enabled an assessment of the efficacy of B2B-RMC in response to a broad range of parameters. The initial tests performed in this chapter (section 4.e.ii) assessed the performance of the phantom in following sinusoidal motion. Subsequently, the phantom was used to validate the NSPCC algorithm for in- and through-plane motion (section 4.e.iii). Tests with the coronary artery and coronary vessel wall test object demonstrated that B2B-RMC outperforms navigator gating with a 5mm gating window for the six physiological respiratory traces obtained from healthy subjects (section 4.e.iv and 4.e.v). The performance of B2B-RMC in correcting for sinusoidal motion was also assessed with the coronary vessel wall phantom (section 4.e.v). It could be argued that these sinusoids do not represent real respiratory motion. However it was consistently these traces which highlighted the limitations of

B2B-RMC performance while the physiological respiratory traces demonstrated the response to more realistic motion. Additionally, the sinusoids enabled separation of the effects of increased respiratory amplitude (A_{pp}) and reduced respiratory period (T).

It was shown (section 4.e.v) that while B2B-RMC was able to track sinusoidal motion in the coronary vessel wall test object with $A_{pp}=15\text{mm}$ and $T=5\text{s}$ (4.5mm of through-plane motion), the performance of B2B-RMC in the through-plane direction was reduced when $A_{pp}=25\text{mm}$ (7.5mm of through-plane motion). In contrast, the simpler test object shown in figure 4.10 was accurately tracked over 12mm of through-plane motion (see section 4.e.iii). This discrepancy in the amount of through-plane (z) motion that was successfully tracked is the result of the fact that the fat surrounding the vessel in the coronary vessel wall test object, (see figure 4.6) changes relatively little along the vessel length (in the through-plane (z) direction), making it more difficult to track over large displacements. Furthermore, the SNR is decreased at the edges of the low resolution volume in the through-plane (z) direction due to the imperfect slice excitation profile, which makes tracking large displacements in this direction even more challenging. This limit to the amount of through-plane (z) motion that may be successfully tracked is also potentially problematic *in-vivo* and to assess the scale of this, the B2B-RMC results obtained from 10 subjects imaged in chapter 6 were reviewed. In these subjects, an average of $19.4\pm 6.3\text{mm}$ (range 13-31mm) of diaphragm motion was corrected for, which was found to correspond to $6.6\pm 1.9\text{mm}$ (range 3.2-9.1mm) in-plane (x), $5.3\pm 2.3\text{mm}$ (range 2.8-9.9mm) in-plane (y) and $5.1\pm 2.8\text{mm}$ (range 1.9-10.5mm) through-plane (z) motion.

Based on the phantom tests using sinusoidal motion and the vessel wall test object (where 4.5mm of through-plane (z) motion was successfully tracked with $A_{pp}=15\text{mm}$ and $T=5\text{s}$), a cautious estimate for the amount of through-plane (z) motion that can be accurately corrected for is $\sim 5\text{mm}$. As a result, it may be beneficial to use diaphragmatic navigator gating to limit through-plane motion during B2B-RMC acquisitions. It should be noted that 5mm of through-plane (z) motion corresponds to a navigator gating window much greater than 5mm, but of variable size depending on the orientation of the imaging slab and relationship between the respiratory motion of the diaphragm and coronary arteries. In addition, this estimate is rather conservative; *in-vivo* respiratory motion is not sinusoidal and in the phantom tests, B2B-RMC was more effective at correcting for physiological respiratory motion than for sinusoidal motion. Furthermore, the through plane changes in *in-vivo* epicardial fat distribution are generally much greater than was simulated using the vessel wall test object.

In section 4.e.v, for physiological respiratory trace 6, B2B-RMC was able to correct for 33mm of in-plane (x) motion. Limitations on the amplitude of translational in-plane motion that may be corrected are not expected for motion at physiological amplitudes. However, at extreme respiratory displacements *in-vivo*, deformation of the tracked anatomy is more likely and simple 3D translational motion correction may no longer be adequate.

While the vessel sharpness measurements used in section 4.e.vi and the FWHM and horizontal intensity profiles used in sections from 4.e.v demonstrated the improvements in image quality enabled by B2B-

RMC, they also emphasized the superiority of the stationary images over the B2B-RMC images in many examples. Imperfections in the correction are caused by a number of factors including:

- i. motion during the low resolution acquisition;
- ii. motion during the high resolution acquisition;
- iii. motion between the low and high resolution acquisitions;
- iv. the limited precision of the B2B-RMC performed;
- v. changes in local B_0 as the phantom moves;
- vi. artefacts caused by the electronic switching of the stepper motor within the phantom.

Throughout this section, the FWHM of intensity profiles has been used as a quantitative measure of the performance of B2B-RMC. However, the complex and often multi-modal shape of the profiles through the vessel wall in the uncorrected images often produced misleadingly low FWHM values. The high levels of in-plane motion in these images resulted in spreading of the vessel wall signal over a considerable spatial region, with a faint vessel wall shape present at the most common displacements (end expiration or the extremes of the sinusoid displacement). Hence the FWHM of the low intensity peaks may be small. In contrast, any residual uncorrected motion in the B2B-RMC or navigator gated images results in very local blurring of the vessel wall and an associated increase in the FWHM.

Both reduced in-plane resolution and reduced SNR of the low resolution images resulted in reduced performance of B2B-RMC. However, the magnitude of the degradation of the corrected high resolution images was considerably less for the reductions in SNR tested here (up to a factor of 25 reduction) than for the reductions in resolution tested (up to a factor of 4.5 reduction). In future studies, B2B-RMC may potentially be further improved by increasing the resolution of the low resolution images, which could be performed at the expense of SNR. Alternatively, reduced SNR may be exchanged for an increased FOV in the through-plane direction or a reduced acquisition window.

The phantom was only able to move in one dimension, but after angulation of the test object the imaging plane could be orientated to result in motion in three directions with respect to the imaging volume. Only rigid motion was modelled in these tests, but future work may include non-rigid elements of motion via basic changes in the phantom and setup.

In conclusion, through a series of tests using a respiratory motion phantom with carefully constructed test objects, the performance of motion detection using B2B-RMC has been validated and assessed in response to various parameters of the motion and acquisition. In the process, the algorithms used in correcting for the motion detected have also been validated. B2B-RMC performs well in correcting normal respiratory motion, although the performance depends on the period and amplitude of the motion, particularly in the through-plane direction. Future work should, in particular, consider the benefits of increasing the through-plane FOV of the low resolution images and reducing the duration of the low resolution acquisition window at the expense of SNR.

5. A direct *in-vivo* comparison between B2B-RMC and navigator gating applied to targeted MR coronary angiography

The work presented in this chapter is modified from the paper Scott et al. (2011a).

5.a Introduction

As discussed in section 2.b, for high resolution applications, the majority of CMR studies are performed using navigator gating (Danas et al., 1997, Ehman and Felmlee, 1989). The accept reject algorithm (ARA) (Sachs et al., 1994, Oshinski et al., 1996), typically used with a navigator to limit respiratory motion to a small (typically 5mm) window around end expiration, is inherently inefficient and unpredictable, particularly in the presence of respiratory drift (Taylor et al., 1997). B2B-RMC on the other hand, can correct for the normal range of tidal respiratory motion, resulting in respiratory efficiencies close to 100%. In the previous section (4.e.iv), a direct quantitative comparison was made between navigator gating with a 5mm window and B2B-RMC using in-plane imaging of a coronary artery test object with the respiratory motion phantom. In this chapter the first *in-vivo* quantitative assessment of the efficacy of B2B-RMC is presented, using 3D high resolution MR coronary angiography of the RCA as the imaging application. As described in section 1.c and chapter 2, the small size and substantial motion of the RCA with both the cardiac and respiratory cycles makes it a particularly challenging target for MR angiography. Here, semi-automatic measurement of vessel diameter and vessel edge sharpness is performed to provide an objective evaluation of the performance of B2B-RMC. This assessment was performed in ten healthy subjects and the results are compared to a widely used navigator-gated coronary artery imaging technique.

5.b Methods

As in all sections, imaging was performed on a Siemens 1.5T Avanto MRI scanner (Siemens Medical Systems, Erlangen, Germany) with maximum gradient amplitude 40mT m^{-1} and maximum slew rate $170\text{mT m}^{-1} \text{s}^{-1}$ using a six-channel anterior phased array coil. For this work, ECG gating was performed using a system which was designed in-house (by Mr Ray Hughes) to minimize mis-triggering due to gradient and RF interference.

An RCA imaging protocol was performed on ten healthy subjects (5 female, 22-53 years old) recruited according to local ethics procedures. As the imaging application in this study was in-plane MR coronary angiography, and not through-plane coronary vessel wall imaging, the imaging protocol varied slightly from that described in section 3.e. The longest RCA rest period (diastolic or systolic) was first determined from a cine acquisition in a plane showing the four-chamber view (Plein et al., 2003). All subsequent high resolution imaging was performed in this rest period. In-plane high resolution RCA angiography was planned from a 3D bSSFP whole-heart study with respiratory gating using CLAWS (Jhooti et al., 2010). The imaging plane was planned by selecting 3 points on the RCA in the whole heart volume and verified by acquiring a rapid, 2D navigator gated bSSFP image. A targeted 3D high resolution acquisition was then performed using a 3D spiral acquisition with B2B-RMC (B2B-RMC 3D spiral). In addition, a standard 3D navigator gated bSSFP (nav-bSSFP) acquisition with T2-prep. (Shea et al., 2002) was also performed with the same spatial resolution. While a three way comparison between 3D spiral imaging with B2B-RMC, 3D spiral imaging with navigator gating and standard nav-bSSFP imaging would have been preferable, two navigator gated 3D acquisitions could not be acquired within a reasonable study duration. Consequently, a comparison between B2B-RMC 3D spiral and nav-bSSFP was chosen as the latter is currently the most widely used MR coronary artery imaging technique. The parameters for these acquisitions are compared in table 5.1 and described in the following sections.

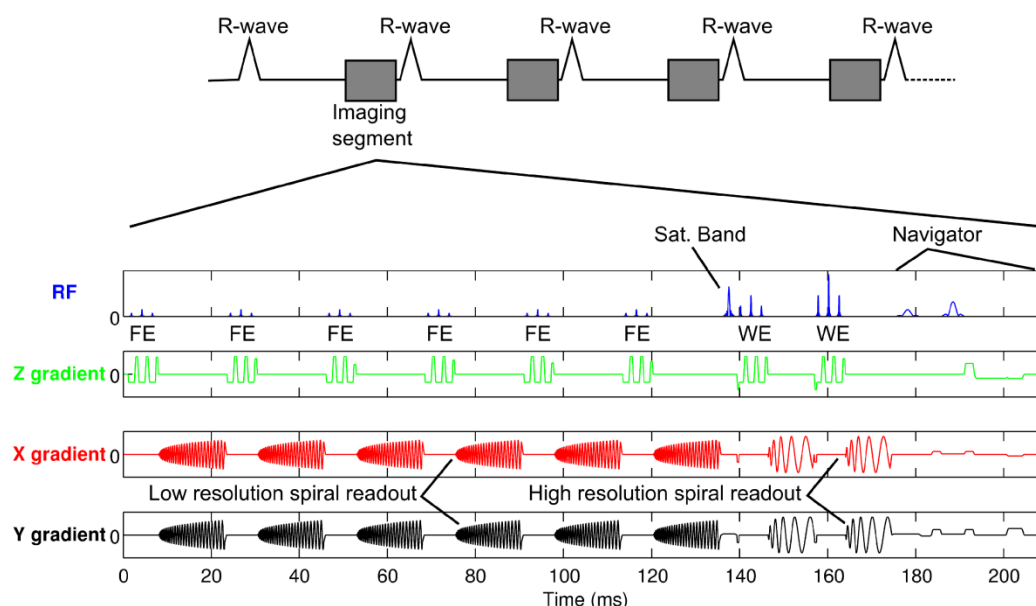
5.b.i B2B-RMC 3D spiral

The B2B-RMC technique used in this study was described in section 3.f but was gated every RR-interval and used without dark blood preparation (figure 5.1). Additionally, a spatial saturation pulse was applied to the chest wall immediately prior to the high resolution imaging segment in order to minimise artefacts from structures not moving with the coronary artery (section 3.c.iv).

The high resolution data was temporally located in the subject specific RCA rest period. Where possible the low resolution data was also acquired during this period of minimal motion, but the timing of the high resolution data was prioritized. Only data acquired at extreme respiratory positions (greater than ± 10 mm outside normal respiratory range) was rejected using the navigator. The acquired resolution was $0.7 \times 0.7 \times 3.0$ mm reconstructed to $0.7 \times 0.7 \times 1.5$ mm. The total acquisition duration was 300 RR-intervals (assuming 100% respiratory efficiency) or 5 minutes (with a heart rate of 60 BPM). All images were corrected, reconstructed and processed offline using the software described in section 3.b.ii. Reference and search ROIs for B2B-RMC were defined around the origin of the RCA on an end-expiratory reference volume, aided by a coloured overlay of the fat image on the uncorrected high resolution water image, as seen in figure 5.2.

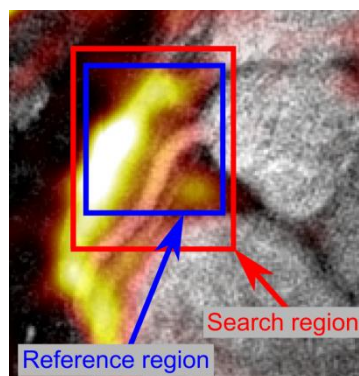
The two high resolution spiral interleaves acquired in each RR-interval were corrected (Ehman and Felmlee, 1989) for respiratory motion using the 3D beat-to-beat translations obtained and high resolution images were reconstructed using the standard techniques described in section 3.b.ii.1.

Figure 5.1: The B2B-RMC 3D spiral sequence used for the MR coronary angiography study



Sequence diagram for the B2B-RMC 3D spiral technique used for coronary MR angiography acquisitions. In contrast to the sequence described in section 3.f, imaging is triggered every RR-interval, a saturation (Sat.) band is applied to the chest wall and there is no dark blood preparation.

Figure 5.2: Transparent overlay of end-expiratory low resolution fat images onto the uncorrected high resolution image to aid ROI positioning



To aid positioning of the search and reference ROIs for the NPSCC of the low resolution images, the reference low resolution fat volume was transparently overlaid ('hot' colour scale) on the uncorrected high resolution water images ('gray' scale). This enables accurate positioning of the regions around the right coronary origin which is otherwise challenging using the fat images alone. Both reference and search ROIs are defined in 3D, extending into multiple slices (not shown here for clarity).

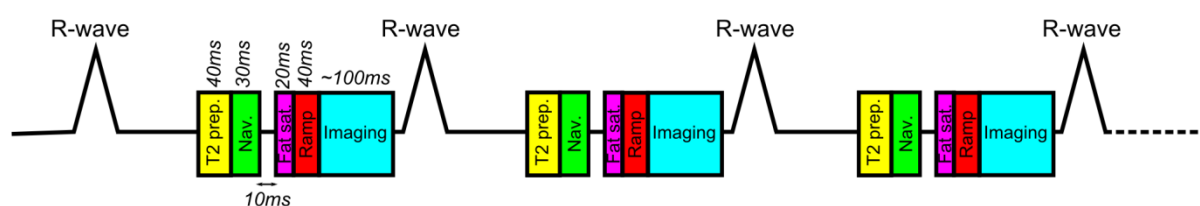
Table 5.1: Comparison of B2B-RMC 3D spiral and nav-bSSFP sequence parameters

Parameter	B2B-RMC 3D spiral	nav-bSSFP
TE/TR	3.4ms/1 RR interval	1.7/4.1ms
Field of view	570x570x24mm	360x360x24mm
Acquired resolution	0.7x0.7x3.0mm	0.7x0.7x3.0mm
Reconstructed resolution	0.7x0.7x1.5mm	0.7x0.7x1.5mm
Points per readout	4096	512 (Asymmetric echo at 37%)
Spiral interleaves in kx-ky/Phase encode lines	75	512 (+20% oversampling)
Through-plane phase encode lines	8	8 (+25% oversampling)
Readouts per RR-interval	2	17-25
Dwell-time per point	2.5 μ s	1.3 μ s
Readout duration	10ms	1.1ms
Acquisition window	30ms	70-100ms
Fat suppression	Binomial water excitation (1-2-1)	Chemical-shift fat saturation
Excitation flip angles	45°/90°	70°
Total duration (at 100% efficiency)	300 RR-intervals	247 RR-intervals (at 25 lines/RR)
Respiratory motion correction	B2B-RMC and navigator gating to a window of $>\pm 10$ mm outside the tidal range	Navigator gating to 5mm window with end expiratory tracking

5.b.ii Navigator gated balanced-steady state free precession

3D navigator-gated balanced steady state free precession (nav-bSSFP) imaging with T2-prep. is currently the most commonly used technique for MR coronary angiography (Shea et al., 2002, Weber et al., 2003, Jahnke et al., 2005b, Leiner et al., 2005, Sakuma et al., 2005, Greil et al., 2007a). Nav-bSSFP datasets with T2-prep. (Shea et al., 2002) (see figure 5.3) were acquired in the same image plane and with the same spatial resolution as the B2B-RMC 3D spiral acquisition. The detailed sequence parameters are given in table 5.1.

Figure 5.3: Schematic diagram of the nav-bSSFP acquisition



Every cardiac cycle the imaging segment (70-100ms) is preceded by T2-prep. pulse (40ms), a navigator echo (30ms), navigator feedback time (10ms), fat saturation (20ms) and a ten RF pulse ramp-up to the steady state (40ms). The main imaging segment is temporally located within the RCA rest period. This schematic diagram is not to scale.

As for the B2B-RMC 3D spiral sequence, the acquisition window was temporally located in the subject specific RCA rest period. The number of phase encode lines acquired per RR-interval was adjusted according to the rest period duration (17-25 lines, 70-100ms acquisition window). Phase oversampling (equivalent to increasing the field of view and subsequently cropping after reconstruction), by a factor of 20% in the phase encode direction and by a factor of 25% in the through plane direction, was used to bolster SNR and generate a similar slice profile to that used for the B2B-RMC 3D spiral technique. Prospective ARA navigator gating was performed with a 5mm navigator acceptance window using the same standard crossed-pair navigator as in the B2B-RMC 3D spiral acquisition. Respiratory gating was performed without slice tracking but with automatic updates of the acceptance window position to follow the end expiratory position (Deshpande et al., 2006, Shea et al., 2007). Acquisition duration was 246 cardiac cycles (assuming 100% respiratory efficiency and 25 phase encode lines per cardiac cycle) or 4 minutes (at 60 beats per minute).

5.b.iii Image processing and analysis

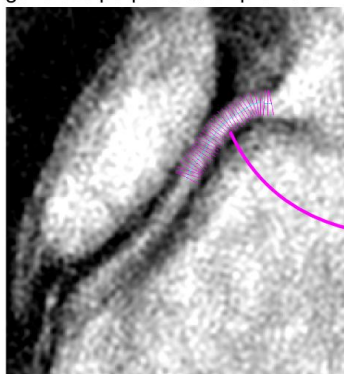
The efficacy of the B2B-RMC 3D spiral technique was assessed by comparing quantitative measures of vessel sharpness and vessel diameter in the proximal and mid coronary arteries with those obtained using the standard navigator gating technique. Signal and contrast to noise ratios were not compared as these are inherently different between the spiral and T2-prep bSSFP techniques.

All images were post-processed using the software tools described in section 3.b.ii.3. Parallel plane MIPs were generated from all slices containing the RCA (typically 5 slices). In each slice, anatomy overlying the

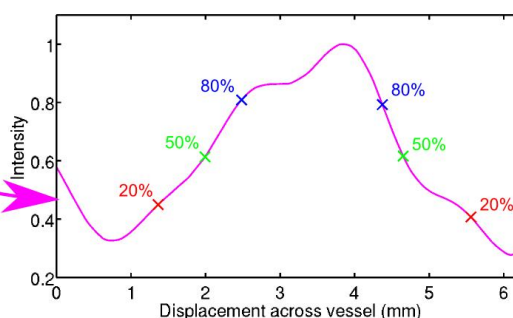
coronary artery (such as the right atrial appendage) was manually segmented and zeroed to show the maximum length of artery. Average vessel sharpness and diameter (see figure 5.4) were obtained from a length of the proximal (0-20mm from the coronary origin) and mid (20-40mm from origin) right coronary artery. As in section 4.e.iv, vessel sharpness was defined as the inverse of the distance between 20% and 80% of the maximum intensity in a profile drawn perpendicular to the vessel and averaged over both vessel edges (Shea et al., 2001). Vessel diameter was defined as the FWHM of the intensity profiles (Shea et al., 2001). Respiratory efficiency and both proximal and mid vessel sharpness and vessel diameter were compared between the B2B-RMC 3D spiral and nav-bSSFP techniques using a two-tailed paired Student's t-test and a 5% significance level.

Figure 5.4: Calculation of the vessel diameter and sharpness from the MIP images

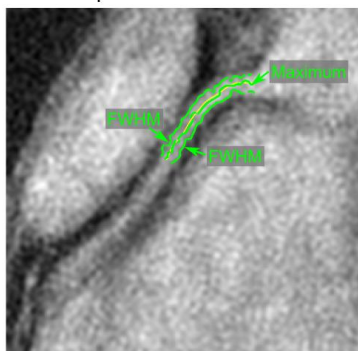
1. Trace centre line of vessel and generate perpendicular profiles



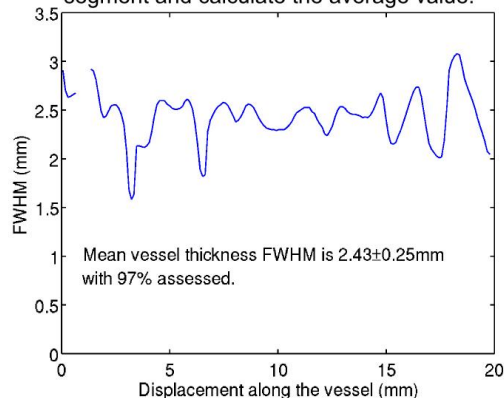
2. Find 20%, 50% and 80% of maximum intensity points.



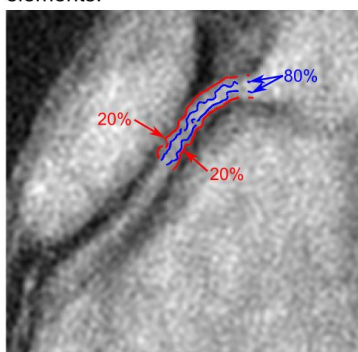
3. Plot FWHM points on image and remove spurious elements.



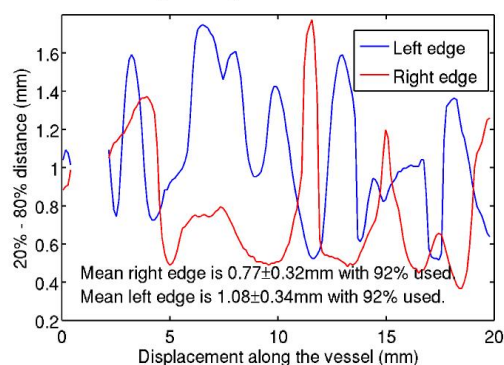
4. Plot FWHM along the length of the segment and calculate the average value.



5. Plot 20% and 80% points on image and remove spurious elements.



6. Plot 20%-80% distance along the length of the segment for each edge and calculate the average sharpness.

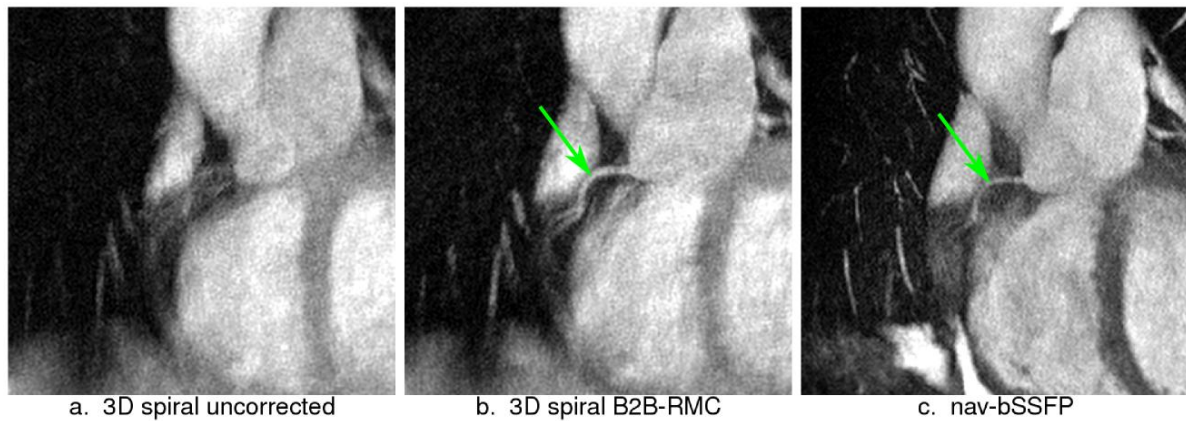


Vessel diameter is calculated as the average FWHM from intensity profiles perpendicular to the vessel in the proximal (0-20mm from the origin – shown here) and mid (20-40mm) RCA. Sharpness is calculated as the inverse of the average 20-80% intensity calculated for the proximal and mid vessel using the same perpendicular profiles. In this case the average proximal vessel diameter and sharpness are 2.43mm and 1.08mm^{-1} respectively. While there is a large variation in sharpness along the segment of the vessel, average values, which are reproducible, are calculated.

5.c Results

The efficacy of B2B-RMC is demonstrated in figure 5.5 which shows example uncorrected (a), and corrected (b) 3D spiral MIP images acquired with 100% respiratory efficiency compared to the equivalent nav-bSSFP image (c) acquired with 44% respiratory efficiency. Before correction, the 3D spiral image is uninterpretable while after B2B-RMC the proximal and early mid section of the RCA are clearly visible before the vessel moves out of the imaging plane.

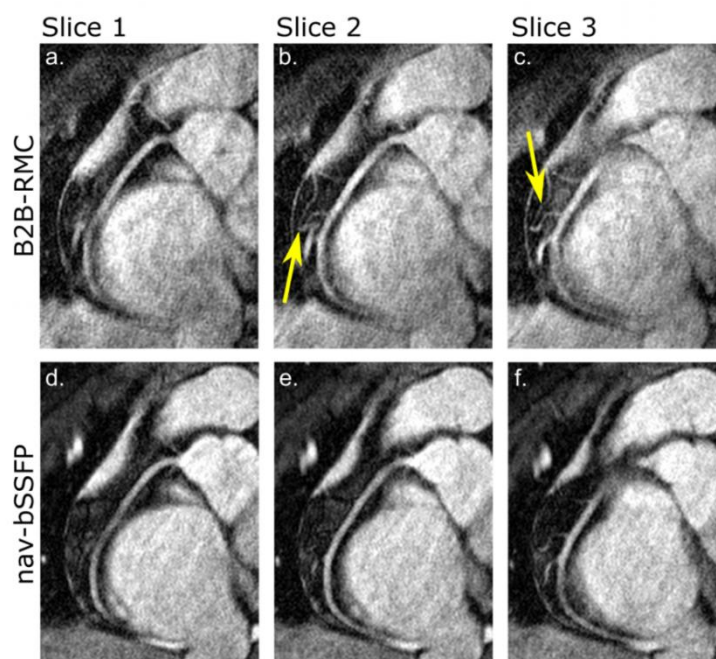
Figure 5.5: Comparison MIP images with and without motion correction



Example MIP images obtained from one subject. 3D spiral images were acquired in 300 RR-intervals (100% respiratory efficiency) and are shown both uncorrected for respiratory motion (a) and corrected with B2B-RMC (b). The corresponding MIP image acquired with nav-bSSFP, acquired in 572 RR-intervals (43% respiratory efficiency) is shown for comparison (c). Note the substantial improvement in RCA visibility (see arrow) after B2B-RMC.

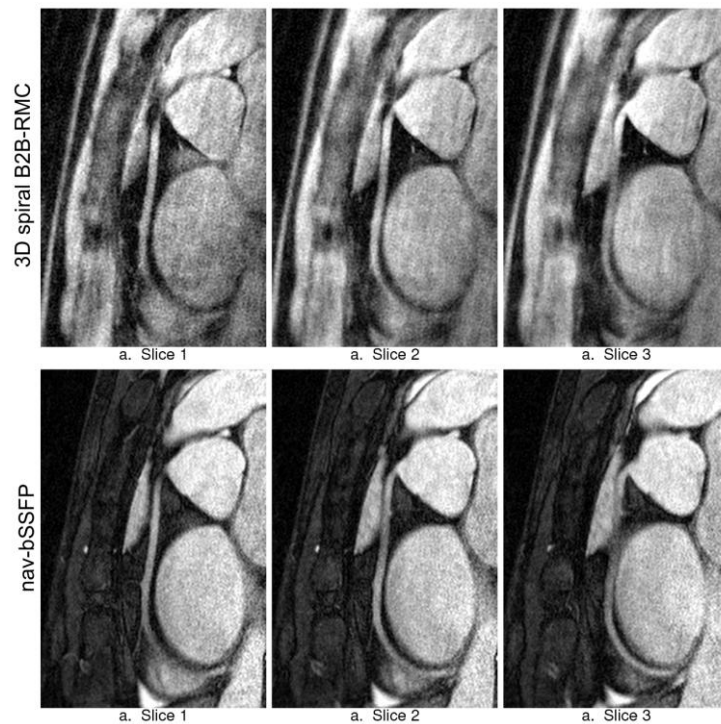
High quality RCA images were obtained in all 10 subjects with both the B2B-RMC 3D spiral and nav-bSSFP techniques. Three contiguous slices from four example subjects using both methods are shown in figures 5.6, 5.7, 5.8 and 5.9. The B2B-RMC 3D spiral images (a – c) in figure 5.6 show sharply delineated branch vessels in the mid-section of the artery which are also present in the nav-bSSFP (d – f). There is however, some visual loss in vessel sharpness in the distal region of the B2B-RMC 3D spiral images caused by the localised nature of B2B-RMC. The example shown in figure 5.7 highlights the need for the spatial saturation pulse applied to the chest wall in the B2B-RMC 3D spiral acquisition. In this example the spatial saturation pulse was not applied, resulting in ghosting of the chest wall signal across the RCA in the B2B-RMC 3D spiral (figure 5.7 (a – c)). As respiratory motion is gated to a small window around end-expiration in the nav-bSSFP acquisition and the T2-preparatory pulse suppresses chest wall signal (figure 5.7 (d – f)), a spatial saturation pulse is not required. Figure 5.8 further highlights the localised nature of the current B2B-RMC. While the proximal RCA is sharp in both the B2B-RMC 3D spiral and the nav-bSSFP acquisition, there is a loss of vessel clarity in the distal section of the B2B-RMC 3D spiral acquisition. The example shown in figure 5.9 clearly shows the proximal and mid RCA in both acquisitions with several branch vessels before the artery curves out of the imaging plane. Images from both acquisitions clearly show the conus artery originating from a common ostium with the RCA. A section of a coronary vein is also present below the RCA.

Figure 5.6: Example images from one subject comparing B2B-RMC 3D spiral to nav-bSSFP



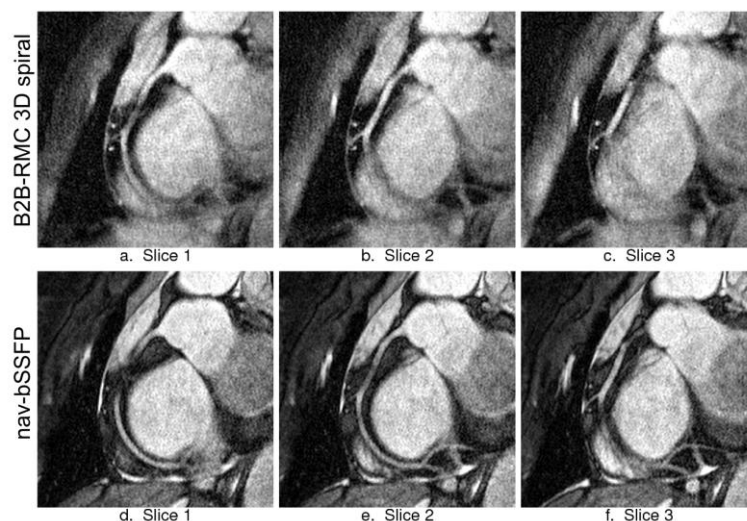
Example images from one subject showing corrected images from the B2B-RMC 3D spiral technique in 3 consecutive slices (a – c) acquired with 99.7% respiratory efficiency and the corresponding slices from the nav-bSSFP technique (d – f) acquired with 63% respiratory efficiency. Note the similar appearance of the RCA in the proximal and mid-sections using both techniques, but increased blurring in the B2B-RMC 3D spiral images in the distal vessel (see text). Also note the clear depiction of the branch vessels in the mid-section in the B2B-RMC 3D spiral images, highlighted by the arrows.

Figure 5.7: Example images from one subject comparing B2B-RMC 3D spiral to nav-bSSFP



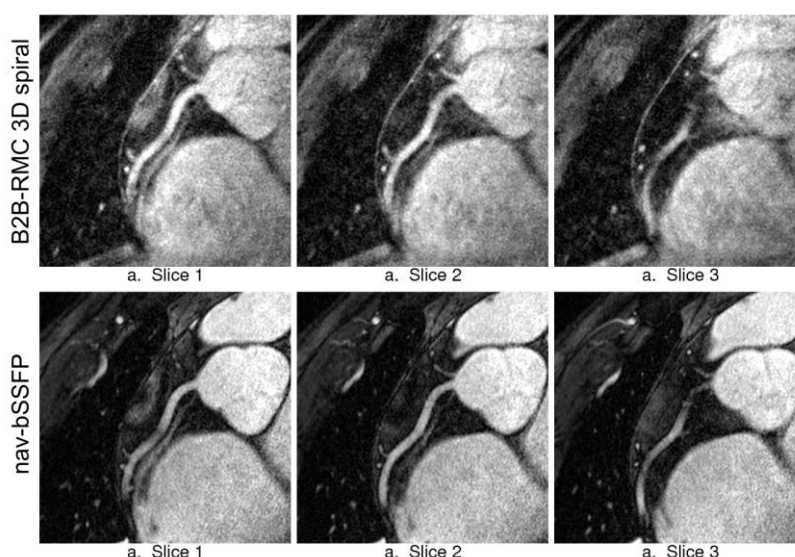
Three consecutive slices acquired using the B2B-RMC 3D spiral acquisition (a – c) acquired with 98.4% respiratory efficiency and the equivalent nav-bSSFP images (d – f) acquired with 35% respiratory efficiency. Note that a spatial saturation pulse was not applied to the chest wall in this B2B-RMC 3D spiral acquisition and there is, hence some chest wall ghosting artefact.

Figure 5.8: Example images from one subject comparing B2B-RMC 3D spiral to nav-bSSFP



Three consecutive slices acquired using the B2B-RMC 3D spiral acquisition (a – c) acquired with 100% respiratory efficiency and the equivalent nav-bSSFP images (d – f) acquired with 41% respiratory efficiency. Note the similar appearance of the proximal vessel but loss of vessel visibility in the distal region of the B2B-RMC 3D spiral images.

Figure 5.9: Example imaging from one subject comparing B2B-RMC 3D spiral to nav-bSSFP



Three consecutive slices acquired using the B2B-RMC 3D spiral acquisition (a – c) acquired with 99.3% respiratory efficiency and the equivalent nav-bSSFP images (d – f) acquired with 41% respiratory efficiency.

Respiratory efficiency of B2B-RMC was near 100% and significantly higher than that of the nav-bSSFP technique ($99.7 \pm 0.5\%$ range 98.4 – 100% vs. $44.0 \pm 8.9\%$ range 33.0 – 62.8%, $p < 0.0001$). Vessel diameter and sharpness were successfully measured for the proximal vessel in all 10 subjects. One subject had a particularly small and tortuous vessel which could not be accurately measured in the mid-section using either technique and as a result, mid-section vessel sharpness and diameter was obtained in 9 subjects. The sharpness and diameter measurements are summarized in table 5.2 together with the average respiratory efficiency of both techniques. Vessel sharpness measured in both the proximal and mid vessel was not significantly different between the two methods. Vessel diameter in the mid artery was not significantly different and although there is a significant difference in the proximal diameter, it is not substantial (0.15mm or ~5%).

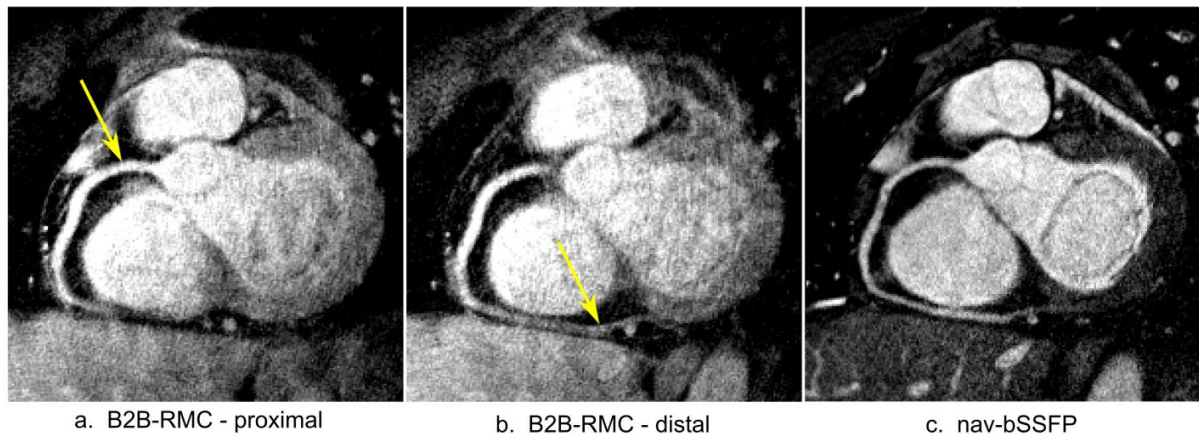
The non-rigid motion of the heart and the localized nature of the cross correlation method used in the B2B-RMC technique means that as expected, the 3D respiratory translations obtained using reference and search ROIs around the coronary artery origin do not provide optimal respiratory motion correction in the distal artery. This is apparent in figures 5.6 – 5.9 where, visually, the distal arteries appear less sharp in the B2B-RMC 3D spiral images than in the corresponding nav-bSSFP images where diaphragm motion is limited to a small range. Figure 5.10 shows a curved-plane reformat of a B2B-RMC 3D spiral image corrected for proximal coronary motion (as performed for the comparisons in table 5.2) (a) and corrected for distal motion (b), together with the equivalent curved-plane reformat of the nav-bSSFP acquisition (c).

Table 5.2: Comparison of the respiratory efficiency, vessel sharpness and vessel diameter between sequences

	Respiratory efficiency (%)	Proximal sharpness (mm ⁻¹)	Mid sharpness (mm ⁻¹)	Proximal diameter (mm)	Mid diameter (mm)
B2B-RMC 3D spiral (SD)	99.7 (0.5)	1.00 (0.14)	1.01 (0.11)	2.85 (0.38)	2.85 (0.39)
nav-bSSFP (SD)	44.0 (8.9)	1.08 (0.11)	1.05 (0.12)	2.70 (0.34)	2.80 (0.35)
p-value	<0.0001	0.15	0.24	0.026	0.60

Proximal and mid results were obtained in 10 and 9 healthy subjects respectively. All values are mean $\pm$ standard deviation (SD).

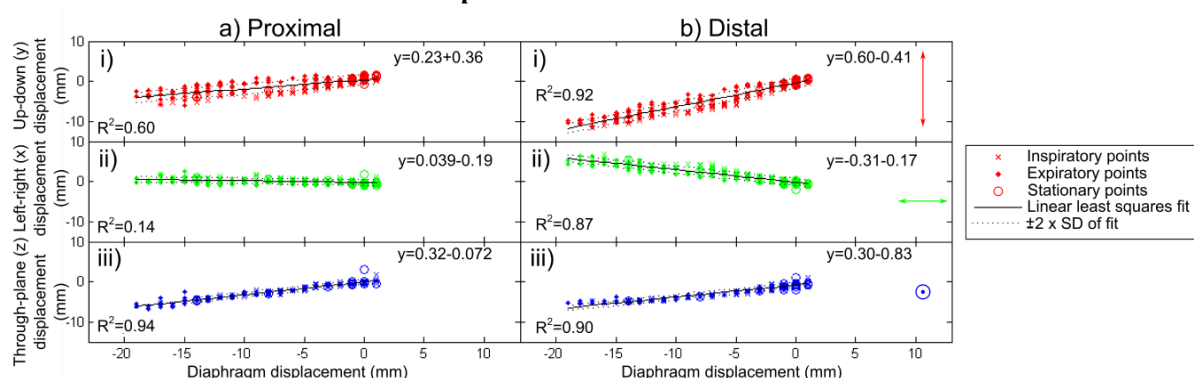
Figure 5.10: Comparison of B2B-RMC 3D spiral images corrected for proximal and distal RCA motion compared to the equivalent images acquired with nav-bSSFP



Curved planar reformat of 3D spiral images acquired with the B2B-RMC technique (0.7x0.7x3mm resolution) in 302 cardiac cycles (99.3% efficient) over 20mm of diaphragm motion, corrected for optimal proximal (a) and distal (b) vessel motion. For comparison the equivalent curved planar reformat of the 3D nav-bSSFP images with identical resolution, acquired in 576 cardiac cycles (43.6% efficient) is shown (c).

For the B2B-RMC 3D spiral images, it is apparent that the distal vessel is sharpest in (b) while the proximal vessel is sharpest in (a). In comparison, the nav-bSSFP image (c) is sharp over both proximal and distal regions, although this has been achieved at the expense of a 2.3 fold decrease in respiratory efficiency. This need for different respiratory motion corrections in the proximal and distal regions is emphasized in figure 5.11 which shows the B2B-RMC in-plane (x and y) and through-plane (z) respiratory translations relating to the corrected images shown in figure 5.10 (a) and (b) plotted against the corresponding diaphragm displacements, as measured with the diaphragmatic navigator.

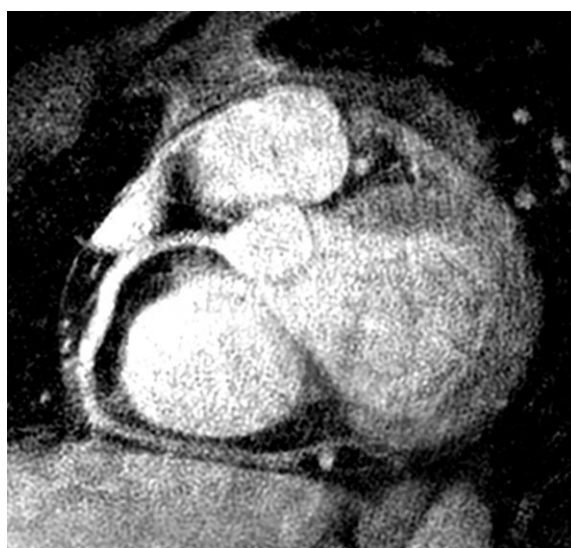
Figure 5.11: B2B-RMC respiratory displacements plotted against navigator displacements in the proximal and distal RCA



The localized in-plane (y (i) and x (ii)) and through-plane (z (iii)) B2B-RMC displacements obtained when the NSPCC is localised around the (a) proximal and (b) distal artery, plotted against the diaphragm displacement obtained from the navigator. Inspiratory, expiratory and stationary points are identified using the difference between successive points in the navigator trace. The increased slope for the in-plane translations observed in the distal artery highlights the need for a localized correction.

In this instance, the slope of the in-plane (y) correction versus the superior-inferior diaphragm displacement was 0.23 in the proximal region and 0.60 in the distal region. Similarly the corresponding slope for the in-plane (x) corrections was 0.039 in the proximal region and 0.31 in the distal region. An initial attempt to combine the B2B-RMC 3D spiral images corrected for both proximal and distal motion was performed by selectively replacing data in the vicinity of the distal artery in the proximally corrected data set with equivalent data from the distally corrected dataset. Voxels in the border region between the two corrected datasets were linearly combined, resulting in a fading effect. The result of this is shown in figure 5.12 and demonstrates high clarity along the entire length of the vessel.

Figure 5.12: Curved planar reformat of combined datasets corrected for proximal and distal RCA motion acquired using the B2B-RMC 3D spiral technique



Curved plane reformat of the data sets shown in figure 5.10.a and 5.10.b combined to correct for both proximal and distal motion. The datasets were combined in a basic manner and further work will address more sophisticated methods.

5.d Discussion

In this chapter, B2B-RMC has been used to correct 3D MR coronary angiography studies with near 100% respiratory efficiency. Proximal and mid vessel sharpness and diameter were used as quantitative markers of the effectiveness of respiratory motion correction and the results were compared to those obtained using the current most popular sequence for MR coronary angiography with conventional navigator gating.

All B2B-RMC 3D spiral and nav-bSSFP acquisitions resulted in high quality images. The respiratory efficiency of the nav-bSSFP technique was more variable as well as being significantly and considerably lower ($44.0 \pm 8.9\%$ vs. $99.5 \pm 0.5\%$, $p < 0.0001$) than the B2B-RMC technique in the healthy subjects studied. This variability of the respiratory efficiency using navigator gating leads to uncertainty regarding the acquisition duration. As B2B-RMC is able to correct for $>99\%$ of respiratory motion, this uncertainty is greatly reduced. Although the nav-bSSFP images had inherently different contrast characteristics to the 3D spiral images acquired with the B2B-RMC technique, there was no disparity in vessel sharpness. A statistically significant difference in proximal vessel diameter was observed between the techniques, but the magnitude of this was small ($\sim 5\%$) and may possibly be due to the use of a T2-preparation pulse with the nav-bSSFP technique which reduces the signal from the coronary vessel wall. The values obtained for vessel sharpness are higher than those obtained in other studies (Li et al., 2001, Shea et al., 2001), which is most likely due to the higher spatial resolution used in this study, while the vessel diameters obtained fall within the range of values obtained in previous studies (Botnar et al., 2000b, Jahnke et al., 2004, Weber et al., 2004, Keegan et al., 2004, Greil et al., 2007a).

This is the first time that this B2B-RMC technique has been applied to bright blood coronary artery imaging and the work clearly demonstrates the expected differences in the motion of the proximal and distal RCA. The proximity of the distal artery to the diaphragm results in a larger range of motion at this level than at the proximal artery which is separated from the diaphragm by a large volume of soft deformable tissue. This non-rigid deformation is highlighted by the increased magnitude of the slope of the linear fit of the in-plane (x and y) B2B-RMC displacements versus the diaphragm displacement in the distal correction when compared to the proximal results (figure 5.11). The spread of the points around the linear fit emphasizes the need for a beat-to-beat correction. The apparent inspiratory-expiratory hysteresis which was observed in the B2B-RMC displacements of several subjects as a loop like trend in the data may be hysteresis between the diaphragm and RCA as previously reported (Nehrke et al., 2001), or may be a result of motion between the low resolution acquisition and the navigator (see section 4.e.v). As has been demonstrated, it is possible to combine multiple datasets corrected optimally for different sections of the vessel. Further work should consider the combination of datasets from more than two corrections, the optimal way of doing this and performing these corrections both rapidly and automatically. However, the relatively short section of artery imaged in 3D cross-sectional coronary vessel wall imaging (chapters 6 and 7) means that non-rigid motion is likely to be less detrimental than for in-plane imaging.

This study has a number of limitations. All acquisitions were performed in healthy volunteers. In general, breathing patterns are more erratic in the patient population with greater respiratory drift than for healthy subjects and one might therefore expect the benefits of B2B-RMC to be more pronounced. Only the RCA was targeted here as it is the more mobile and therefore the more challenging imaging target. However, preliminary attempts at imaging the left coronary artery system have also been successful despite a generally reduced volume of fat surrounding these arteries (see section 8.b). Also vessel diameter and sharpness were only measured in the first 40mm of the artery. This is partly due to the localized nature of the NSPCC which was used to selectively correct for the respiratory motion of the proximal/mid artery, but these measurements also become increasingly difficult to make around the escalating number of branch points more distally. Nonetheless, we have qualitatively demonstrated that B2B-RMC may be used to correct for respiratory motion in the distal right coronary artery by selecting appropriate ROIs for the NSPCC and in future, non-rigid implementations could correct whole heart 3D coronary artery acquisitions. A further limitation of this study is that although SNR and CNR are important determinants of image quality, the inherently different image contrast between the 3D spiral and 3D bSSFP techniques used here, meant that such measures were inappropriate for comparing the performance of respiratory compensation strategies. The ideal solution would have been to perform an additional identical 3D spiral acquisition with a 5mm navigator gating window. However, at an average respiratory efficiency of 44% this acquisition would have required 682 RR-intervals (much longer in many subjects), therefore, prohibiting this additional comparison. One potential alternative would have been to acquire a navigator gated 3D spiral acquisition with B2B-RMC and a 5mm gating window, to enable gated and corrected images to be reconstructed from the same data set, although this would also have extended the imaging time. Alternatively, it is also possible to implement bSSFP with the B2B-RMC technique enabling a direct comparison of the gating strategies. Both of these options require considerable modification to the pulse sequence and image reconstruction software which were not possible at the time of this work. Instead, a comparison between B2B-RMC and navigator gating in otherwise identical sequences is presented in section 4.e.iv using a realistic respiratory motion phantom.

In conclusion the B2B-RMC technique can be used to correct for respiratory motion with 99.7% respiratory efficiency as well as a navigator based technique with a 5mm gating window (44.0% efficient), using vessel sharpness and vessel diameter from MR coronary angiography of the RCA to quantitatively compare the methods.

6. 3D spiral coronary artery wall imaging with beat to beat respiratory motion correction: Reproducibility and comparison with standard methods

The work presented in this chapter was recently published in Scott et al. (2011b).

6.a Introduction

As discussed in section 1.e.ii, MR coronary vessel wall imaging has demonstrated the ability to detect coronary vessel wall thickening in asymptomatic subjects (Fayad et al., 2000, Botnar et al., 2000a, Kim et al., 2002, Macedo et al., 2008, Gerretsen et al., 2010a). However, for any coronary vessel wall imaging technique to achieve clinical acceptance for assessment of disease progression and regression, such a technique must be reliable, reproducible and efficient. High resolution 3D MR coronary artery vessel wall imaging is typically performed with ARA navigator gating, which is inherently inefficient and unreliable. Previous sections of this thesis have demonstrated the competence of B2B-RMC in correcting for respiratory motion at, or near 100% respiratory efficiency in phantom work (chapter 4) and in an *in-vivo* MR coronary angiography study (chapter 5). In this chapter a direct comparison between 3D spiral imaging with B2B-RMC (B2B-RMC 3D spiral) and both 2D spiral imaging with navigator gating and 2D TSE imaging with navigator gating, as are often used in coronary artery wall imaging, is presented. Initial tests in section 3.d suggested that the additional SNR and robustness to variations in RR-interval enabled by triggering data acquisition every other RR-interval (2RR gating) make it preferable to triggering every RR-interval (1RR gating). However, several authors have achieved high quality imaging with 1RR gating (Meyer et al., 1998, Keegan et al., 2007, Abd-Elmoniem et al., 2010, Terashima et al., 2010) which results in a very welcome factor of 2 increase in overall imaging efficiency. As a result, the B2B-RMC 3D spiral was performed here with both 2RR and 1RR gating, hence providing the first *in-vivo* comparison of these two gating regimes in coronary artery vessel wall imaging. Measurements of RCA vessel wall thickness were compared in images acquired in ten healthy subjects using all four acquisitions. In addition, all four acquisitions in all subjects were repeated on a separate occasion to assess the reproducibility of wall thickness measurements, which is crucial for studies of disease progression and regression.

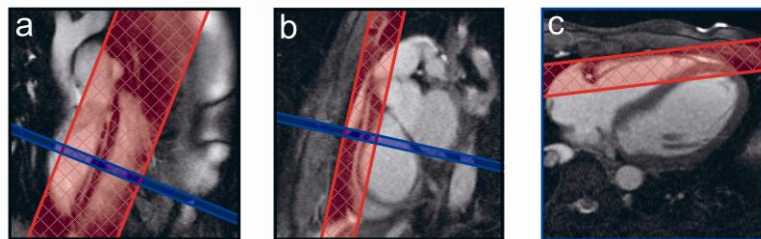
6.b Methods

Ten healthy subjects (mean age 38 ± 11 years old, range 28 – 59 years old and four female) were recruited according to local ethics regulations and were each scanned on two separate occasions (subsequently referred to as the initial and repeat studies).

6.b.i Preparatory imaging

The preparatory imaging followed the protocol described in section 3.e, with the exception of step 7 where the cine acquisition in the selected coronary vessel wall imaging plane was performed at a temporal resolution of 42ms, as used for the initial 4-chamber cine acquisitions (step 4). Typical orientation of the selected imaging plane for coronary vessel wall imaging and the location of the selective reinversion slab are shown in figure 6.1.

Figure 6.1: Cross-sectional 2D MR coronary angiography planning studies



Orthogonal in-plane RCA MR angiography images (a and b). The position of the cross-sectional right coronary artery plane (c) is shown in blue. The selective reinversion pulse of the dark blood preparation is shown in red and was positioned to reinvert the coronary vessel wall while minimizing the reinversion of blood in the aortic root, ventricles and chest wall.

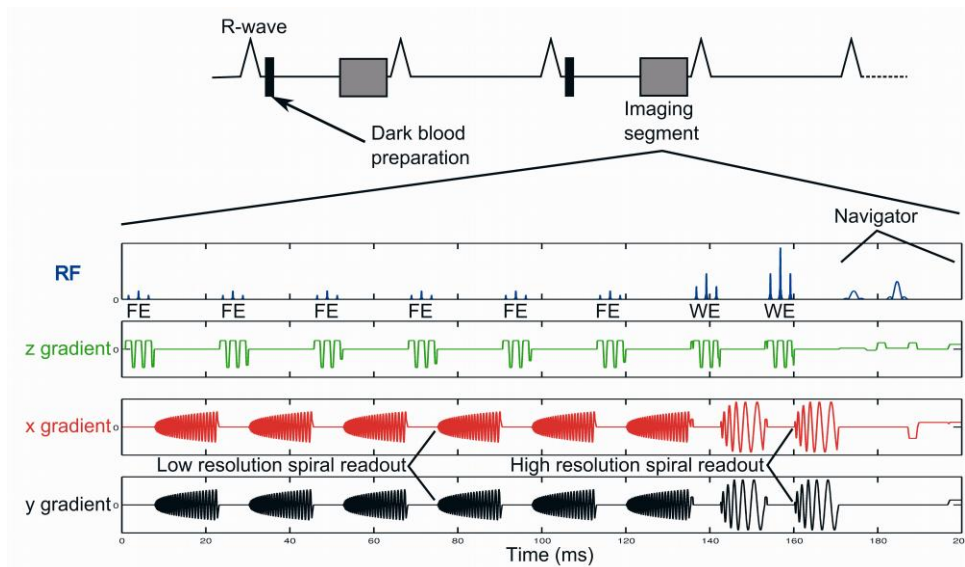
6.b.ii Right coronary artery vessel wall imaging

For each subject on each occasion, four acquisitions of the RCA vessel wall were obtained using the sequences described below in a randomized order (80 acquisitions in total). The sequence parameters (see table 6.1) were selected to obtain equivalent high in-plane spatial resolution and sufficient SNR within an acceptable duration for each acquisition. The in-plane resolution was identical for all sequences (0.7×0.7 mm). For comparison with the 3D spiral B2B-RMC acquisitions, 2D acquisitions were performed with navigator gating, as is commonly used for coronary artery wall assessment. While a direct comparison with navigator gated 3D acquisitions would have been preferable, to do so with comparable spatial resolution and SNR to that used in the 3D acquisition with B2B-RMC would have resulted in a prohibitively long scan time, due to the typically low respiratory efficiency ($\sim 40\%$ (Oshinski et al., 1996)) of navigator gating. The slice thickness for the 2D acquisitions was 6.0mm while for the 3D acquisitions, 8×3.0 mm slices were acquired and reconstructed to 16×1.5 mm slices. Although the 2D acquisitions would have ideally been performed with a 3.0mm slice thickness, this was not possible due to SNR and time considerations. To minimize through-plane partial volume effects, which may result in artificially high vessel wall thickness measurements, care was taken to place the imaging slice or slab perpendicular to the straightest section of artery available.

6.b.iii B2B-RMC 3D spiral acquisitions

The sequence diagram for the B2B-RMC 3D spiral acquisition is shown in figure 6.2 and is identical to that described in section 3.f. In every other cardiac cycle, dark blood double inversion preparation was followed by the low resolution 3D volume with fat selective excitation. Immediately after the low resolution 3D acquisition, two interleaves of a high resolution 3D stack of spirals acquisition were obtained with water selective excitation. A standard, crossed pair diaphragmatic navigator was acquired immediately after the high resolution spiral readouts. The dark blood inversion time, was typically 625ms (which is optimal for 2RR gating and a heart rate of 60BPM). This was, however, reduced in subjects with an early coronary rest period so that the acquisition of the high resolution imaging data (30ms acquisition window) could be performed during minimal RCA motion. The following navigator was used to reject and reacquire data acquired at very extreme respiratory positions ($>\pm 10$ mm outside the subjects normal tidal diaphragm range). The total acquisition duration was 600 RR-intervals (for 2RR gating and assuming 100% respiratory efficiency).

Figure 6.2: The sequence diagram for the 3D spiral with B2B-RMC acquisition



The sequence is as described in section 3.f. Every imaging segment consists of a full low resolution 3D spiral fat selective (FE) acquisition immediately followed by 2 interleaves of a high resolution 3D spiral acquisition with water selective excitation (WE). Finally a standard crossed pair navigator is used to monitor the position of the diaphragm and exclude data acquired at very extreme diaphragm positions.

Images were reconstructed and processed offline using the tools described in section 3.b.ii.

The acquisition was repeated with 1RR gating. In this case the dark blood inversion time was reduced to ~400ms in order to maintain effective suppression of blood signal. All other parameters were fixed. The total acquisition duration was 300 RR-intervals (for 1RR gating and assuming 100% respiratory efficiency).

Table 6.1: High resolution coronary artery wall imaging parameter comparison

Parameter	3D spiral B2B-RMC	2D spiral navigator gating	2D TSE navigator gating
TE	3.4ms	7.0ms	6.8ms
TR	1 RR- or 2 RR-intervals	2 RR-intervals	2 RR-intervals
Field of view	570x570x24mm	570x570x6mm	403x403x6mm
Resolution	0.7x0.7x3.0mm	0.7x0.7x6.0mm	0.7x0.7x6.0mm
Points per readout	4096	4096	576
Spiral interleaves per kx-ky / phase encode lines	75	75	576 (+77% oversampling)
Through-plane phase encode lines	8	1	1
Readouts per RR interval / echo train length (ETL)	2	2	<15
Dwell-time per point	2.5 μ s	2.5 μ s	2.9 μ s
Readout duration	10ms	10ms	3.3ms
Acquisition window	30ms	35ms	76ms (ETL=10)
Fat suppression	Binomial water excitation	Binomial water excitation	AASPIR
Flip angles	45/90°	45/90°	90/180-180-...-180°
Dark blood preparation	User positionable slab selective	User positionable slab selective	Standard (3 x slice thickness)
Dark blood inversion time	625ms/400ms (2RR/1RR)	625ms	625ms
Respiratory motion compensation	B2B-RMC + navigator gating – tidal range $\pm$ 10mm	Navigator gating – 5mm window + end expiratory tracking	Navigator gating – 5mm window + end expiratory tracking
Total duration (100% efficiency)	600RR/300RR (2RR/1RR)	76RR	204RR (ETL=10)

Parameters were identical for the B2B-RMC 3D spiral acquisition with 2RR and 1RR gating, except where noted.

ETL – TSE echo train length.

AASPIR – adiabatic asymmetric spectral inversion recovery

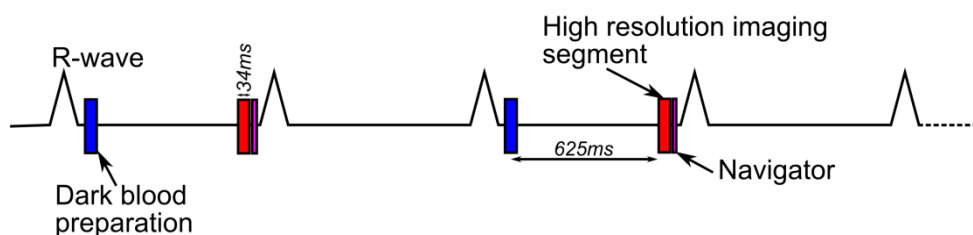
6.b.iv Navigator gated 2D spiral

A single slice 2D spiral acquisition was acquired with 2RR gating as shown in figure 6.3. The k-space trajectories and dark blood preparation were identical to those used for the 3D spiral sequence.

Sequence parameters are given in table 6.1. In every other cardiac cycle, 2 spiral readouts were acquired sequentially with a total cardiac acquisition window of 35ms, using binomial water excitation.

Respiratory gating was performed using a standard crossed pair navigator positioned over the right hemi-diaphragm with a 5mm end-expiratory ARA window and end-expiratory position tracking (Deshpande et al., 2006, Shea et al., 2007). The total acquisition duration was 76 RR-intervals (for 2RR gating and assuming 100% respiratory efficiency).

Figure 6.3: A schematic of the 2D spiral navigator gated sequence

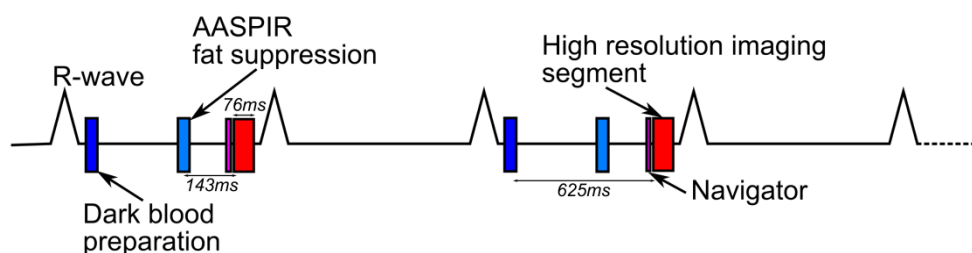


Every other cardiac cycle the high resolution image segment is preceded by slab selective dark blood preparation. A navigator is acquired immediately after the high resolution segment.

6.b.v Navigator gated 2D Turbo-Spin Echo

A single slice 2D TSE acquisition was acquired with 2RR gating as shown in figure 6.4. The sequence parameters are given in table 6.1. The images were acquired with standard double inversion recovery dark blood preparation using a reinversion pulse slice thickness of 3 times the imaging slice thickness and an inversion time defined as for the 3D spiral B2B-RMC acquisition with 2RR gating. Fat suppression was performed with an asymmetric adiabatic short TI spectral inversion recovery (AASPIR) pulse (Rosenfeld et al., 1997, Shea et al., 2007). As averaging is performed on the fly, the acquisition of multiple averages was not possible in combination with navigator gating. Instead, the SNR in the 2D TSE images was increased by using phase oversampling of 77%. The echo train length was chosen to fit within the subject-specific cardiac rest period and constrained to a maximum of 15 (i.e. acquisition window <110ms). Navigator gating was performed as for the 2D spiral technique. The total acquisition duration was 204 RR-intervals (for 2RR gating, assuming 100% respiratory efficiency and a typical echo train length of 10).

Figure 6.4: A schematic of the 2D TSE navigator gated sequence



Every other cardiac cycle the imaging segment (typically an echo train length of 10) is preceded by standard dark blood preparation, AASPIR fat suppression and a navigator.

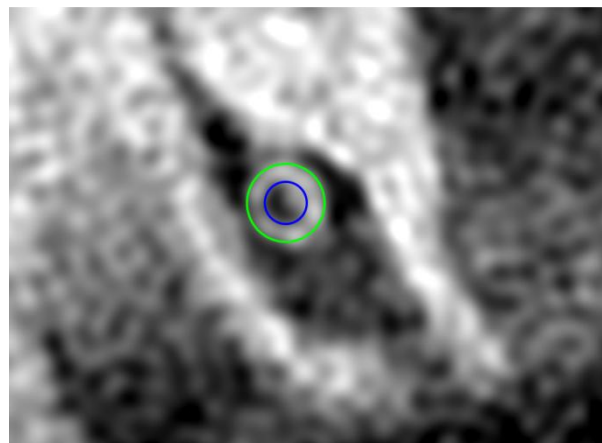
6.b.vi Repeat Studies

The repeat studies for each subject were performed in an identical manner. The imaging plane for the dark blood cross-sectional right coronary acquisitions was positioned the same distance from the aortic root using screen grabs and tracings from the initial studies (see figure 6.1).

6.b.vii Data Analysis

Quantitative comparison of each of the four techniques was performed using the average thickness of the right coronary vessel wall. For each B2B-RMC 3D spiral study (both 1RR and 2RR gating), the slice with the sharpest vessel wall from the 4 x 1.5mm slices which correspond to the 6.0mm 2D slice was selected visually for comparison. The images were presented for analysis in a randomised order to avoid bias and the decision on which slice to analyze was made independently for each B2B-RMC 3D spiral acquisition (1RR and 2RR). All images were Fourier interpolated by a factor of 4 and then zoomed (using bilinear interpolation) for the subsequent analysis. Average thickness measurements were calculated from circular ROIs manually drawn around the inner and outer vessel wall (see figure 6.5 and movie S.7 in the supplementary material) using the tools described in section 3.b.ii. The intra and inter observer reproducibility of this measurement technique was determined in a randomly selected subset of 20 images as the mean $\pm$ standard deviation of the signed differences between two measurements made by the same observer and by two independent observers respectively.

Figure 6.5: Circular ROIs drawn around the coronary vessel wall for wall thickness measurements



Circular ROIs are drawn around the outer (green) and inner (blue) edge of the coronary vessel wall. Average vessel wall thickness is calculated from these ROIs. Also see movie S.7 for an example of this process.

Comparison of vessel wall thickness obtained using all four acquisitions was performed using repeated measures analysis of variance on the data acquired in the initial studies. Using both the initial and repeat data sets, the inter-study reproducibility of vessel wall thickness measured with each of the techniques was assessed using the intra class correlation coefficient (MacLennan, 1993) and by the method of Bland and Altman (Bland and Altman, 1986).

All coronary artery wall vessel images used for the wall thickness measurements were scored on a three point scale (1=vessel wall not visualized, 2=adequate, 3=good) (Miao et al., 2009). Only those coronary wall images with a score of 2 or 3 were analyzed as described above. Image quality scores were compared between techniques using the Friedman test.

6.c Results

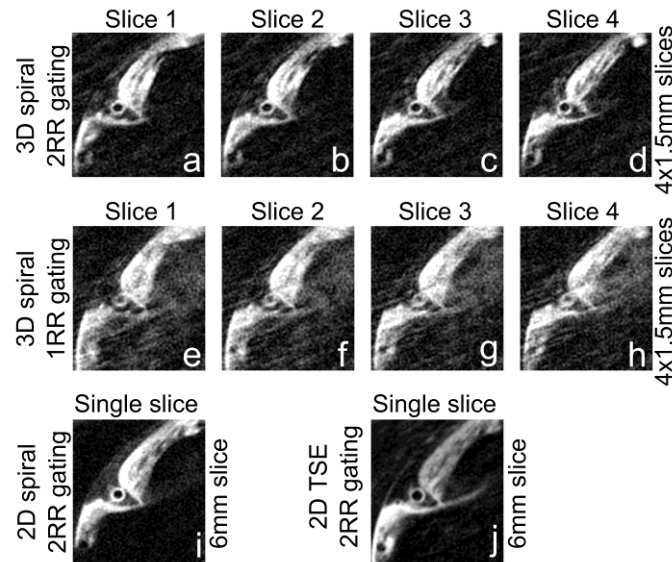
The mean heart rate for all (initial and repeat) studies was 61 ± 8 BPM (range 46 – 73 BPM) and the mean duration of the diastolic right coronary rest periods was 119 ± 59 ms (range 50 – 226 ms). During the initial studies, a fault was found in the TSE sequence which caused the scanner to ignore the phase oversampling if the echo train length was modified. As a result, four of the TSE acquisitions in subjects with longer rest periods were acquired without the prescribed 77% phase oversampling. In three of these subjects the image quality was high regardless and they were included in the subsequent analysis. The image quality was poor in the fourth subject but this was primarily attributed to cardiac motion, as discussed later, rather than to reduced SNR. The fault was resolved prior to beginning the repeat studies and all further TSE acquisitions were performed with the phase oversampling.

Example images from all techniques obtained in the initial studies of two subjects are shown in figure 6.6 and 6.7 including the four reconstructed 1.5 mm slices of each of the 3D techniques corresponding to the 6.0 mm slices obtained with the 2D acquisitions. Equivalent images from all techniques obtained in the repeat study of one subject are shown in figure 6.8. In each of these examples, image quality was sufficient to measure the vessel wall thickness. The B2B-RMC 3D spiral images shown in figure 6.6 are good in the case of the 2RR gated acquisition ((a – d), scored 3), but adequate in the 1RR gated acquisition ((e – h), scored 2) due to severe ghosting of the chest wall across the anatomy of interest (discussed further later). In this subject the 2D spiral (i) and 2D TSE (j) acquisitions both resulted in excellent image quality (both scored 3). The 2D spiral (i) and 2D TSE images (j) shown in figure 6.7 are of good quality (both scored 3) and the vessel wall is also clearly visible in the B2B-RMC 3D spiral acquisition using 2RR gating ((a – d), scored 2). However, there is some blurring of the vessel wall in these images (figure 6.7 (a – d)). This was caused by imperfect respiratory motion correction of this subject's erratic and drifting respiratory trace. There is also a substantial loss of contrast between the vessel wall and lumen in the 1RR gated 3D spiral with B2B-RMC acquisition (figure 6.7 (e – h), scored 2), thought to be the result of the reduced robustness of 1RR gating to variations in RR-interval. The B2B-RMC 3D spiral images shown in figure 6.8 are good for the 2RR gated acquisition ((a – d), scored 3) and 1RR gated acquisitions ((e – h), also scored 3) although there is a visible loss of SNR with 1RR gating. In this example, image quality is poorer in the 2D spiral image ((i), scored 2) and in the 2D TSE image ((j), scored 2), due to poorer fat suppression.

The four acquisitions in each study were performed in a random order and were typically completed within approximately 30 minutes. Of the 80 acquisitions performed (10 subjects with four acquisitions on two occasions), 73 (91%) produced images with image quality scores of 2 or 3 from which measurement of the RCA vessel wall thickness could be obtained. Table 6.2 documents the image quality score and vessel wall thickness of each acquisition in each subject, together with the heart rate and coronary rest period duration (as estimated from the cine acquisition in the same plane). Four rejected datasets (red cells in table 6.2) were TSE acquisitions, two were 3D spiral acquisitions with 1RR gating and one was a 3D spiral acquisition with 2RR gating. In one subject (subject 9), the failed acquisitions appeared to correspond to an increase in heart rate (discussed fully later). For the remaining subjects

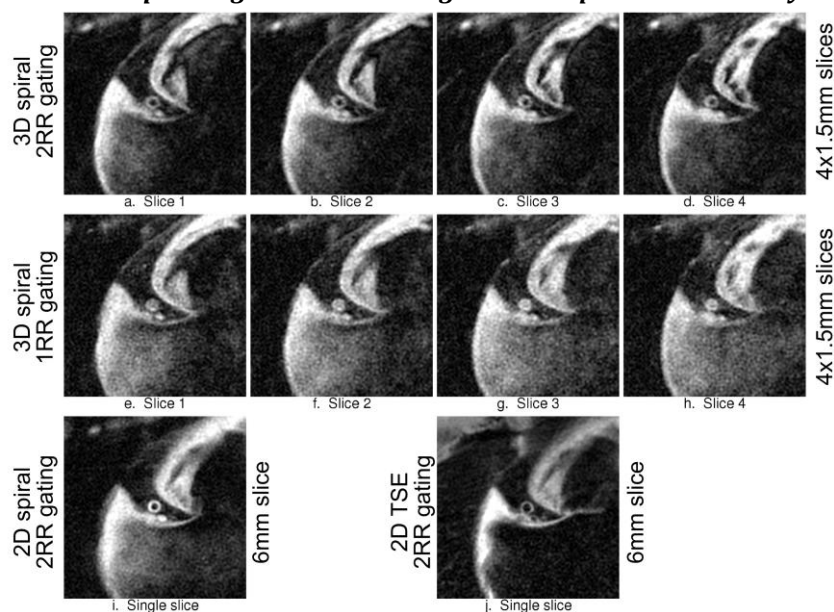
however, no changes in heart rate were observed during the 4 acquisitions in each study and the success or failure of an acquisition was not dependent on the order in which it was performed. Of the successful datasets 42 were scored 2 (amber cells in table 6.2) and 31 were scored 3 (green cells). Of these 31 datasets that were scored 3, eight were 3D spiral acquisitions with 2RR gating, five were 3D spiral with 1RR gating, eight were 2D spiral and 10 were 2D TSE acquisitions. There was no significant difference in image quality score between techniques ($p=ns$).

Figure 6.6: Example images obtained using all techniques in one healthy subject



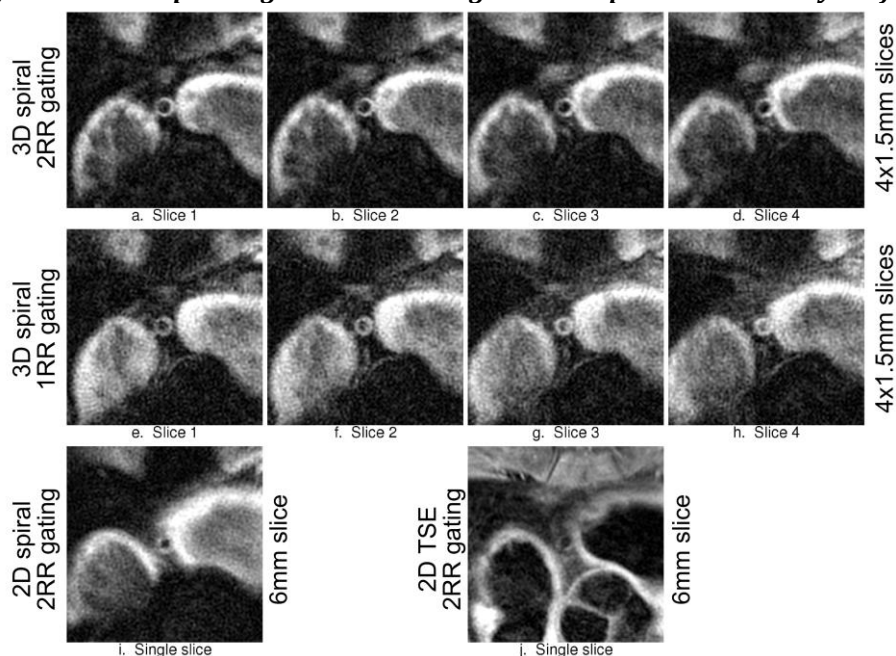
Images from the initial study of subject 10 using all four methods. The four 1.5mm slices (a – d and e – h) of the 3D spiral techniques are shown along with the equivalent single 6.0mm slices obtained using the 2D TSE (i) and 2D spiral (j) techniques. Both of the B2B-RMC 3D spiral techniques were acquired with respiratory efficiencies of 100% and the range of diaphragm displacements corrected was 18mm and 23mm using 2RR gating and 1RR gating respectively. The 2D images were acquired with respiratory efficiencies of 45% (2D spiral) and 39% (2D TSE). The measured vessel wall thicknesses were 1.31mm (B2B-RMC 3D spiral with 2RR gating), 1.39mm (B2B-RMC 3D spiral with 1RR gating), 1.29mm (2D spiral) and 1.36mm (2D TSE). In both B2B-RMC 3D spiral images a degree of ghosting artefact is observed (as discussed in the text). The effect is worse in the 1RR gated images (scored 2) than in the 2RR gated images (scored 3).

Figure 6.7: Example images obtained using all techniques in one healthy subject



Images from the initial study of subject 5 using all four methods. The four 1.5mm slices (a – d and e – h) of the 3D spiral techniques are shown along with the equivalent single 6.0mm slices obtained using the 2D TSE (i) and 2D spiral (j) techniques. The B2B-RMC 3D spiral images were acquired with respiratory efficiencies of 94.9% and 99.3% for the 2RR and 1RR gated acquisitions respectively. The 2D images were acquired with respiratory efficiencies of 45% (2D spiral) and 45% (2D TSE). The measured vessel wall thicknesses were 1.31mm (3D spiral with 2RR gating), 1.23mm (3D spiral with 1RR gating), 1.23mm (2D spiral) and 1.21mm (2D TSE). The blood suppression in the 3D spiral images with 1RR is less effective than in the 2RR gated images.

Figure 6.8: Example images obtained using all techniques in one healthy subject



Images from the repeat study of subject 6 using all four methods. The four 1.5mm slices (a – d and e – h) of the 3D spiral techniques are shown along with the equivalent single 6.0mm slices obtained using the 2D TSE (i) and 2D spiral (j) techniques. The 3D spiral with B2B-RMC images were acquired with respiratory efficiencies of 99.3% and 100% for the 2RR and 1RR gated acquisitions respectively. The 2D images were acquired with respiratory efficiencies of 33% (2D spiral) and 27% (2D TSE). The measured vessel wall

thicknesses were 1.15mm (B2B-RMC 3D spiral with 2RR gating), 1.37mm (B2B-RMC 3D spiral with 1RR gating), 1.35mm (2D spiral) and 1.22mm (2D TSE).

Table 6.2: Image quality scores from the high resolution coronary artery vessel wall acquisitions

Subject	Initial				Repeat							
	Heart rate (BPM)	Rest period (ms)	3D spiral 2RR (mm)	3D spiral 1RR (mm)	2D spiral 2RR (mm)	2D TSE 2RR (mm)	Heart Rate (BPM)	Rest period (ms)	3D spiral 2RR (mm)	3D spiral 1RR (mm)	2D spiral 2RR (mm)	2D TSE 2RR (mm)
1	51	172	✓	✓	✓	✓†	68	46	✓	✓	✓	✗
2	61	75	✓	✓	✓	✗†	58	85	✓	✓	✓	✓
3	65	85	✓	✓	✓	✓	67	50	✓	✓	✓	✓
4	57	174	✓	✓	✓	✓†	56	226	✓	✓	✓	✓
5	47	223	✓	✓	✓	✓†	55	97	✓	✓	✓	✓
6	72	50	✓	✓	✓	✗	68	90	✓	✓	✓	✓
7	60	190	✓	✓	✓	✓	46	182	✓	✓	✓	✓
8	59	153	✓	✗	✓	✓	66	101	✓	✓	✓	✓
9	73	50	✓	✓	✓	✓	72	83	✗	✗	✓	✗
10	54	146	✓	✓	✓	✓	59	110	✓	✓	✓	✓

Acquisitions resulting in images scored 3, 2 and 1 (fail) are coloured green, amber and red respectively.

† - studies acquired without the prescribed 77% phase oversampling (see text for details).

6.c.i Acquisition Duration and Respiratory Efficiency

For each of the techniques, table 6.3 gives the respiratory efficiency, acquisition duration, acquisition duration per slice and range of diaphragm motion in the initial studies. A one tailed paired t-test was used to compare the respiratory efficiency of the B2B-RMC techniques with the navigator gated techniques, and indicated that the B2B-RMC technique is significantly more efficient ($99.6 \pm 1.2\%$ vs. $39.0 \pm 7.5\%$ respectively, $p < 0.0001$). In addition, the much lower standard deviation of the respiratory efficiencies indicates that the B2B-RMC technique is substantially less variable than the navigator technique. While the acquisition duration of the 2D spiral technique was shorter than all other techniques, the acquisition duration per reconstructed slice of the B2B-RMC 3D spiral techniques was considerably less. On average the B2B-RMC technique corrected for 20 ± 6 mm of diaphragm motion in the initial study (range 15 – 36mm) in contrast to the 5mm nominal gating window used in the navigator gated acquisitions.

Table 6.3: Overview of respiratory efficiency, duration and related parameters in the initial study by imaging technique

Method	3D spiral 2RR	3D spiral 1RR	2D spiral 2RR	2D TSE 2RR
Respiratory efficiency [†] (SD) (%)	99.5 (1.6)	99.8 (0.3)	39.0 (9.4)	39.3 (4.6)
Diaphragm motion compensated (SD) (mm)	21.3 (6.9)	18.4 (6.0)	5.0*	5.0*
Reconstructed slices (number x thickness (mm))	16 x 1.5	16 x 1.5	1 x 6.0	1 x 6.0
Total acquisition duration [‡] (SD) (RR intervals)	603 (10)	301 (1)	209 (59)	479 [‡] (74)
Acquisition duration per reconstructed slice [•] (SD) (RR intervals)	37.7 (0.6)	18.8 (0.1)	209 (59)	479 [‡] (74)
N	10	9	10	8

[†] - $p < 0.0001$ when comparing the respiratory efficiency of the navigator gated techniques with the B2B-RMC techniques.

* - nominal navigator acceptance window.

[‡] - $p < 0.001$ - 2D TSE vs. 2D spiral, 2D spiral vs. 3D spiral 2RR, 3D spiral 1RR vs. 3D spiral 2RR; $p < 0.01$ - 2D TSE vs. 3D spiral 1RR; $p < 0.05$ - 2D spiral vs. 3D spiral 1RR; $p = ns$ - 2D TSE vs. 3D spiral 2RR.

[•] - $p < 0.001$ - 2D TSE vs. 2D spiral, 2D TSE vs. 3D spiral 1RR, 2D TSE vs. 3D spiral 2RR; 3D spiral 1RR vs. 3D spiral 2RR; $p < 0.01$ - 2D spiral vs. 3D spiral 1RR, 2D spiral vs. 3D spiral 2RR.

[‡] - the acquisition duration for the 2D TSE technique was corrected for the 77% phase oversampling error. The variation between subjects therefore reflects differences in echo train length and respiratory efficiency.

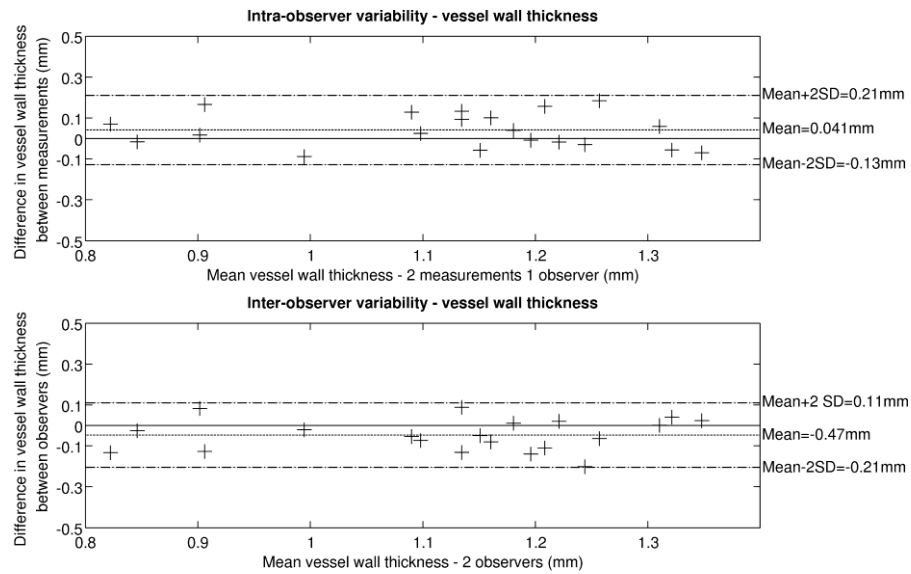
6.c.ii Vessel Wall Thickness

Bland-Altman plots for the intra and inter observer reproducibility of the vessel wall thickness measurements obtained in a subset of 20 images are shown in figure 6.9. The mean intra-observer difference was 0.04 ± 0.09 mm and the mean inter-observer difference was -0.05 ± 0.08 mm.

Vessel wall thickness measurements were obtained in 37 datasets from the initial study, see table 6.4.

The average vessel wall thickness for all techniques in the initial study was 1.11 ± 0.19 mm with repeated measures analysis of variance showing no significant differences between techniques.

Figure 6.9: Intra- and inter-observer reproducibility of the vessel wall thickness measurement technique



Bland-Altman plots showing (a) the intra- and (b) inter-observer reproducibility of the method used to measure the coronary vessel wall thickness. The intra- and inter-observer differences were (mean $\pm$ SD) 0.04 ± 0.09 mm and -0.05 ± 0.08 mm respectively.

Table 6.4: Vessel wall thicknesses obtained in the initial and repeat studies

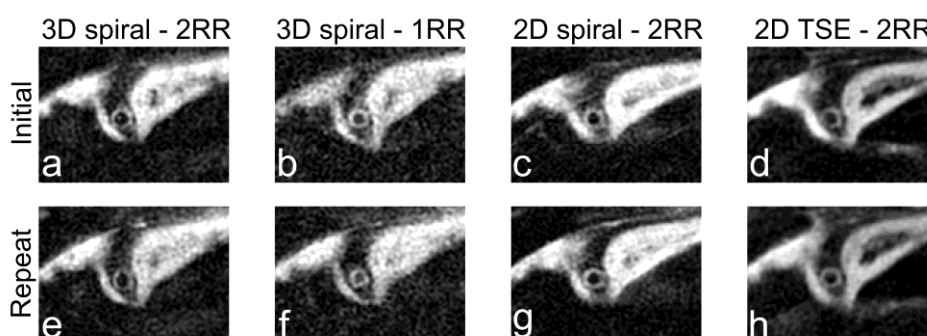
Subject	Initial				Repeat			
	3D spiral 2RR (mm)	3D spiral 1RR (mm)	2D spiral 2RR (mm)	2D TSE 2RR (mm)	3D spiral 2RR (mm)	3D spiral 1RR (mm)	2D spiral 2RR (mm)	2D TSE 2RR (mm)
1	1.11	1.04	0.95	1.35 [†]	0.90	1.23	0.98	✕
2	0.99	1.14	1.15	✕ [†]	0.96	0.92	1.07	1.01
3	1.28	1.20	1.24	1.19	1.28	1.29	1.23	1.27
4	1.09	1.29	1.34	1.35 [†]	1.02	1.12	1.05	1.05
5	1.31	1.23	1.23	1.21 [†]	1.34	1.35	1.20	1.16
6	1.07	1.34	1.21	✕	1.15	1.37	1.35	1.22
7	0.91	0.94	0.97	1.18	1.05	1.02	0.98	1.04
8	0.86	✕	0.90	0.84	0.79	0.77	0.81	0.85
9	1.09	1.20	1.12	1.19	✕	✕	0.92	✕
10	1.31	1.39	1.29	1.36	1.38	1.37	1.27	1.39
Mean (SD)	1.10 (0.14)	1.20 (0.16)	1.14 (0.15)	1.21 (0.17)	1.10 (0.20)	1.16 (0.22)	1.09 (0.17)	1.12 (0.17)
N	10	9	10	8	9	9	10	8

[†] - studies acquired without the prescribed 77% phase oversampling (see text for details).

6.c.iii Reproducibility

The mean time between the initial and repeat studies was 37 ± 16 days (range 28 – 77 days). In one subject (subject 3), the heart rate at the time of the repeat scan was faster than during the initial scan and there was no identifiable coronary rest period. The study was consequently abandoned and repeated at a later date when the heart rate was similar to that in the initial study. Initial and repeat images (acquired 29 days apart) in an example subject are shown in figure 6.10 demonstrating a high degree of visual similarity between the initial and repeat studies. Vessel wall thickness measurements were made in 36 repeat datasets. The results of the reproducibility tests, comparing the initial and repeat studies for each imaging technique are given in table 6.5 and the associated Bland-Altman plots are shown in figure 6.10. The intraclass correlation coefficients ranged from good for the B2B-RMC 3D spiral with 1RR gating (0.65) to excellent (0.87) for the B2B-RMC 3D spiral with 2RR gating acquisition (Landis and Koch, 1977). The standard deviation of the signed differences in vessel wall thickness between studies ranged from 0.10mm (B2B-RMC 3D spiral with 2RR gating) to 0.14mm (2D TSE and B2B-RMC 3D spiral with 1RR gating).

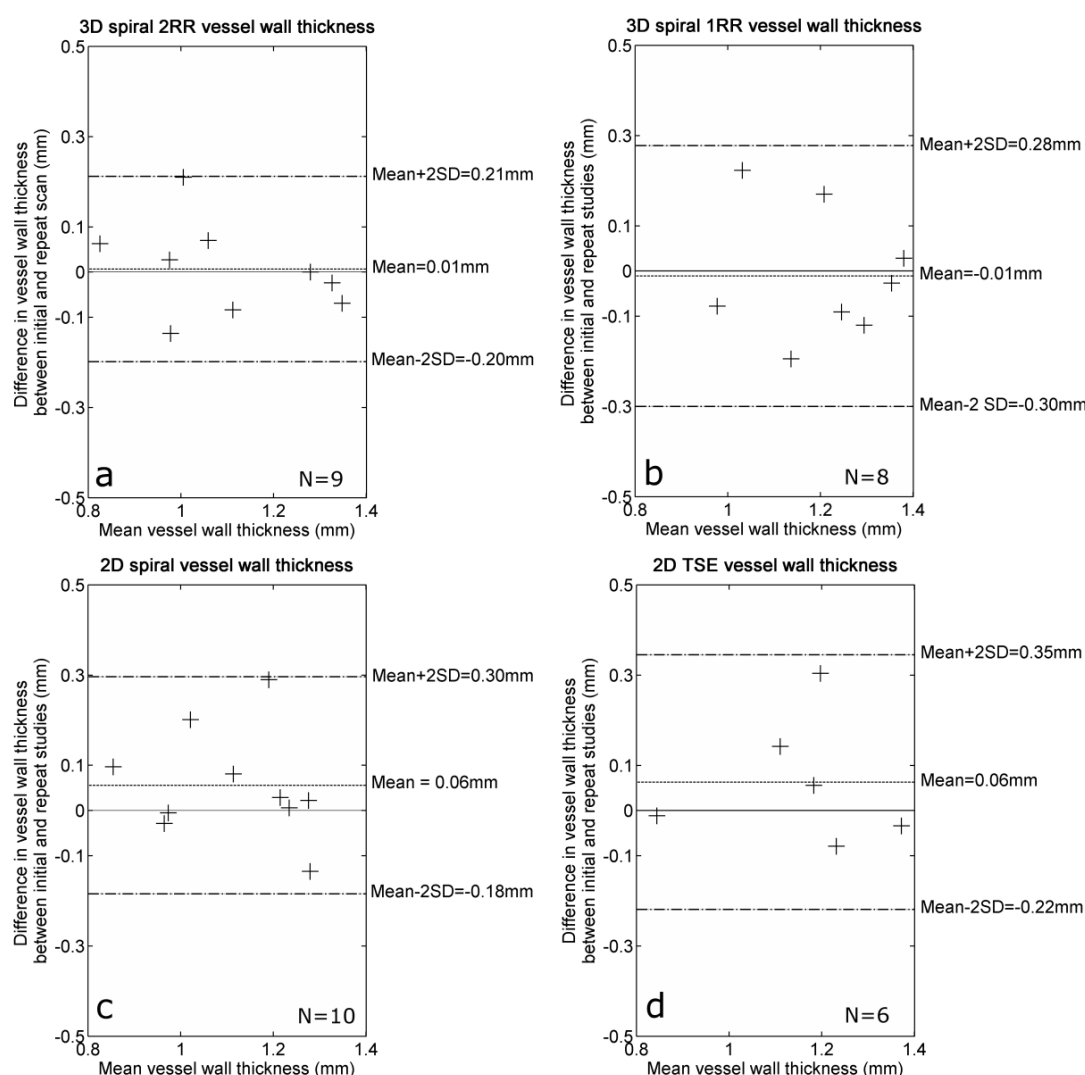
Figure 6.10: Example initial and repeat image acquired in one subject



The initial (a – d) and repeat (e – h) results obtained using each method in an example healthy volunteer (subject 4). The single slices chosen for quantitative vessel wall thickness comparisons from the 3D spiral techniques are shown here. There is a high degree of visual similarity between the initial and repeat images (acquired 29 days apart). Respiratory efficiencies and measured vessel wall thickness, on the top row from left to right are: 100% 1.09mm, 100% 1.29mm, 40% 1.34mm and 38% 1.35mm. On the bottom row, also from left to right, the respiratory efficiencies and measured vessel wall thicknesses are: 100% 1.02mm, 100% 1.12, 55% 1.05mm and 40% 1.05mm. In the initial study the B2B-RMC technique corrected for 14mm and 20mm of diaphragm motion when acquired with 2RR and 1RR gating respectively. In the repeat study the B2B-RMC technique corrected for 18mm of diaphragm motion when acquired with both 1RR and 2RR gating. The 2D TSE acquisition in the initial study was one of the four studies acquired without the 77% phase oversampling resulting in a lower SNR. Despite this image quality is good.

Table 6.5: Inter-study reproducibility

Method	3D spiral 2RR	3D spiral 1RR	2D spiral 2RR	2D TSE 2RR
Mean difference (SD) (mm)	0.01 (0.10)	-0.01 (0.14)	0.06 (0.12)	0.06 (0.14)
Intra-class correlation	0.87	0.65	0.70	0.72
N	9	8	10	6

Figure 6.11: Inter-study reproducibility

Bland-Altman plots for the reproducibility comparison between imaging techniques. The reproducibility was highest for (a) the B2B-RMC 3D spiral technique with 2RR gating: 0.01 ± 0.10 mm, followed by (c) the 2D spiral technique: 0.06 ± 0.12 mm, (d) the 2D TSE technique: 0.06 ± 0.14 mm and finally (b) the B2B-RMC 3D spiral with 1RR gating (the same standard deviation on the vessel wall thickness differences as the TSE technique but a lower intra-class correlation coefficient): -0.01 ± 0.14 mm.

6.d Discussion

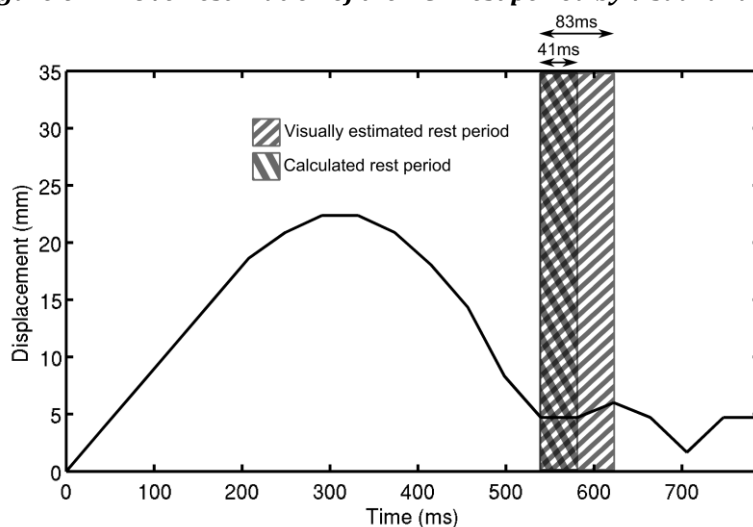
B2B-RMC enables the acquisition of high resolution 3D *in-vivo* images of the coronary vessel wall with near 100% respiratory efficiency. For both 2RR and 1RR gating, the vessel wall thicknesses measured using the B2B-RMC 3D spiral technique are not significantly different from those measured with conventional navigator techniques and the reproducibility is good (with 1RR gating) or excellent (with 2RR gating). The B2B-RMC technique compensated for 20 ± 6 mm of diaphragm motion which results in much improved and less variable respiratory efficiency compared with conventional navigator techniques ($99.6 \pm 1.2\%$ vs. $39.0 \pm 7.5\%$ respectively, $p < 0.0001$). This enables 3D coverage of the vessel with high resolution in a predictable and clinically feasible imaging time. In a patient cohort, where the

respiratory patterns are generally more variable, the advantages of 3D imaging and B2B-RMC in coronary vessel wall imaging are expected to be even more evident.

Overall, 91% of the 80 acquisitions performed were successful. Of the seven studies that failed, four were TSE acquisitions, two were B2B-RMC 3D spiral acquisitions with 1RR gating and one was a B2B-RMC 3D spiral acquisition with 2RR gating. Although the TSE sequence resulted in the highest number of images scored 3, it also result in the largest number of failed studies (scored 1). The TSE sequence is particularly sensitive to motion and an accurate assessment of the coronary rest period is imperative, as has been demonstrated in previous studies (Kim et al., 2001b, Malayeri et al., 2009). In this study, the mean heart rate in the failed TSE acquisitions (subjects 2 and 6 (initial studies) and subjects 1 and 9 (repeat studies)) was higher than in the successful TSE acquisitions (68 ± 5 BPM vs. 59 ± 8 BPM, $p < 0.05$) and the visually estimated coronary rest period was shorter (57 ± 18 ms vs. 133 ± 64 ms, $p < 0.05$). Retrospective quantitative analysis of the corresponding cine images in the plane of interest using local normalized cross correlation was performed to determine the true coronary rest period (defined as that period with < 1 pixel (1.7mm) of motion in either in-plane direction). Figure 6.12 plots the magnitude of the in-plane motion of the RCA obtained in this way for subject 9 (repeat study), where the estimated rest period was longer than the measured rest period and therefore, the implemented echo train length was too long. Similar results were found for the other failed TSE acquisitions. For comparison figure 6.13 plots the in-plane motion of the RCA for subject 10, where the rest-period was substantially under-estimated. One of the failed TSE acquisitions (subject 2 (initial study)) was not imaged with 77% phase oversampling due to the sequence error previously discussed, but this is not thought to be a key reason for the poor image quality. The first of the rejected B2B-RMC 3D spiral acquisitions with 1RR gating was acquired in a subject (subject 8 (initial study) – see figure 6.14) with a dominant left coronary artery system and, hence, a narrow RCA (luminal diameter=0.7mm and outer vessel diameter=2.7mm, measured on the 3D spiral with 2RR gating images). A combination of the small vessel size and both the inferior SNR and reduced robustness to RR-interval variations with 1RR gating resulted in insufficient contrast between the lumen and vessel wall (figure 6.14 (b)) to perform the thickness measurement. The equivalent repeat study was successful (figure 6.14 (f)), possibly due to less variation in RR-interval, or to subtle changes in the slice orientation and the dark blood reinversion slab location which may have improved the contrast between the vessel wall and lumen. The second failed B2B-RMC 3D spiral acquisition with 1RR gating and the only failed B2B-RMC 3D spiral acquisition with 2RR gating were obtained in subject 9 (repeat study – see figure 6.15) where only the 2D spiral acquisition, which was performed first, was successful (figure 6.15 (g)). During the repeat studies, the subject reported feeling uncomfortable during the last three acquisitions (figure 6.15 (e), (f), and (h)) which were those that failed. The rest period in the repeat studies was visually estimated at 83ms from the cine acquisition performed immediately before the 2D spiral imaging, but subsequent quantitative analysis of the cine acquisition demonstrated that the actual rest period was only 41ms (see figure 6.12). The subject's discomfort was accompanied by a heart rate increase of approximately 5BPM and a resultant reduction in the already short rest period duration is thought to be the cause of the acquisition failures.

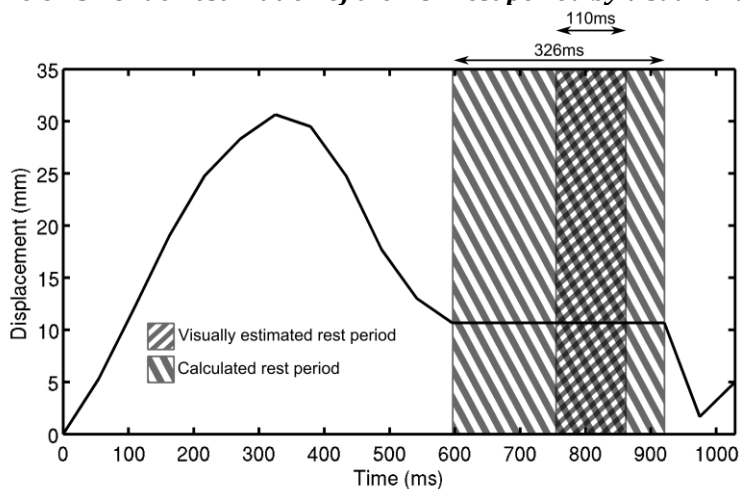
Small errors in determining the onset and duration of the coronary rest period have greatest impact in subjects with short rest periods. While we estimated the onset and duration of the coronary rest period from a cine acquisition in the same plane as the vessel wall image, subsequent quantitative analysis of the motion of the artery showed that in some cases this was inaccurate (figure 6.12 and 6.13). Automatic determination of rest period (Jahnke et al., 2005a), improved temporal resolution of the cine acquisitions (currently 20 reconstructed frames /RR-interval, actual temporal resolution 42ms) and/or repeat cine acquisitions for determining the rest period could potentially improve image quality and reduce the number of failed acquisitions. In work subsequent to this study the temporal resolution of the cine acquisition used to determine the rest period was increased to 19ms (64 reconstructed frames/RR-interval).

Figure 6.12: Over-estimation of the RCA rest period by visual analysis



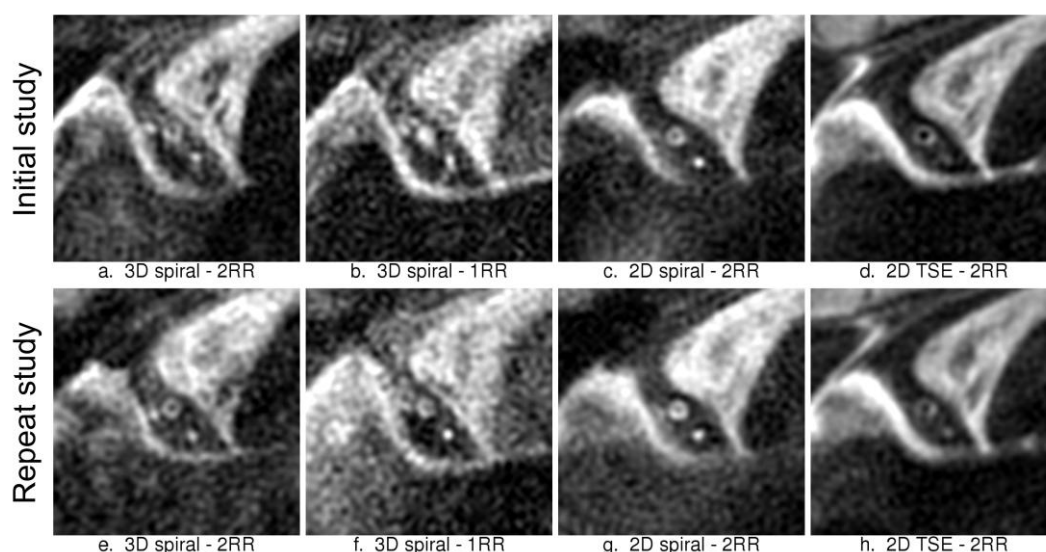
The in-plane motion of the RCA obtained from cine images in the imaging plane of the coronary vessel wall acquisitions for subject 9. The visually estimated rest period is longer (83ms) than the rest period determined by local normalized cross-correlation of the cine images (41ms).

Figure 6.13: Under-estimation of the RCA rest period by visual analysis



The in-plane motion of the RCA obtained from cine imaging in the plane of the coronary vessel wall acquisitions for subject 10. The visually estimated rest period (110ms) is much shorter than the rest period determined by local normalized cross-correlation of the cine images (326ms).

Figure 6.14: Example images from the initial and repeat studies of subject 8

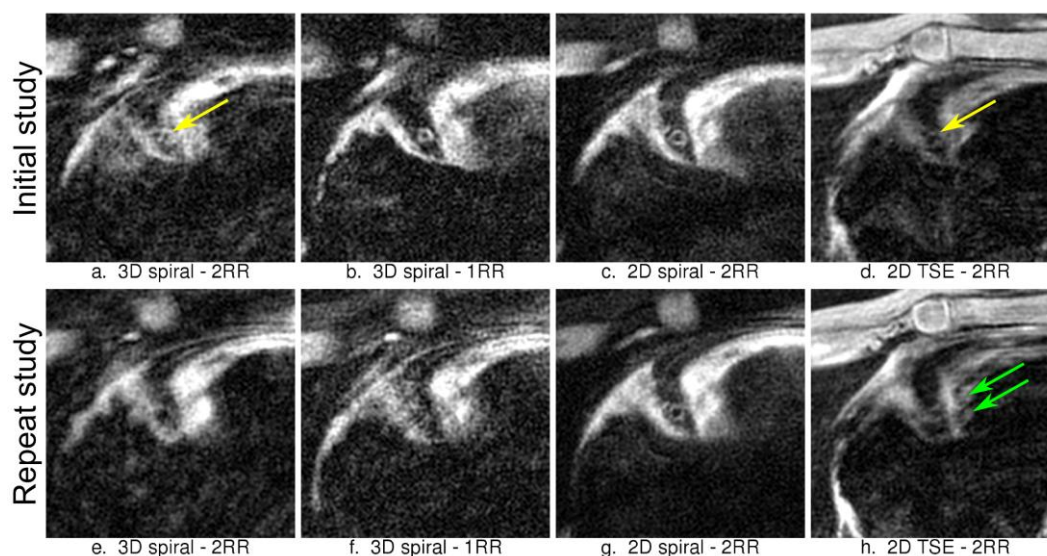


The initial (a – d) and repeat (e – h) results obtained using each method in subject 8, acquired 28 days apart. The single slices chosen for quantitative vessel wall thickness comparisons from the B2B-RMC 3D spiral techniques are shown here. The B2B-RMC 3D spiral acquisition with 1RR gating (b) resulted in images with insufficient vessel/lumen contrast for assessment of the coronary wall thickness in the initial study. The equivalent image from the repeat study (f), however, did permit vessel wall thickness measurement. Respiratory efficiencies and measured vessel wall thickness, on the top row from left to right are: 100% 0.86mm (a), N.A. (b), 38% 0.90mm (c) and 39% 0.84mm (d). On the bottom row, also from left to right, the respiratory efficiencies and measured vessel wall thicknesses are: 100% 0.79mm, 100% 0.77, 36% 0.81mm and 35% 0.85mm.

The B2B-RMC 3D spiral technique with 2RR gating was highly successful. Only one acquisition failed of 20 performed (subject 9, repeat study – as discussed above), 95% were scored 2 or 3, the respiratory efficiency was close to 100% and the reproducibility measures were excellent. While the B2B-RMC 3D spiral technique with 1RR gating allows a factor of 2 reduction in imaging time, the reproducibility was lower and problems imaging small arteries due to the reduced SNR were observed. In addition, this sequence is more sensitive to heart rate variations (due to less complete longitudinal magnetization recovery between sequence repeats) which can potentially lead to ghosting and poor dark blood suppression. The generally reduced image quality in the B2B-RMC 3D spiral 1RR gated acquisitions (see figures 6.6, 6.7, 6.8, 6.10 and 6.14) is reflected in the poorer image quality scores and is due primarily to lower SNR. In addition, the B2B-RMC 3D spiral images in figure 6.6 exhibit some ghosting from a section of the chest wall which is reinverted by the navigator restore pulse of the dark blood preparation (see section 3.c.ic). As the chest wall does not move rigidly with the coronary artery, the retrospective motion correction results in ghosting artefact from this reinverted section. This effect appears more prominent in the 1RR gated images due to the increased effect of additional ghosting artefacts caused by variations in RR interval. In the example shown in figure 6.6, the effect was further exacerbated in the 1RR gated images (scored 2) when compared to the 2RR gated images (scored 3) as the mean respiratory amplitude was larger (maximum diaphragm displacement 23mm vs. 18mm respectively). The section of chest wall reinverted in the other examples shown was sufficiently far from the right coronary artery to avoid this artefact. An alternative approach to reducing the overall imaging time of 2RR gated acquisitions would be

to increase the cardiac acquisition window (currently only 30ms) in subjects with longer rest periods (see figure 6.13 for example) by acquiring more spiral interleaves after each low resolution volume.

Figure 6.15: Example images from the initial and repeat studies of subject 9



The initial (a – d) and repeat (e – h) results obtained using each method in subject 9, acquired 28 days apart. The single slices chosen for quantitative vessel wall thickness comparisons from the B2B-RMC 3D spiral acquisitions are shown here. The coronary vessel wall was delineated from images from all acquisitions in the initial study, despite the relatively low image quality obtained with the B2B-RMC 3D spiral acquisition (a) with 2RR gating and the 2D TSE acquisition (d). Yellow arrows highlight the vessel wall in these cases. In the repeat study, only the 2D spiral acquisition (g), which was acquired first, was successful. Clear ghosting of cardiac structures is seen in the repeat 2D TSE acquisition ((h) – green arrows). Respiratory efficiencies and measured vessel wall thickness, on the top row from left to right are: 100% 1.09mm (a), 100% 1.20mm (b), 44% 1.12mm (c) and 38% 1.09mm (d). The respiratory efficiency and vessel wall thickness of the 2D spiral acquisition in the repeat study (g) was 36% and 0.92mm respectively.

The vessel wall thickness measured will clearly depend on the acquired spatial resolution. In this work, using an in-plane resolution of 0.7×0.7 mm, the average vessel wall thickness in the initial studies across all acquisitions was 1.11 ± 0.19 mm. This lies within the range obtained in healthy volunteers using MR by other groups (0.75 ± 0.17 mm (Fayad et al., 2000), 1.0 ± 0.2 mm (Botnar et al., 2000a), 1.14 mm (range 0.63 – 1.74 mm) (Hazirolan et al., 2005), 0.79 ± 0.23 mm (Koktzoglou et al., 2005), 1.0 ± 0.2 mm (Kim et al., 2002) and 1.6 ± 0.2 mm (Desai et al., 2005)).

Vessel wall thickness measurements obtained using circular ROIs drawn around the inner and outer vessel are reproducible (intra- and inter- observer differences in wall thickness measurements were 0.04 ± 0.09 mm and -0.05 ± 0.08 mm respectively). For comparison, in a previous study of reproducibility (Hazirolan et al., 2005) using multiple cross-sectional 2D TSE images of the RCA vessel wall an ROI based method was used to obtain intra- and inter-observer differences in wall thickness measurements of -0.07 ± 0.10 mm and -0.02 ± 0.20 mm respectively. The inter-study difference from the same work (Hazirolan et al., 2005) was 0.02 ± 0.20 mm which also compares well to the values of 0.01 ± 0.10 mm (B2B-RMC 3D spiral with 2RR gating), -0.11 ± 0.14 mm (B2B-RMC 3D spiral with 1RR gating), 0.06 ± 0.12 mm (2D spiral) and 0.06 ± 0.14 mm (2D TSE) found here. In addition, the intra class correlation coefficients closely

agree with those obtained by Desai et al. (2005) (0.86) using in-plane 3D spiral imaging. However, this is the first study to directly compare the reproducibility of coronary vessel wall thickness measurements between techniques.

There are a number of limitations to this study. Firstly, the B2B-RMC 3D spiral technique was not compared with a navigator gated 3D technique. However, the poor respiratory efficiency of navigator gating made this unfeasible at the desired resolution. At the average navigator efficiency of 39%, for example, a similar 3D spiral study with navigator gating would have taken 1535 cardiac cycles or approximately 25 min to acquire (at a heart rate of 60 BPM). The navigator gated techniques used here for comparison were therefore 2D techniques, as are frequently used in assessing the coronary artery wall. A further limitation is that all subjects in this work were healthy volunteers, but section 8.d describes initial work applying B2B-RMC in a patient cohort. In addition, all acquisitions in this study were performed in the RCA. While this is the more mobile artery – and hence the more challenging to image – its proximity to the surface receive coil is beneficial. Application of B2B-RMC to left coronary vessel wall imaging is discussed in section 8.b.

In conclusion, high resolution dark blood prepared 3D spiral imaging with B2B-RMC permits highly reproducible assessment of coronary vessel wall thickness when performed with 2RR cardiac gating. Furthermore, the significantly and substantially improved respiratory efficiency of the B2B-RMC technique over standard navigator gating with a 5mm acceptance window permits acquisition of a 3D high resolution volume in a reasonable time scale.

7. Non-invasive detection of coronary artery wall thickening with age in healthy subjects using 3D spiral imaging with B2B-RMC

The work presented in this chapter forms the basis of the paper: Scott AD, Keegan J, Mohiaddin RH. Non-invasive detection of coronary artery wall thickening with age in healthy subjects using high resolution magnetic resonance imaging with beat-to-beat respiratory motion correction. Journal of Magnetic Resonance Imaging 2011. In Press.

7.a Introduction

Autopsy studies have demonstrated thickening of the coronary artery vessel wall with age in normal subjects (Velican and Velican, 1981, Ozolanta et al., 1998). This thickening, primarily of the intimal layer, may be a precursor to atherosclerosis or may be a part of the normal aging process, or these may be one and the same thing. Velican and Velican (1981) analyzed autopsy specimens from subjects who primarily died in car accidents (80%) and demonstrated an increase in the average thickness of the intima from 0.037mm in neonates to 0.184mm in subjects aged 36–40. Another autopsy study (Ozolanta et al., 1998) of 121 subjects who did not die of coronary artery disease found increases in male right coronary wall thickness from 0.40 ± 0.13 mm at age 8 – 19 years old to 0.78 ± 0.20 mm at age 60 – 80 years old. The gold standard for *in-vivo* coronary vessel wall imaging is intravascular ultrasound and more recently, OCT is also used (see chapter 1). However, these are invasive techniques requiring catheterisation and x-ray contrast angiography for guidance and are consequently not suitable for studies of healthy volunteers or serial examinations. X-ray CT has also demonstrated coronary artery vessel wall thickening with age in 151 patients with suspected coronary artery disease (mean age 63 ± 13) (Matsunaga et al., 2009). However, CT also involves a significant ionizing radiation dose, together with potentially nephrotoxic contrast agents, and its use is consequently also limited. A non-invasive low risk technique is therefore desirable for assessment of the ageing process, pre-clinical disease and the progression or regression of disease in longitudinal studies.

MR vessel wall imaging has been used to demonstrate coronary vessel wall thickening in subjects with asymptomatic coronary disease (Fayad et al., 2000, Botnar et al., 2000a, Kim et al., 2007, Kim et al., 2002, Macedo et al., 2008, Gerretsen et al., 2010a) and has also been used to demonstrate carotid artery wall thickening with age in normal subjects (Keenan et al., 2009). However the smaller size, deeper location

and mobile nature (with both the cardiac and respiratory cycles) of the coronary arteries makes equivalent studies of coronary vessel wall ageing using MR considerably more challenging (see section 1.e.ii and chapter 2). In the previous chapter MR coronary vessel wall imaging using a 3D spiral acquisition with B2B-RMC and 2RR gating was shown to perform with a high degree of reproducibility while efficiently dealing with respiratory motion (>99% respiratory efficiency). In this chapter, it is proposed that 3D high resolution imaging with B2B-RMC may be used to demonstrate right coronary artery vessel wall thickening with age in healthy subjects within a clinically feasible timescale.

7.b Methods

7.b.i Subjects

Twenty one healthy adult subjects (mean age 39 ± 13 , range 22-62 years old, 11 female) were recruited according to local ethics committee approval. All subjects had no history of cardiovascular disease and were assumed to have normal coronary arteries. Ten of these subjects were recruited for the study described in chapter 6 and the data from the B2B-RMC 3D spiral acquisition with 2RR gating was re-used here.

7.b.ii Imaging

Preparatory imaging is described fully in chapter 3. The selected imaging plane was located in a straight section of the proximal/mid (within ~40mm of the origin) RCA. Cine images in this plane were analyzed to determine the coronary rest period and therefore establish subsequent acquisition timings. Cross-sectional right coronary wall images were acquired using a 3D spiral acquisition with B2B-RMC and 2RR gating. Key high resolution imaging parameters were: in-plane resolution 0.7×0.7 mm, 8×3.0 mm slices (reconstructed to 16×1.5 mm slices), acquisition duration 600s (assuming 100% respiratory efficiency and a heart rate of 60 BPM), typical dark-blood inversion time 625ms (optimal for a heart rate of 60BPM and 2RR gating) and acquisition window 30ms. One subject was imaged at a higher acquired resolution of $0.57 \times 0.57 \times 3.0$ mm and a field of view of $390 \times 390 \times 24$ mm as part of initial tests. All other parameters were identical. In all studies a diaphragmatic navigator was used to reject data acquired at extreme respiratory positions ($> \pm 10$ mm outside normal range), typically resulting in >99% respiratory efficiency. Respiratory motion in the acquired data was retrospectively corrected using B2B-RMC as described in chapter 3.

7.b.iii Analysis

The central slice from the high resolution 3D cross-sectional coronary artery wall imaging volume was selected for analysis. If this slice was not suitable, due to vessel curvature or vessel branching for example, the nearest acceptable slice was analyzed. For the acquisitions performed for the reproducibility work described in chapter 6, the study (initial or repeat) most clearly depicting the vessel wall was used here. For each chosen slice, lumen area and outer wall (lumen + vessel wall) area were measured by drawing circular regions of interest around the inner and outer vessel wall. These measurements were used to determine vessel wall area, mean vessel wall thickness and wall/outer wall

area ratio (W/OW) (Saam et al., 2005). The intra- and inter-observer, and inter-study reproducibility of this measurement technique for assessing vessel wall thickness was measured at 0.09mm and 0.08mm respectively (quoted as one standard deviation of the signed differences) in chapter 6.

7.b.iv Statistics

Measurements of wall thickness, wall area, lumen area, outer wall area and W/OW were compared between the sexes using 2 tailed unpaired t-tests. Regression analysis using a least squares linear fit and Pearson's correlation coefficient was performed for: (i) vessel wall thickness with age; (ii) W/OW with age; (iii) outer wall area with vessel wall thickness; (iv) lumen area with vessel wall thickness.

7.c Results

Images acquired in three subjects (14%) were rejected due to excessive cardiac or respiratory motion artefact which resulted in poor image quality. Table 7.1 summarizes the BMI, blood pressure and smoking history of the remaining 18 subjects. No subject was obese ($>30 \text{ kg m}^{-2}$ (2000)), none were hypertensive ($>140\text{mmHg}$ systolic or $>90\text{mmHg}$ diastolic (2004)) and none were known diabetics. One was a current smoker.

Table 7.2 shows the measured parameters averaged for male, female and all subjects. Outer wall area and mean lumen area were significantly smaller in female subjects (both $p<0.05$) while vessel wall area, mean wall thickness and W/OW showed no significant difference between sexes. Example images are shown in figure 7.1. Average respiratory efficiency was $99.3\pm1.7\%$ (range 94.6 – 100.0%), corresponding to an average acquisition duration of 604s assuming a heart rate of 60BPM.

Table 7.1: Summary of subject characteristics

Subject	Age (years)	Sex	BMI (kg m⁻²)	BP (systolic) (mmHg)	BP (diastolic) (mmHg)	Smoking history
1	22	M	24	119	69	Never
2	24	M	25	123	60	Never
3	24	M	29	130	70	Never
4	27	M	25	124	71	Never
5	28	F	25	120	69	Previous
6	29	M	23	117	67	Previous
7	31	F	22	114	70	Previous
8	31	F	22	110	82	Never
9	35	M	24	115	70	Never
10	37	F	24	118	68	Previous
11	40	F	22	119	77	Never
12	40	M	26	121	69	Previous
13	48	F	18	122	79	Never
14	49	F	20	118	75	Never
15	53	M	27	132	84	Never
16	57	F	26	115	68	Current
17	59	M	23	140	89	Never
18	62	F	23	121	75	Previous

*BMI – body mass index**BP – blood pressure*

Table 7.2: Summary of results by sex

Parameter	Mean value (all subjects) ± SD	Mean value (male subjects) ± SD	Mean value (female subjects) ± SD	p-value male vs. female
Vessel wall thickness	1.14±0.22mm	1.18±0.26mm	1.11±0.17mm	0.51
W/OW	0.727±0.085	0.70±0.10	0.758±0.055	0.12
Lumen area	5.3±2.7mm ²	6.7±2.9mm ²	3.8±1.6mm ²	0.020*
Outer wall area	18.6±6.4mm ²	21.8±6.6mm ²	15.4±4.6mm ²	0.031*
Wall area	13.3±4.5mm ²	15.0±5.0mm ²	11.6±3.3mm ²	0.099

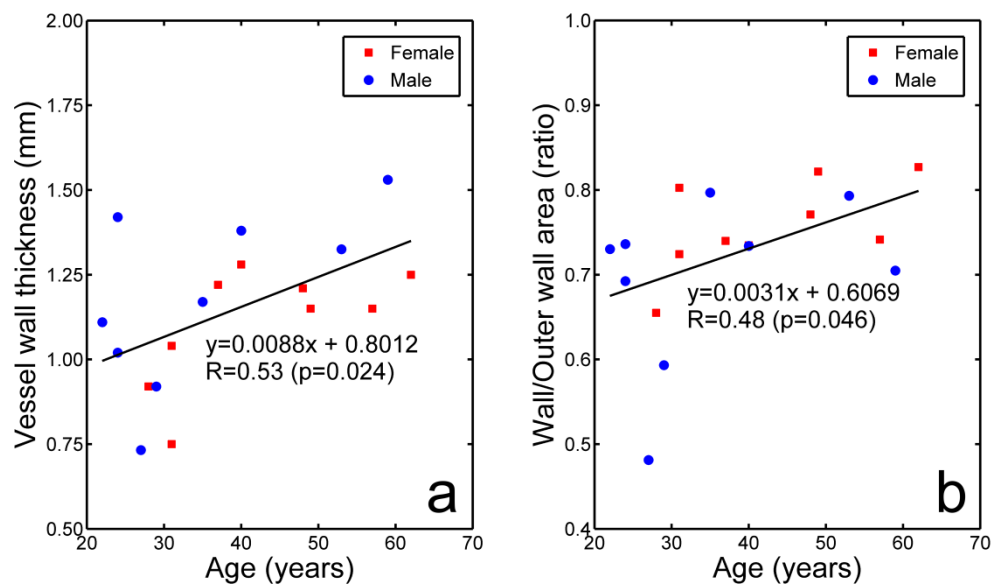
* – A significant difference is present between male and female subjects at the $p=0.05$ level.
SD – Standard deviation.

Figure 7.1: Example coronary vessel wall images from three healthy subjects

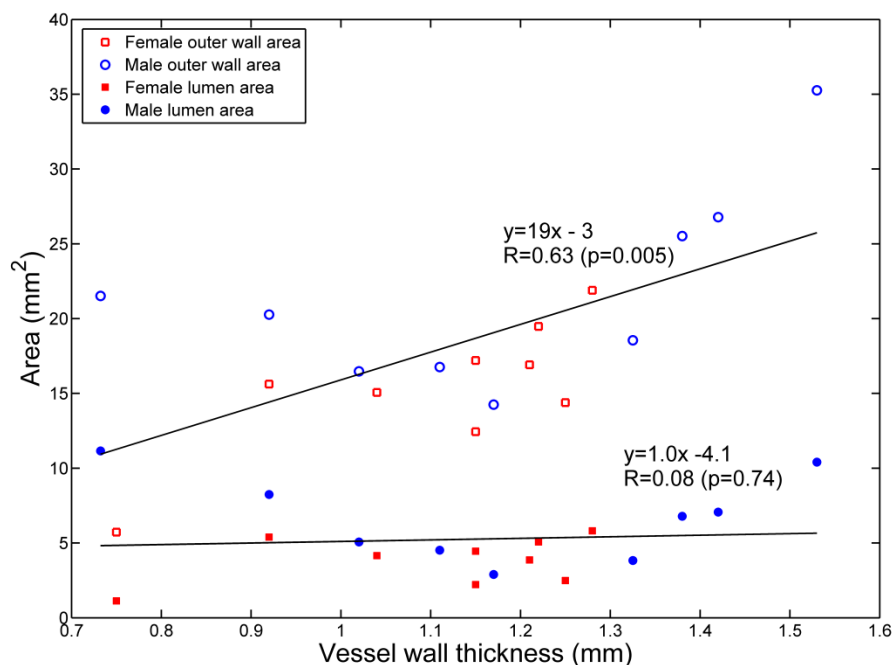
Example cross-sectional right coronary artery MR vessel wall images are shown from three healthy male volunteers aged 24 years (wall thickness 1.02mm and W/OW 0.69) (a), aged 40 years (wall thickness 1.38mm and W/OW 0.73) (b) and aged 59 years (wall thickness 1.53mm and W/OW 0.70) (c). One slice, as shown here, was selected from the 3D volume for analysis in each subject. These images show a well delineated vessel wall with good blood suppression.

Figure 7.2 plots vessel wall thickness (a) and W/OW (b) with subject age and demonstrates positive correlations ($R=0.53$, $p=0.024$ and $R=0.48$, $p=0.046$ respectively), with an increase in vessel wall thickness of 0.088mm per decade and an increase in W/OW of 0.031 per decade.

In line with previous work by Miao et al.(2009) and Terashima et al. (2010), figure 7.3 plots lumen area and outer wall area against vessel wall thickness. Lumen area does not increase with vessel wall thickness ($R=0.08$, $p=0.74$) while the outer wall area increases (19mm² per mm of vessel wall) with a significant correlation ($R=0.63$, $p=0.005$).

Figure 7.2: The change in coronary vessel wall thickness and W/OW with age

Coronary vessel wall thickness (a) and W/OW (b), measured using circular ROIs drawn around the inner and outer vessel wall, are plotted with subject age. Both measurements demonstrate a significant correlation with age – vessel wall thickness increasing by 0.088mm per decade ($p=0.024$) and W/OW by 0.031 per decade ($p=0.046$) despite the small number of subjects. Red square markers indicate the data from female subjects, while blue circular markers indicate the data from male subjects. The sample size was insufficient to derive independent relationships by sex.

Figure 7.3: The change in coronary outer wall area and lumen area with vessel wall thickness

Coronary artery outer wall (lumen + wall) area and lumen area are plotted against vessel wall thickness, as performed by Miao et al. (2009). Lumen area does not significantly increase with vessel wall thickness. However, the increase in outer wall area with vessel wall thickness demonstrates a significant correlation (an increase of 19 mm^2 per mm, $p=0.005$). This data is consistent with outward remodelling of the coronary vessel wall.

7.d Discussion

For the first time, this study has demonstrated a significant increase in vessel wall thickness with age in a cohort of healthy volunteers. This has been achieved despite a small sample size. The proportion of vessel that is vessel wall (W/OW) also increases with subject age and the correlation coefficient ($R = 0.48$) is similar to that observed in larger studies of carotid wall thickening in healthy subjects (Keenan et al. (2009) found $R=0.50$ in males and $R=0.46$ in females).

By using the highly efficient B2B-RMC technique these results were achieved within a relatively fixed and clinically feasible imaging period (~600 cardiac-cycles or 10minutes at 60BPM). Images in only 14% of subjects were of insufficient quality for vessel wall thickness measurement, which compares well to rejection rates of 33% of segments (Terashima et al., 2010) and 53% of segments (Malayeri et al., 2009) in recent larger coronary artery vessel wall imaging studies.

In previous work at autopsy, Ozolanta et al. (1998) observed an increase in average coronary wall thickness from 0.40mm at age 8 – 19 to 0.78mm at age 60 – 80 years old in male right coronary arteries, equivalent to 0.067mm per decade. Similarly at autopsy, Velican and Velican (1981) demonstrated an increase in the average thickness of the intimal layer from 0.133mm at age 21 – 25 to 0.188mm at age 36 – 40 years old, corresponding to an increase of 0.023mm per decade. Using CT, Matsunaga et al. (2009) found a significant correlation between maximum vessel wall thickness and age ($R=0.34$, $p<0.001$) in older subjects with suspected coronary artery disease. However, in a previous MR coronary vessel wall imaging study, vessel wall thickness was not found to be significantly different between disease free subjects aged 46 – 64 and subjects aged 65 – 76 years old (Macedo et al., 2008) (48 subjects). Similarly, age was not found to be significant in a multivariate analysis of coronary vessel wall area and vessel wall thickness measured by MR in subjects without cardiovascular disease aged 60 – 72 years old (223 subjects) (Terashima et al., 2010). In this small study of younger subjects, the increase in mean vessel wall thickness was 0.088mm per decade ($R=0.53$, $p<0.05$). This is the first time a relationship between coronary vessel wall thickness and age in a healthy subject cohort has been demonstrated using non-invasive imaging.

Using MR coronary vessel wall imaging, Miao et al. (2009) found a significant correlation between coronary outer wall area and lumen area with vessel wall thickness (25.9mm² per mm and 3.1mm² per mm respectively) in a large cohort of subjects without known disease (170 subjects, age 45 – 85, see discussion of the MESA in section 1.e.ii.5). In another MR study of older subjects without disease (223 subjects, aged 60 – 72) (Terashima et al., 2010), coronary outer wall area was found to significantly increase with vessel wall thickness, while there was no relationship between lumen area and vessel wall thickness. In this study, there was an increase in outer wall area of 19mm² per mm of wall thickness, which is slightly lower than that found by Miao et al. (2010) and, similar to Terashima et al. (2010), no significant increase in lumen area with wall thickness was observed here. These results are consistent with outward remodelling of the coronary vessel wall.

There are a number of limitations to this preliminary study. Firstly, the number of subjects was low and it was consequently not possible to discriminate between the sexes. Despite this, a significant correlation between vessel wall thickness and age with similar rates of increase to those observed in autopsy was demonstrated. Secondly, other common risk factors were not included in the analysis, although the cohort was relatively young and in good health. Finally, while the average vessel wall thickness ($1.14 \pm 0.22 \text{ mm}$) lies within the range of values obtained using MR techniques (Fayad et al., 2000, Hazirolan et al., 2005, Koktzoglou et al., 2005, Botnar et al., 2000a, Kim et al., 2002, Desai et al., 2005), it is greater than that obtained using histology (average right coronary wall thickness 0.68mm males aged 20–59 (Ozolanta et al., 1998)). As discussed in chapter 1.e.ii.4, this is likely to be the result of the more limited resolution achievable using MR imaging ($0.7 \times 0.7 \times 3.0 \text{ mm}$ in this case), which is known to result in an over-estimation of vessel wall thicknesses (Schär et al., 2003).

Future work will involve further, larger studies in age matched groups of subjects with a Frammingham risk score analysis. Further improvements are expected at the higher resolutions enabled by 3T MR systems and using improved receive coils.

In conclusion, using high resolution 3D MR imaging with the B2B-RMC technique increasing coronary vessel wall thickness with age was demonstrated in a small healthy subject cohort.

8. Further applications of B2B-RMC to coronary vessel wall imaging

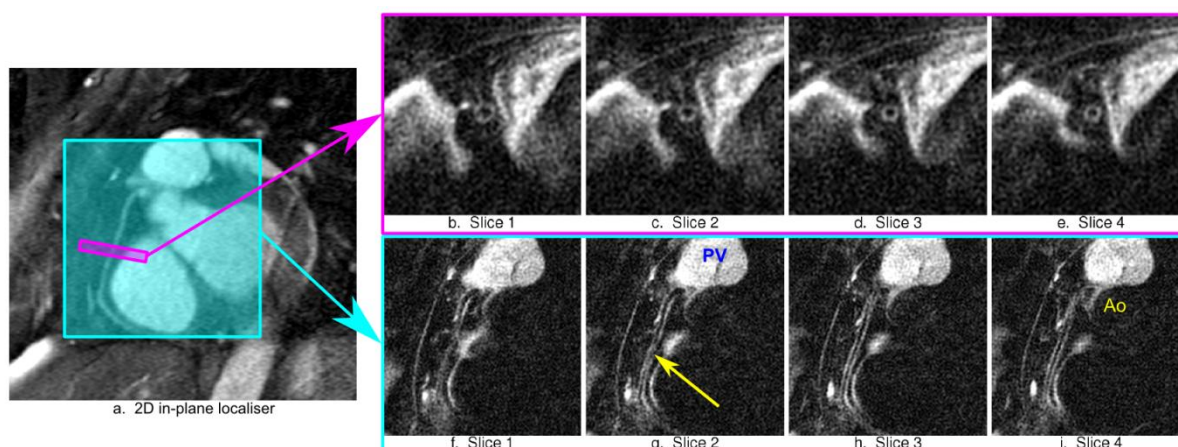
8.a In-plane RCA vessel wall imaging

In previous sections, 3D spiral imaging with B2B-RMC was shown to perform reliably and reproducibly for cross-sectional vessel wall imaging of the RCA when performed with 2RR gating. This technique was also used to demonstrate thickening of the RCA wall with age in healthy subjects. While 3D cross-sectional imaging has the potential to evaluate changes in plaque morphology, it is limited to the assessment of short, relatively straight sections of vessel. As a result, in arteries with only localized outward remodelling and therefore, normal angiography studies, cross-sectional coronary artery wall imaging may suggest the artery is free of disease if the imaging volume does not coincide with the diseased region. Several 3D coronary vessel wall imaging studies have imaged in the plane of the vessel (see section 1.e.ii), thus enabling the evaluation of longer sections of artery. Ideally such studies should be acquired at near isotropic resolution, therefore allowing reconstruction of images in any plane without asymmetric partial volume effects. B2B-RMC previously (chapter 5) demonstrated the ability to correct in-plane MR coronary angiography images of the RCA (bright blood imaging). In this section, a series of *in-vivo* examples are presented, demonstrating the application of the B2B-RMC 3D spiral technique to in-plane imaging of the RCA vessel wall.

Dark blood prepared in-plane B2B-RMC 3D spiral acquisitions were obtained in six of the healthy subjects imaged specifically for the study described in chapter 7. Multiple in-plane navigator gated 2D bSSFP MR coronary angiography acquisitions were performed as planning acquisitions and the imaging plane demonstrating the greatest visible in-plane length of the RCA was then used for the in-plane 3D spiral with B2B-RMC acquisition. The high resolution in-plane B2B-RMC 3D spiral acquisitions were acquired with the same voxel volume as in previous sections, but with a reduced slice thickness ($0.9 \times 0.9 \times 1.8\text{mm}$ vs. $0.7 \times 0.7 \times 3.0\text{mm}$ previously), corresponding to a FOV of $733 \times 733 \times 14.4\text{mm}$. Images were reconstructed to $0.9 \times 0.9 \times 0.9\text{mm}$ isotropic resolution. Other sequence parameters were as described in section 3.f. The slab selective reinversion of the dark blood preparation was orientated to avoid reinverting blood within the left ventricle and the chest wall. Imaging was performed with 2RR gating and an inversion time of 625ms where possible. Total acquisition duration was 600 RR-intervals (assuming 100% respiratory efficiency). Images were corrected and reconstructed as described in chapter 3 using search and reference ROIs placed around the proximal RCA.

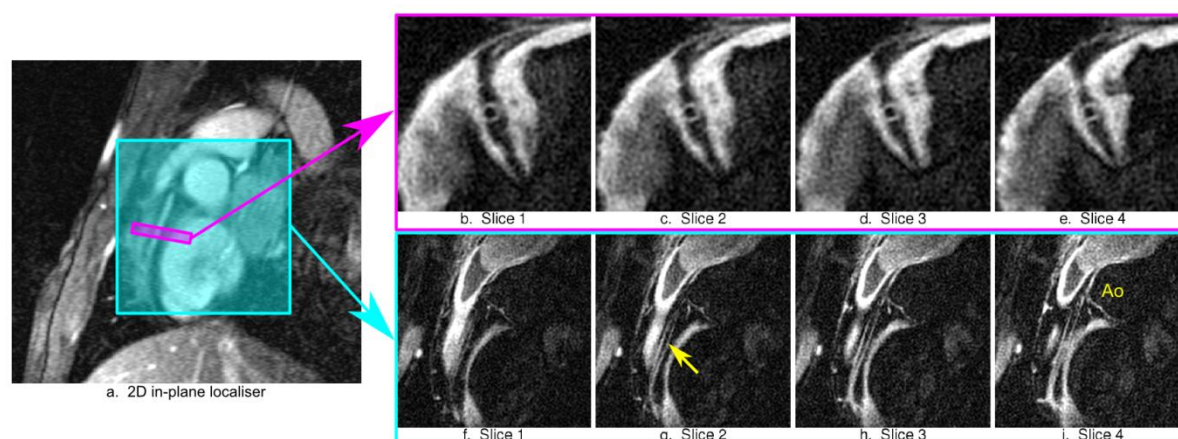
Images were successfully acquired in 5 of the 6 healthy subjects. The single failed acquisition was due to operator error in positioning the imaging slab. Figures 8.1 – 8.4 show example cross-sectional and in-plane vessel wall images of the RCA in four of the subjects. The location and orientation of the vessel wall images is also shown on a 2D bSSFP MR coronary angiography study used in the planning stages of each study. The example shown in figure 8.1 was acquired in a 57 year old female (lumen diameter 2.38mm, average vessel wall thickness 1.15mm). The RCA vessel wall is clearly delineated in the cross-sectional images (figure 8.1 (b – e)). The corresponding in-plane images (f – i) show a long section of well delineated RCA vessel wall, highlighted by the yellow arrow (g). The aorta (Ao) and pulmonary valve (PV) are also labelled. Clarity of the vessel wall is lost as it curves sharply in the distal section. This is partly the result of the localized nature of the current B2B-RMC implementation, as discussed in chapter 5. Figure 8.2 shows images from a 22 year old male subject (lumen diameter 2.40mm, average wall thickness 1.11mm). Both the cross-sectional and in-plane images are good quality with high SNR. Due to the through-plane curvature of the vessel (also shown in the 2D bSSFP planning image (a)), the in-plane images show a shorter length of artery than in the previous example but the edges of the vessel wall are very sharp. Figure 8.3 shows images obtained from a 40 year old female subject (lumen diameter 2.72mm, average wall thickness 1.28mm). The cross-sectional images are good quality but the in-plane images are noisy. This is thought to be the result of a fault with the receive coil, diagnosed soon after this acquisition. Despite the additional noise, the in-plane images (figure 8.3 (f – i)) clearly show a straight section of the mid RCA vessel wall. A branch bifurcating from the RCA is seen in the distal artery (blue arrow) where a combination of slow flow and insufficient resolution results in a lack of vessel wall to lumen contrast. RCA images from a 48 year old subject are shown in figure 8.4 (lumen diameter 2.22mm, average wall thickness 1.21mm). While the cross-sectional images are noisy, potentially as a result of the receive coil fault described above, the in-plane images show a number of interesting anatomical features. Due to the curvature of the vessel into the through-plane direction at the origin, the ostium of the RCA appears loop like (dashed yellow arrow). The proximal and mid RCA is more curved than in the previous examples, but a relatively long section is imaged (yellow arrow). In addition a short section of a cardiac vein is seen almost parallel to the RCA (green arrow) and the origin of the conus artery is also seen (blue arrow).

Figure 8.1: Example of cross-sectional and in-plane right coronary vessel wall imaging using B2B-RMC 3D spiral imaging



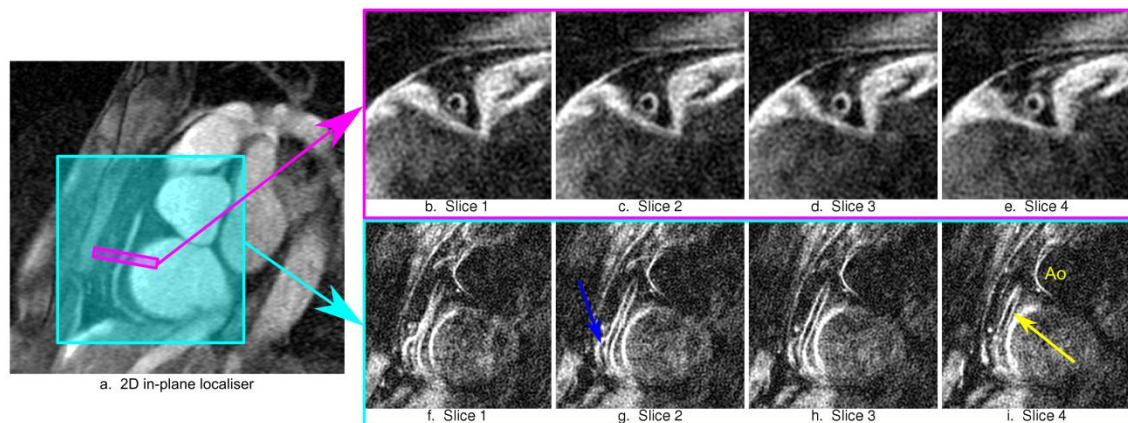
A 2D navigator gated bSSFP acquisition (a) used in planning the later acquisitions highlights the location of the cross-sectional (magenta) and in-plane (cyan) coronary vessel wall images shown. On the top line, four 1.5mm thick (reconstructed) cross-sectional coronary vessel wall slices (b – e) acquired at 0.7 x 0.7 x 3.0mm resolution are shown from the mid RCA. On the bottom line, four 0.9mm thick (reconstructed) in-plane coronary vessel wall slices (f – i) acquired at 0.9 x 0.9 x 1.8mm resolution are shown from the RCA. The pulmonary valve (PV) and aorta (Ao) are labelled in the in-plane images and the yellow arrow indicates the RCA vessel wall.

Figure 8.2: Example of cross-sectional and in-plane right coronary vessel wall imaging using B2B-RMC 3D spiral imaging



A 2D navigator gated bSSFP acquisition (a) used in planning the later acquisitions highlights the location of the cross-sectional (magenta) and in-plane (cyan) coronary vessel wall images shown. On the top line, four 1.5mm thick (reconstructed) cross-sectional coronary vessel wall slices (b – e) acquired at 0.7 x 0.7 x 3.0mm resolution are shown from the RCA. On the bottom line, four 0.9mm thick (reconstructed) in-plane coronary vessel wall slices (f – i) acquired at 0.9 x 0.9 x 1.8mm resolution are shown from the RCA. The aorta (Ao) is labelled and the yellow arrow indicates the RCA vessel wall in the in-plane images.

Figure 8.3: Example of cross-sectional and in-plane right coronary vessel wall imaging using B2B-RMC 3D spiral imaging

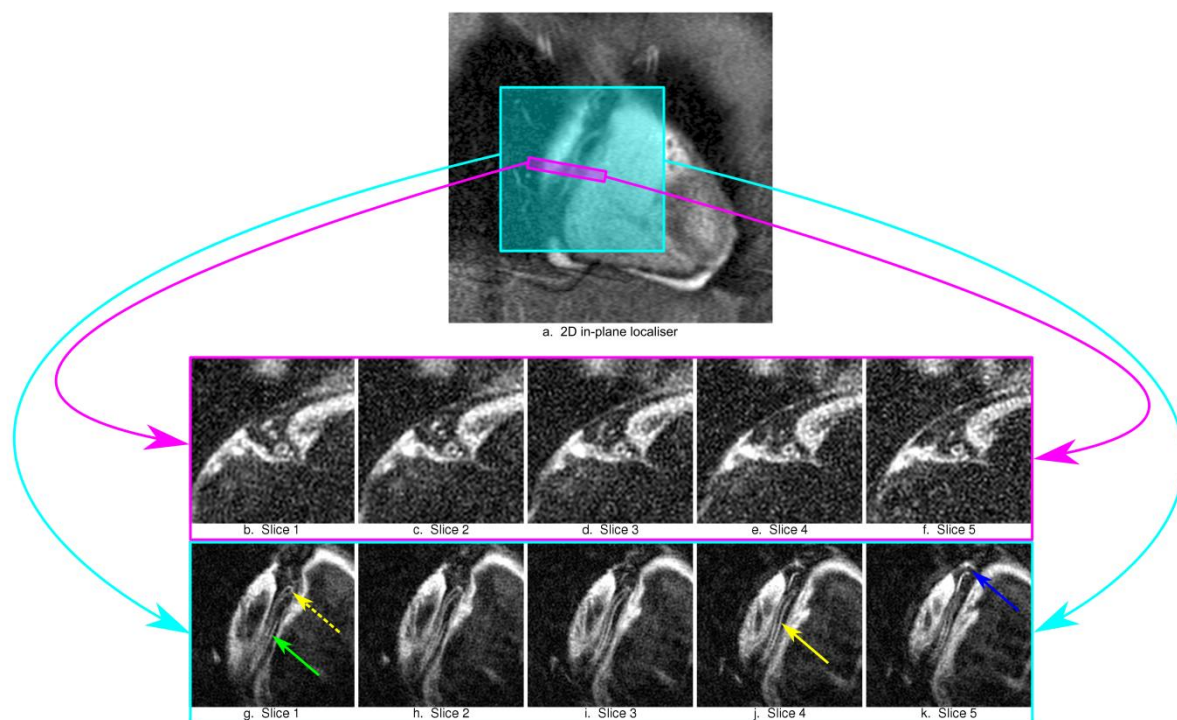


A 2D navigator gated bSSFP acquisition (a) used in planning the later acquisitions highlights the location of the cross-sectional (magenta) and in-plane (cyan) coronary vessel wall images shown. On the top line, four 1.5mm thick (reconstructed) cross-sectional coronary vessel wall slices (b – e) acquired at $0.7 \times 0.7 \times 3.0\text{mm}$ resolution are shown from the mid RCA. On the bottom line, four 0.9mm thick (reconstructed) in-plane coronary vessel wall slices (f – i) acquired at $0.9 \times 0.9 \times 1.8\text{mm}$ resolution are shown from the RCA. In the in-plane images, the aorta (Ao) is labelled, the yellow arrow indicates the RCA vessel wall and the blue arrow highlights a branch vessel with slow and therefore, unsuppressed flow.

The examples shown here demonstrate that B2B-RMC 3D spiral imaging can be applied to in-plane coronary vessel wall imaging of the RCA as is often performed using 3D spiral imaging with navigator gating. The proximal and mid-artery is clearly delineated in these examples, but further operator experience and advanced visualization tools are required to obtain clear images of the RCA origin due to the curvature of the vessel into the through-plane direction in the very proximal section. As also demonstrated in chapter 5 for MR coronary angiography, the localised nature of B2B-RMC results in degradation of the performance of the respiratory motion correction in the distal artery where the motion differs from that in the proximal artery. However, future non-rigid implementations of B2B-RMC could result in images fully corrected for motion along the length of the artery. Blood suppression in the distal RCA and small side branches is often sub-optimal as flow is reduced and there is insufficient time for suppressed blood from the left ventricle to reach these regions within the $\sim 625\text{ms}$ inversion time. This could potentially be improved by using diffusion like blood suppression (Wang et al., 2009, Gerretsen et al., 2010b), but this technique is very sensitive to motion and may result in loss of signal from the artery itself.

While a full study of in-plane coronary vessel wall imaging has not been performed as part of this thesis, the success of these initial tests suggests that in-plane 3D spiral vessel wall imaging with B2B-RMC is possible. The technique therefore has the potential to identify regions of locally thickened RCA wall in patients. Subsequently, plaque morphology within the identified thickened regions could then be examined in more detail using cross-sectional B2B-RMC 3D spiral vessel wall imaging.

Figure 8.4: Example of cross-sectional and in-plane right coronary vessel wall imaging using B2B-RMC 3D spiral imaging



A 2D navigator gated bSSFP acquisition (a) used in planning the later acquisitions highlights the location of the cross-sectional (magenta) and in-plane (cyan) coronary vessel wall images shown. On the top line, five 1.5mm thick (reconstructed) cross-sectional coronary vessel wall slices (b – f) acquired at $0.7 \times 0.7 \times 3.0\text{mm}$ resolution are shown from the RCA. On the bottom line, five 0.9mm thick (reconstructed) in-plane coronary vessel wall slices (g – k) acquired at $0.9 \times 0.9 \times 1.8\text{mm}$ resolution are shown from the RCA. A dashed yellow arrow highlights the ostium and a solid yellow arrow the course of the RCA. A short section of a cardiac vein can also be seen (green arrow), as can the origin of the conus artery (blue arrow).

8.b Left coronary vessel wall imaging

Previous sections have focused on imaging the RCA which is more mobile than the left. However, the left coronary arteries are located further from the chest wall, which is likely to result in poorer SNR in MR vessel wall imaging. Furthermore, the volume of epicardial fat surrounding the left coronary arteries is less, potentially making B2B-RMC difficult. Nevertheless, as the culprit lesion in myocardial infarction is most commonly located in one of the left coronary arteries (Fuster, 2008), the LAD and LCX are desirable targets in MR vessel wall imaging. In this section, the first demonstration of 3D coronary vessel wall imaging with B2B-RMC applied to the left coronary artery system is presented.

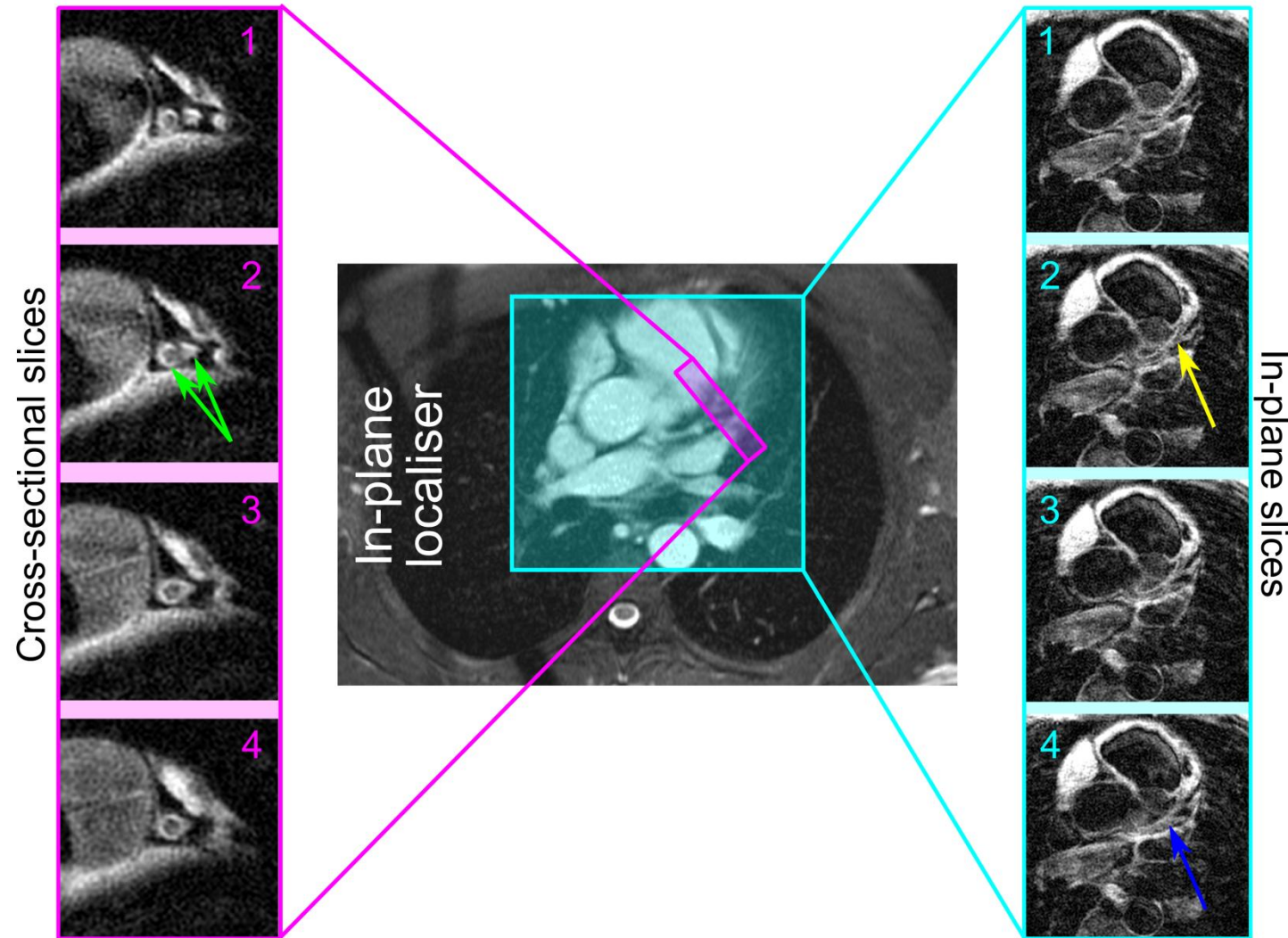
One healthy subject was imaged following the protocol described in section 3.f. However, the 2D bSSFP MR coronary angiography studies targeted the LM and proximal LAD arteries rather than the RCA. Coronary vessel wall acquisitions were performed in the subject-specific LAD rest period. A high resolution cross-sectional 3D spiral acquisition with B2B-RMC was performed in the LAD at the bifurcation of the first diagonal branch. Image resolution was $0.7 \times 0.7 \times 3.0\text{mm}$ and other parameters

were as described in section 3.f. The dark blood reinversion slab was positioned to reinvert the LAD while aiming to avoid reinversion of the left ventricle and chest wall close to the LAD. A second 3D spiral acquisition with B2B-RMC was performed with the high resolution volume orientated to obtain in-plane images of the proximal left coronary artery system. Acquired image resolution was $0.9 \times 0.9 \times 1.8\text{mm}$, reconstructed to $0.9 \times 0.9 \times 0.9\text{mm}$. Both 3D spiral acquisitions were acquired with 2RR gating and 625ms dark blood inversion time. Images were corrected using the standard B2B-RMC techniques with the search and reference ROIs positioned around the LAD in both cases.

Four example slices from both the in-plane and cross-sectional 3D spiral coronary vessel wall acquisitions with B2B-RMC are shown in figure 8.5. The approximate locations of the in-plane and cross-sectional slices shown are outlined on a corresponding in-plane 2D MR coronary angiography image acquired in the planning stages. The cross-sectional images clearly show the bifurcation of the first diagonal branch from the larger LAD (green arrows). The in-plane images show two bifurcations: the bifurcation of the first diagonal from the LAD is shown in slice 2 (yellow arrow); and the bifurcation of the LM into the LAD and intermediate artery is shown in slice 4 (blue arrow). The LCX is not seen in these images due to its small size in this subject, but it also bifurcates from the LM close to the blue arrow. The origin of the LM is also depicted in slices 2 and 3. Both the cross-sectional and in-plane images are well corrected for respiratory motion using B2B-RMC. However, there is some ghosting from the chest wall in the in-plane images caused by the non-rigid motion of the chest wall with the coronary artery (see section 3.c.iv). This may be reduced in future studies by more careful positioning of the dark blood reinversion slab to avoid reinversion of the chest wall, as performed for the RCA studies in this thesis.

Despite the deeper location of the left coronary arteries, B2B-RMC 3D spiral imaging was successfully applied to the LAD with both in-plane and cross-sectional images successfully acquired and corrected for respiratory motion. While this is just a single example of B2B-RMC 3D spiral imaging for left coronary vessel wall imaging, it clearly demonstrates potential. Future studies using more carefully positioned dark blood reinversion slabs may improve the image quality and SNR will be improved using higher field strengths and dedicated cardiac receive coils.

Figure 8.5: Cross-sectional and in-plane images of the LAD vessel wall acquired in a healthy subject using B2B-RMC 3D spiral imaging



Four consecutive slices of a dark blood prepared B2B-RMC 3D spiral acquisition showing cross-sectional (left column) and in-plane (right column) images of the LAD. A 2D bSSFP MR coronary angiography image used in the planning stages is also shown with the location of the dark blood vessel wall images (magenta – cross-sectional, cyan – in-plane) super-imposed. The cross-sectional images were positioned at the bifurcation of the first diagonal from the LAD (green arrows). The in-plane images show the bifurcation of the first diagonal from the LAD (yellow arrow) and the intermediate artery from the LM (blue arrow).

8.c Simultaneous left and right coronary vessel wall imaging

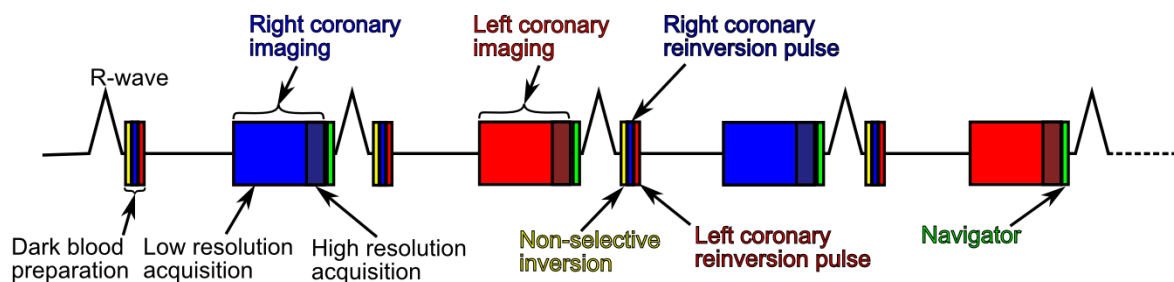
8.c.i Introduction

As demonstrated in chapter 6, the acquisition duration of MR coronary vessel wall imaging can be reduced by a factor of 2 using 1RR gating, but the loss of SNR and reduced robustness to changes in RR-interval result in less consistent image quality. As a result, the studies performed in chapters 6, 7 and 8 were performed with 2RR gating which allows more T1 recovery of the longitudinal magnetisation between repeats of both the dark blood double inversion preparation and the high resolution data acquisition. However, this results in every other RR-interval being lost as dead-time. Previous 2D TSE vessel wall imaging studies in the carotid artery (Parker et al., 2002, Mani et al., 2004) have used this dead-time to acquire additional slices. This was achieved by modifying the dark blood double inversion preparation to reinvert several slices in each RR-interval while only imaging one slice in each RR-interval. In this section it is proposed that a similar methodology can be applied to 3D coronary artery vessel wall imaging, allowing two 3D volumes to be imaged simultaneously. In combination with B2B-RMC this modification could permit 3D imaging of both the left and right coronary artery wall in a single acquisition of duration ~10minutes.

8.c.ii Methods

The B2B-RMC 3D spiral acquisition for coronary artery vessel wall imaging, as described in chapter 3, was modified as shown in figure 8.6. The dark blood preparation was modified to reinvert two user defined slabs in every RR-interval. Two volumes were imaged – the low resolution data for the first volume immediately followed by the corresponding high resolution data was acquired in odd RR-intervals and the equivalent data for the second volume was acquired in even RR-intervals. On the premise that the two imaging volumes do not overlap, the effective TR for the tissue imaged in both the first and second volumes is 2RR, thus theoretically maintaining the SNR advantages of 2RR gating.

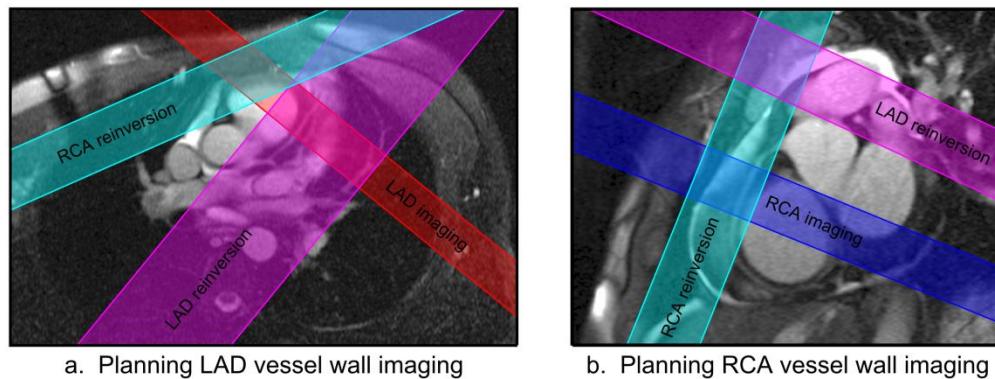
Figure 8.6: A schematic diagram of the modified B2B-RMC 3D spiral sequence used for simultaneous left and right coronary vessel wall imaging



Every cardiac cycle, a modified dark blood preparation is followed by a full low resolution 3D spiral fat volume, two spiral interleaves of a high resolution water selective 3D spiral acquisition and a standard navigator. The dark blood preparation consists of a non-selective inversion (yellow) followed by two slab selective reinversion pulses to selectively reinvert the right (blue) and left (red) coronary arteries respectively and finally a navigator restore pulse (not shown). The left and right coronary arteries are imaged in alternate RR-intervals, thus maintaining $TR=2RR$ for the coronary vessel wall.

Simultaneous cross-sectional left and right 3D coronary vessel wall imaging was performed in three healthy subjects. The initial planning stages of each acquisition were similar to those described in section 3.e for the RCA. The 2D in-plane bSSFP MR coronary angiography studies were then repeated for the LAD in order to identify a suitable, straight section of artery for vessel wall imaging. A cine acquisition was performed in the selected LAD imaging plane to verify that the rest period of the RCA was temporally coincident with that of the LAD. Finally the modified 3D spiral with B2B-RMC sequence for simultaneous imaging was performed. Orientating the imaging planes and dark blood reinversion pulses was rather more complicated for these acquisitions (see figure 8.7). The first reinversion slab of the modified dark blood preparation was orientated to reinvert the RCA whilst minimizing reinversion of the chest wall and the left ventricular blood pool. Similarly the second reinversion slab was positioned to reinvert the LAD. The low and high resolution acquisitions performed in even RR-intervals were positioned to image the RCA and the low and high resolution acquisitions performed in odd RR-intervals were positioned to image the LAD. Fine adjustment of the positioning of the RCA reinversion slab was performed to minimise reinversion of tissue within the LAD imaging volume and vice-versa. The acquired resolution of the high and low resolution volumes was $0.7 \times 0.7 \times 3.0\text{mm}$ and $4.8 \times 4.8 \times 3.0\text{mm}$ respectively for both the LAD and RCA imaging volumes. The dark blood inversion time was 400ms for both arteries, which is optimal for 1RR gating at 60BPM. As in previous sections, data acquired at extreme diaphragm displacements ($>\pm 10\text{mm}$ outside the normal tidal range) were rejected using the diaphragmatic navigator. The remaining respiratory motion was corrected independently for each artery using B2B-RMC as described in chapter 3.

Figure 8.7: Location of the imaging volumes and the dark blood reinversion slabs used for simultaneous left and right coronary artery imaging



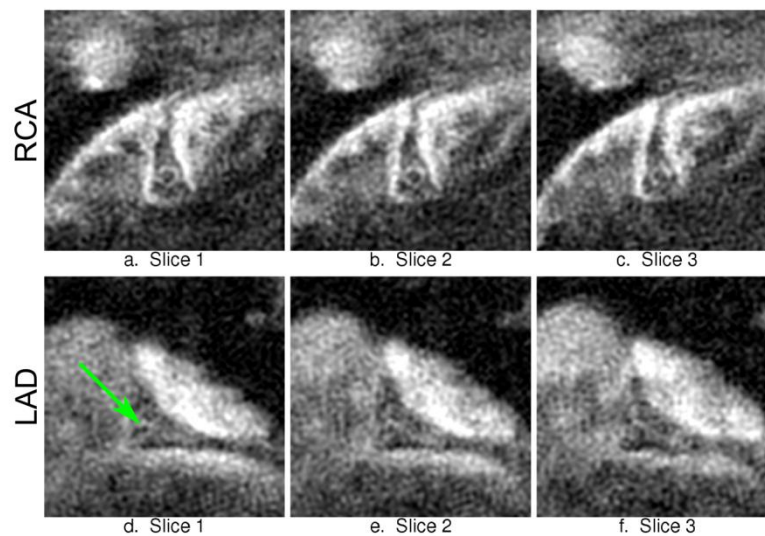
The imaging setup is more complex for simultaneous left and right coronary vessel wall imaging, as shown on these 2D MR coronary angiography images used in the planning stages. The position of the RCA imaging volume is shown in blue and the LAD imaging volume in red. The selective reinversion slab relating to the RCA is shown in cyan and the equivalent slab for the LAD is shown in magenta. Both reinversion slabs must be positioned to minimise the amount of blood in the aorta and tissue in the chest wall that is reinverted. In addition, the LAD reinversion slab must be positioned to minimise the volume of reinverted tissue in the RCA imaging slab and vice versa for the RCA imaging slab.

8.c.iii Results

Images of the RCA and LAD were obtained in all three subjects using the simultaneous imaging technique. Figure 8.8 shows vessel wall images acquired in the first healthy subject with an acquisition duration of 600 RR-intervals (respiratory efficiency 100%). The RCA vessel wall (a – c) is clearly visible and the vessel wall of the LAD is visible (green arrow) but the CNR is insufficient to confidently delineate the full LAD wall. The poorer quality images in the LAD in this example (d – f) are the result of reduced experience in imaging this vessel, its deeper location which reduces the SNR available and poorer fat suppression in these images, thought to be the result of a poorer shim in this region. Figure 8.9 shows vessel wall images acquired in 600 RR-intervals (respiratory efficiency 100%) in a second subject. The vessel walls of the RCA (a – c) and LAD (d – f) are clearly visible. There is, however, some chest wall ghosting artefact (see section 3.c.iv) present in both sets of images due to the increased difficulty in avoiding chest wall reinversion while positioning two reinversion slabs. This is particularly detrimental in the LAD images due to the already reduced SNR and smaller vessel size. Figure 8.10 shows example cross-sectional images of the RCA vessel wall (a – c) from a standard B2B-RMC 3D spiral acquisition with 2RR gating compared to the equivalent images acquired with the simultaneous technique (d – f). Example images of the LAD vessel wall from the same acquisition (g – i) are also shown. The RCA images acquired with the standard technique (a – c) were acquired in 650 RR-intervals (respiratory efficiency 92%) whereas the simultaneous acquisition (d – i) was acquired in 629 RR-intervals (respiratory efficiency 95%). The standard acquisition demonstrates good delineation of the anatomy, but there is some residual signal in the centre of the RCA. This subject had a particularly low heart rate of 44BPM, corresponding to an optimal dark blood inversion time of 500ms for 1RR gating and 715ms

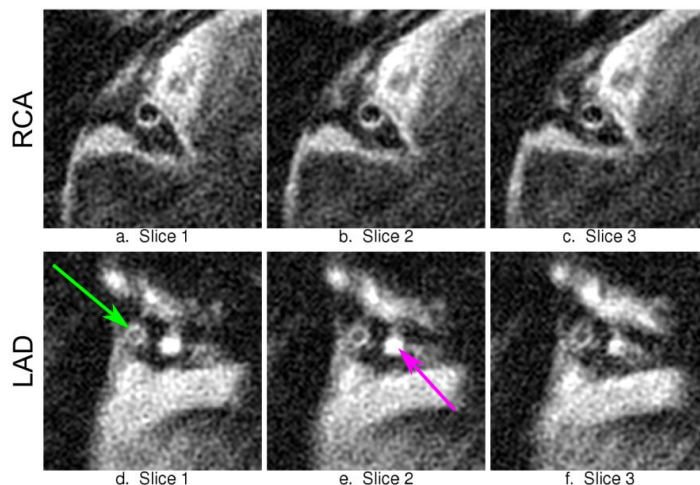
for 2RR gating. As a result, the inversion time of 625ms in the standard acquisition resulted in insufficient longitudinal relaxation for complete blood signal nulling with 2RR gating, hence the residual signal within the RCA lumen. The anatomy in the RCA images from the simultaneous acquisition closely resembles that from the standard acquisition, although blood suppression within the ventricles is less complete. The LAD vessel wall images from the simultaneous acquisition show a clearly delineated vessel wall with good blood suppression. The simultaneous acquisition was incorrectly performed with an inversion time of 625ms (400ms is optimal for the gating regime in the simultaneous acquisitions with a heart rate of 60BPM), but good blood suppression within the vessel lumen is present in the images. This is likely to be the result of the particularly low heart rate of this subject (optimal inversion time 500ms at 44BPM).

Figure 8.8: Example images from a simultaneous left and right 3D coronary vessel wall acquisition with B2B-RMC



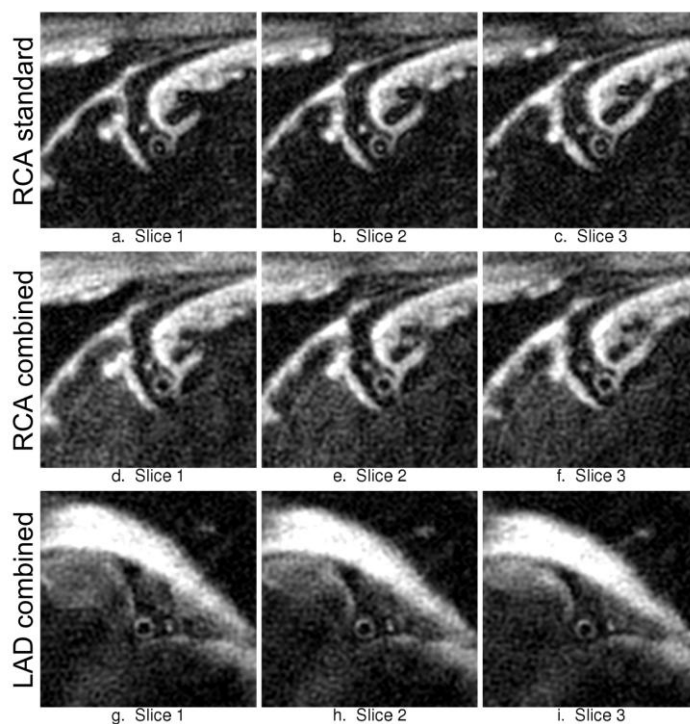
Images of the RCA (a – c) and LAD (d – f) vessel wall obtained in one healthy subject in one acquisition over 600 RR-intervals (100% respiratory efficiency). While the RCA vessel wall is clearly delineated, the LAD vessel wall is barely visible (green arrow) due to reduced SNR and poorer fat suppression at this deeper anatomical location.

Figure 8.9: Example images from a simultaneous left and right 3D coronary vessel wall acquisition with B2B-RMC



Images of the RCA (a – c) and LAD (d – f) vessel wall obtained in one healthy subject in one acquisition over 600 RR-intervals. The vessel wall of the large RCA is clearly visible and the LAD vessel wall is also visible (green arrow) as is the coronary vein (magenta arrow) with slow flow and, therefore unsuppressed blood signal. In both sets of images some ghosting is present from unsuppressed chest wall signal.

Figure 8.10: Example images from a simultaneous left and right 3D coronary vessel wall acquisition with B2B-RMC compared to a standard acquisition



Images of the RCA vessel wall acquired with the standard B2B-RMC 3D spiral acquisition (a – c) in 650 RR-intervals compared to the equivalent RCA vessel wall images acquired in 625 RR-intervals with the simultaneous acquisition (d – f) and the LAD vessel wall images acquired in the same acquisition (g – h). All images were acquired with a dark blood inversion time of 625ms, which resulted in some residual signal in the vessel lumen in the images from the standard acquisition, due to the particularly low heart rate of this subject (44BPM). The vessel wall is clearly delineated in both sets of images from the simultaneous acquisition.

8.c.iv Discussion

Using a novel simultaneous acquisition strategy, cross-sectional images of the LAD and RCA vessel wall have been acquired in ~10minutes, which is the same duration as an equivalent standard acquisition of one artery. Images were obtained of both arteries in three subjects with good vessel delineation in five of the six arteries imaged. By modifying the dark blood preparation to reinvert two user defined slabs in every RR-interval, the effective TR experienced by tissue in the vessel wall is 2 RR-intervals, hence maintaining the SNR increase of 2RR gating. B2B-RMC was used independently for each artery, correcting for vessel specific respiratory motion with near 100% respiratory efficiency.

There are several limitations to this initial demonstration. Time restrictions meant that only three healthy subjects were acquired and the LAD vessel wall images from one subject were poor (figure 8.9 (d – f)). Furthermore, imaging time is relatively long (~80 minutes for a study including a comparison of the combined acquisition and individual B2B-RMC 3D spiral acquisitions in both arteries) due to the complexity of planning the acquisitions. However, imaging is likely to be more reliable and more rapid with increased operator experience. A direct comparison between the simultaneous and standard acquisition was only performed successfully in one subject, again due to time constraints and inexperience. As the signal within the blood and surrounding tissue experiences an effective TR of 1RR interval, it remains to be seen how robust this sequence is to variations in RR-interval. Further direct comparisons between the standard and simultaneous technique should clarify this.

While studies have demonstrated simultaneous TSE imaging of multiple 2D slices within the carotid arteries using similar techniques, this is the first time that this modification of dark blood preparation to reinvert multiple slabs has been used to perform simultaneous imaging of multiple 3D volumes. It is also the first time that this technique has been used to simultaneously image multiple arteries. Furthermore, while reinversion of multiple slices has been used to image multiple slices of the coronary artery wall within the same cardiac cycle using TSE imaging and a long cardiac acquisition window (~200ms, (Song et al., 2002)), this is the first time that reinversion of multiple slabs has been applied to maintain SNR in coronary artery vessel wall imaging.

The simultaneous left and right coronary imaging technique described here performed well in this small pilot study. This technique is not limited to cross-sectional imaging and future studies should consider simultaneous in-plane coronary vessel wall imaging. Similarly, multiple non-overlapping cross-sectional imaging planes could be positioned along the same artery (as in the carotids (Parker et al., 2002)) to obtain non-contiguous volumes. This simultaneous acquisition strategy may also benefit from the use of 2D pencil beam selective reinversion rather than the slab selective reinversion applied here. This would ease the complexity of the setup by reducing the possibility of reinverting sections of the chest wall.

In conclusion, this preliminary study has demonstrated the feasibility of simultaneous 3D high resolution left and right coronary artery wall imaging in ~10minutes using a modified 3D spiral acquisition with B2B-RMC. In future studies this may permit more rapid assessment of disease or more extensive coverage of the coronary arteries within the same imaging duration.

8.d Preliminary experience using 3D spiral imaging with B2B-RMC for coronary vessel wall imaging in patients

8.d.i Introduction

Previous sections have demonstrated the performance and reproducibility of 3D spiral imaging with B2B-RMC for coronary artery vessel wall imaging and its ability to detect small changes in wall thickness with age. Nevertheless, for widespread clinical use, the performance of this technique must be established in a patient cohort with known coronary artery disease. The increased drift and irregularity of respiratory motion in patients when compared to healthy subjects is expected to accentuate the benefits of B2B-RMC over navigator gating. However, coronary artery imaging is more challenging in patients due to their: generally increased BMI; often limited ability to breath-hold during planning acquisitions; increased heart rates and frequent arrhythmias; and increased anxiety about such procedures. This section describes initial experience imaging the coronary vessel walls in five patients with confirmed coronary artery disease.

8.d.ii Methods

8.d.ii.1 Recruitment

Patients were recruited from the clinical cardiovascular MR scanning list at the Royal Brompton Hospital over a period of 9 months according to local ethics regulations and approval. The referral letters of patients scheduled for ischemic heart disease related MR imaging studies were examined in relation to the inclusion criteria (see below). Suitable patients were asked to return to the cardiovascular MR department for the research scan at a later date.

Inclusion criteria

Patients recruited for this study fulfilled the following inclusion criteria:

1. Confirmed coronary artery disease by x-ray contrast angiography in the proximal or mid RCA, LAD or LCX.
2. No previous coronary stent implantation or coronary artery bypass graft surgery.
3. Resting heart rate (in MR scanner) of <80BPM.
4. Absence of arrhythmias on the ECG trace which may affect triggering.
5. Previous successful CMR scan at the Royal Brompton Hospital (a condition of the ethics approval).
6. No contra-indications to MR imaging.

7. Able and willing to return to the Royal Brompton Hospital for a CMR scan, self-consent, lie still for ~1 hour and perform breath-holds for the planning images.

8.d.ii.2 MR imaging

Coronary vessel wall imaging was planned according to the protocol described in section 3. The imaging plane for vessel wall imaging was centred on the expected location of the coronary stenosis in the left or right coronary arteries according to the original referral letter for clinical CMR and aided by the MR coronary angiography studies performed in the planning stages. Cross-sectional or in-plane coronary vessel wall imaging using the 3D spiral acquisition with B2B-RMC was performed using the parameters described in section 3.f and 8.a.

8.d.iii Results

Fifteen patients conforming to the inclusion criteria were approached and five returned for coronary vessel wall imaging. The age, weight, sex, location of coronary disease and extent of the known coronary artery disease is given in table 8.1 for the five patients imaged.

Table 8.1: Patient characteristics and the corresponding B2B-RMC 3D spiral acquisition parameters

Patient	Age (yrs)	BMI (kg m ⁻²)	Disease	Heart rate (BPM)	Respiratory efficiency (%)	Diaphragm motion (mm)
1	60	31.7	No significant stenosis but mildly atheromatous and slow flow. β-blockers.	50	93.2	31
2	64	26.5	99% occlusion of mid RCA. Significant stenosis in LAD. β-blockers.	50	92.0	53
3	56	30.3	Occluded RCA. Severe lesion to mid LAD.	65	100	27
4*	59	26.1	Proximally occluded RCA. Diffuse disease in proximal LAD.	75	99.3	45
5	38	25.7	Complicated disease of proximal RCA. Occluded LAD.	60	99.7	51
Mean (SD)	55 (11)	28.6 (2.9)		60 (8)	96.2 (4.2)	41 (13)

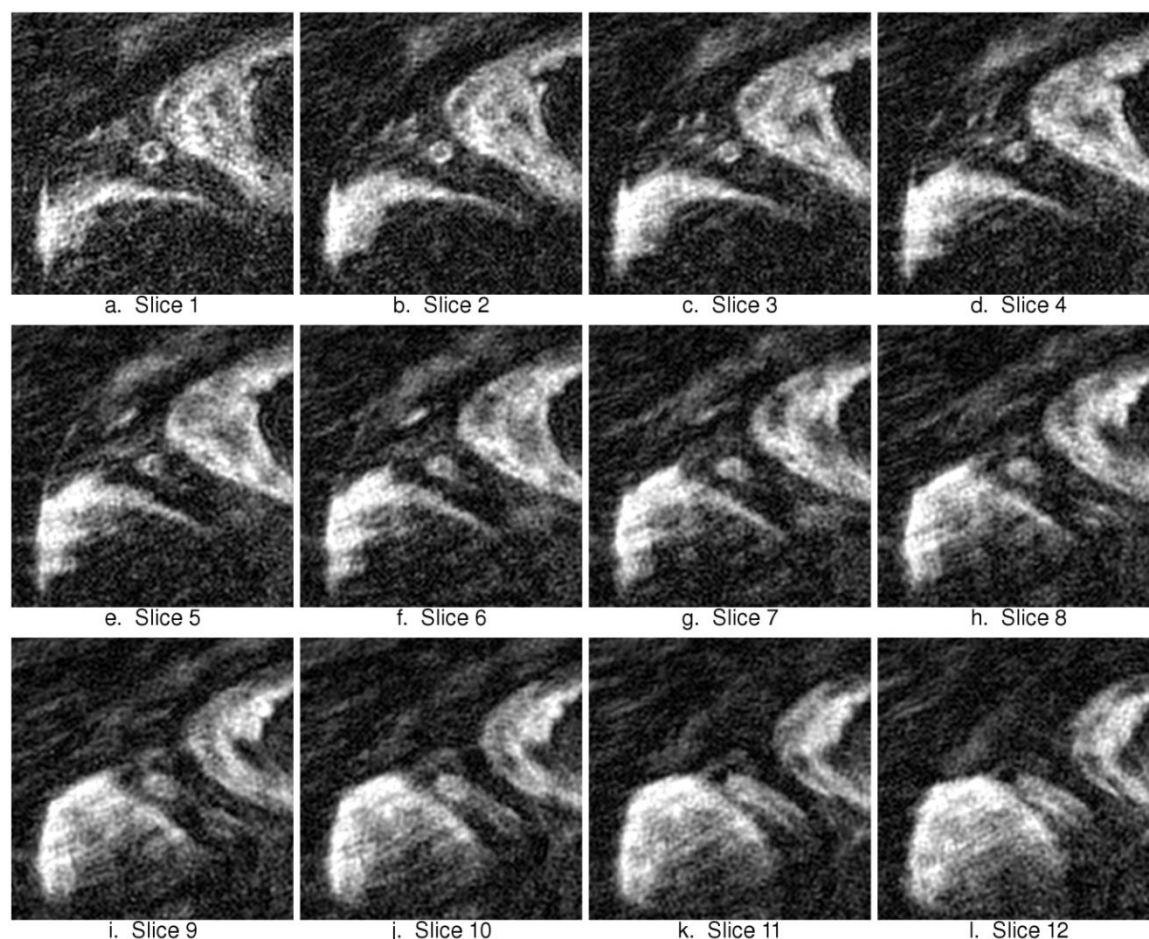
* The coronary vessel wall acquisition of patient 4 was a failure and not included in further analysis.

yrs – years.

BMI – body mass index

All five subjects were male, mean age 55 ± 10 years old (range 38 – 64 years old). The RCA was imaged in cross-section in 4 patients and the LAD in one (patient 4). The respiratory efficiency and range of diaphragm motion during the 3D spiral with B2B-RMC acquisitions is given in table 8.1. The coronary vessel wall is visible in the cross-sectional images acquired using the B2B-RMC 3D spiral imaging technique for all patients except patient 4 where low SNR due to the deeper location of the LAD resulted in poor image quality. In-plane images of the RCA were also acquired for patient 5. Figures 8.11 shows 12 slices from the 3D spiral acquisition with B2B-RMC positioned in a curved section of the RCA from patient 1. Slices 1 (a) and 2 (b) clearly show the vessel wall of the RCA before the artery curves into the through-plane (z) direction. This vessel curvature is such that the more proximal RCA is seen partially in-plane (slices 11 and 12). Severe ghosting of the chest wall is present in the area of interest around the vessel wall. The patient's referral letter described an x-ray contrast angiography study which found mild atheroma and slow flow within all coronary arteries. While there is no clear localised thickening of the vessel wall, the signal within the lumen is not completely suppressed, particularly within the curved section of the artery, which is likely to be the result of the known slow flow within this patient's coronary arteries.

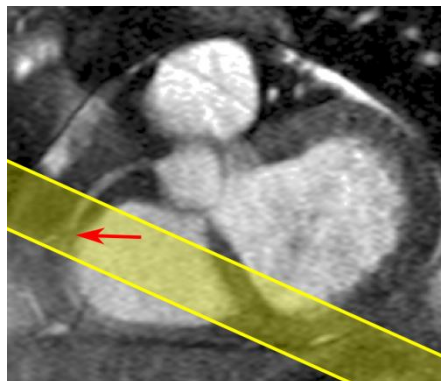
Figure 8.11: Cross-sectional B2B-RMC 3D spiral images acquired in patient 1



Twelve consecutive slices of the B2B-RMC 3D spiral acquisition in the RCA of patient 1. Images were acquired in a curved section of artery, resulting in the partially in-plane images shown in slices 10 – 12 (j – l).

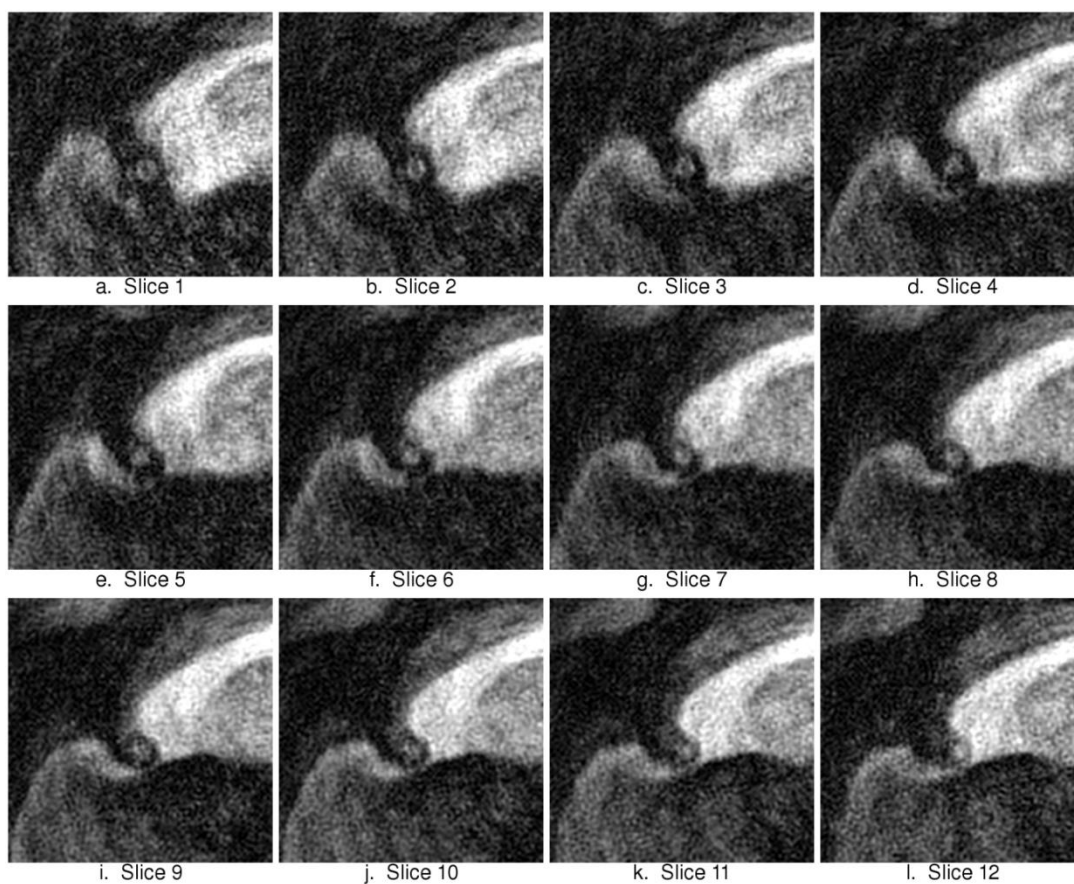
Figure 8.12 shows a 2D in-plane MR coronary angiography study of patient 2 acquired in the planning stages, showing the location of the B2B-RMC 3D spiral coronary vessel wall imaging acquisition. The location of the mid RCA occlusion is also highlighted. The equivalent coronary vessel wall images are shown in figure 8.13. While the SNR of these images is low, a vessel wall can be delineated in slices 1 – 3 (a – c). However, in subsequent slices there is no clear distinction between vessel wall and lumen. This is consistent with a near total occlusion of the RCA as reported from the x-ray contrast angiogram.

Figure 8.12: MR coronary angiography planning study for patient 2 showing the location of the coronary vessel wall imaging volume



A 2D MR coronary angiography image used in the planning of the B2B-RMC 3D spiral acquisition for patient 2. The approximate location of the 3D coronary vessel wall imaging volume is shown in yellow and the location of a stenosis is highlighted by the red arrow.

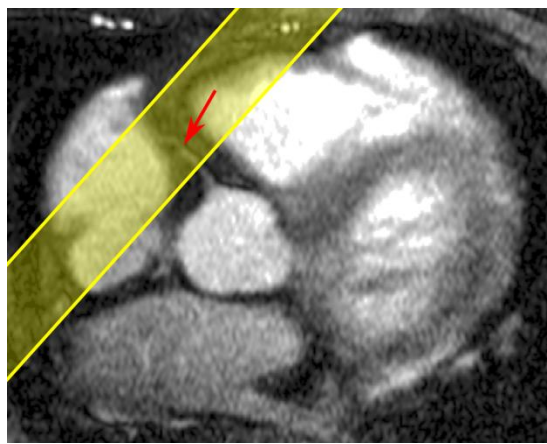
Figure 8.13: Cross-sectional B2B-RMC 3D spiral images acquired in patient 2



Twelve consecutive slices of the B2B-RMC 3D spiral acquisition in the RCA of patient 2. The vessel wall is delineated in slices 1 – 3 (a – c), while there is no clear distinction between the lumen and vessel wall in the later slices. This is consistent with the x-ray contrast angiography finding of a near total occlusion.

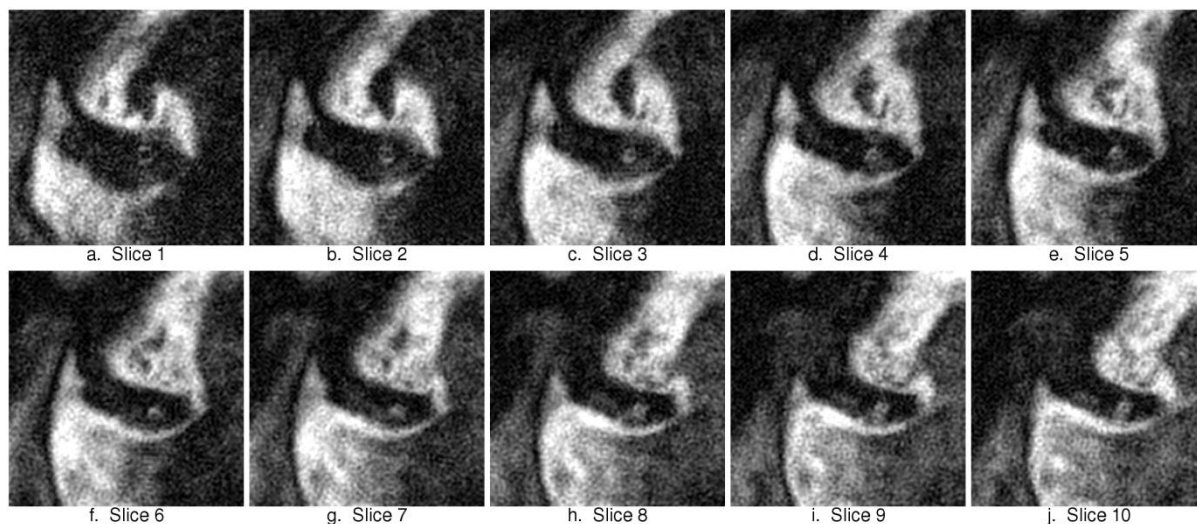
Figure 8.14 shows a 2D in-plane MR coronary angiography planning image from patient 3, with the location of the coronary vessel wall imaging volume superimposed (yellow box) and the location of a narrowing in the RCA highlighted (red arrow). The equivalent cross-sectional B2B-RMC 3D spiral vessel wall images in figure 8.15 show a thickening vessel wall and a reducing total vessel diameter in the first 4 slices (a – d), followed by an apparently almost completely blocked lumen in the remaining slices (e – j). This may be consistent with the occluded RCA described in this patient's referral letter.

Figure 8.14: MR coronary angiography planning study for patient 3 showing the location of the coronary vessel wall imaging volume



A 2D MR coronary angiography image used in the planning of the B2B-RMC 3D spiral acquisition for patient 2. The approximate location of the 3D coronary vessel wall imaging volume is shown in yellow and the location of an almost total occlusion of the RCA is highlighted by the red arrow.

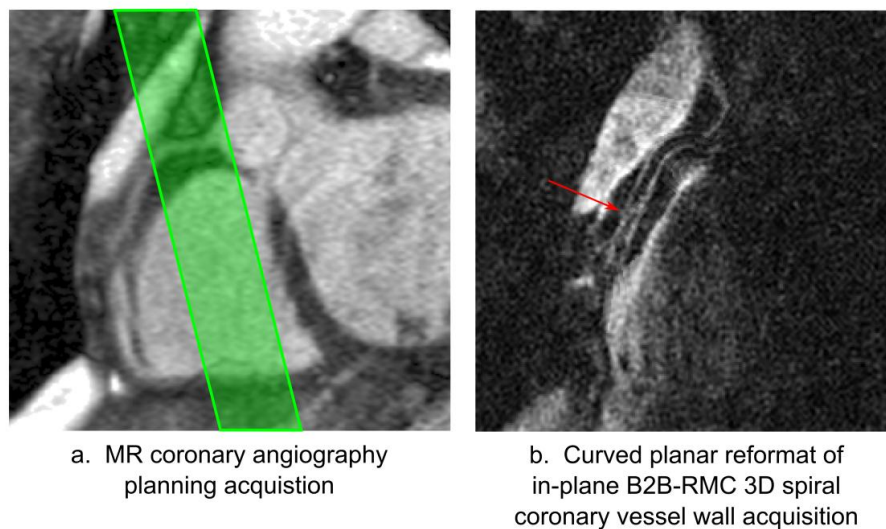
Figure 8.15: Cross-sectional B2B-RMC 3D spiral images acquired in patient 3



Ten consecutive slices of the B2B-RMC 3D spiral acquisition in the RCA of patient 3. The vessel wall appears thin and the lumen large in slice 1 (a). However, the vessel wall thickens in slices 2 (b) and 3 (c), the outer diameter of the vessel reduces and the boundary between the lumen and the vessel wall is not clearly visible from slice 4 (d) through slice 10 (j).

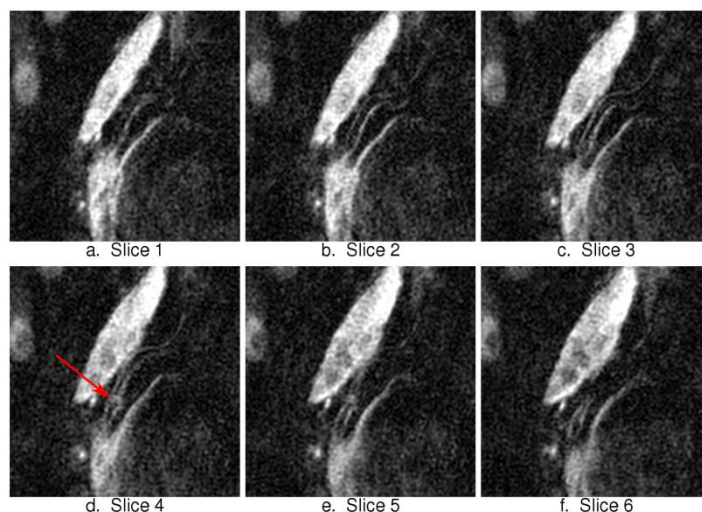
Figure 8.16 shows a 2D in-plane MR coronary angiography image (a) used in planning the vessel wall imaging for patient 5 and a curved planar reformat of the in-plane B2B-RMC 3D spiral coronary vessel wall acquisition in the same plane (b). The location of the cross-sectional coronary vessel wall imaging volume near the origin of the RCA is shown in (a) (green box). The corresponding individual slices of the in-plane vessel wall acquisition are shown in figure 8.17. A region with high signal within the vessel lumen is evident in the in-plane images (8.16 (b) and 8.17 – red arrow). This is thought to be the result of a branch vessel bifurcating in the through-plane direction. The corresponding cross-sectional coronary vessel wall images with B2B-RMC are shown in figure 8.18. There is some residual signal within the lumen in the first five slices (a – e) and the vessel wall appears thin. In contrast, the vessel wall appears to thicken while the lumen signal reduces in slices 6 – 10 (f – j), which is partially the result of the curvature of the RCA in this region. This incomplete suppression of the signal within the proximal lumen is unlikely to be disease as the in-plane images and MR coronary angiography images appear to show a patent lumen. This signal is more likely to be the result of a combination of noise and ghosting artefacts.

Figure 8.16: In-plane MR coronary angiography and coronary vessel wall images acquired in patient 5



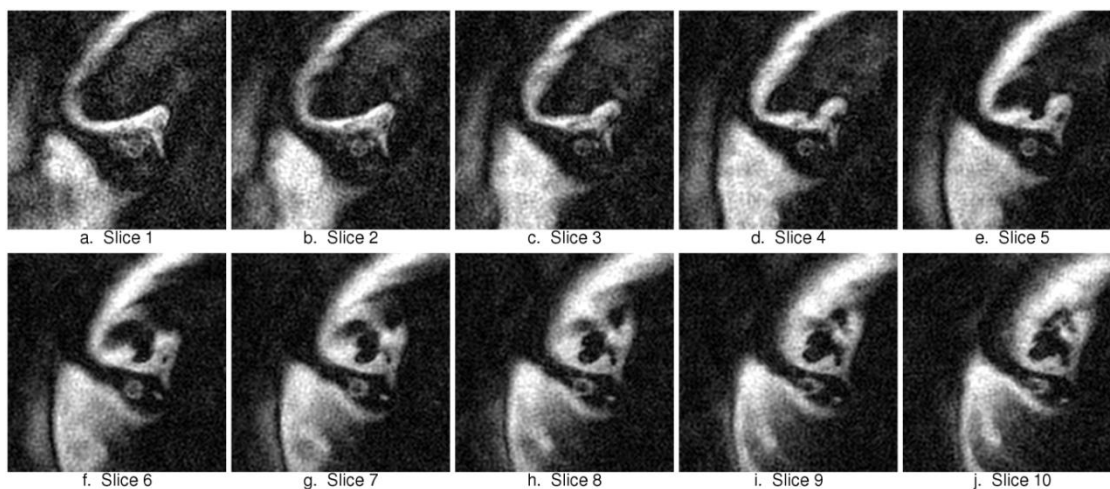
An in-plane MR coronary angiography 2D bSSFP planning image showing the location of the subsequent cross-sectional B2B-RMC 3D spiral coronary vessel wall acquisition (green box) (a) and an equivalent curved plane reformatted image from the in-plane B2B-RMC 3D spiral acquisition (b) from patient 5. There is some signal within the lumen of the coronary vessel wall image (red arrow) caused by a through-through plane bifurcation of this vessel.

Figure 8.17: In-plane B2B-RMC 3D spiral images acquired in patient 5



Six consecutive slices of the B2B-RMC 3D spiral acquisition performed in the RCA of patient 5. As in the equivalent curved planar reformatted image shown in figure 8.16 (b) some signal is present within the lumen (red arrow), which is thought to correspond to a branch vessel bifurcating in the through-plane direction.

Figure 8.18: Cross-sectional B2B-RMC 3D spiral images acquired in patient 5



Ten consecutive slices of the B2B-RMC 3D spiral acquisition in the RCA of patient 5. The vessel wall is visible in each of the slices. However, there is some residual signal from the lumen in slices 1 – 6 (a – f) and the vessel is not perpendicular to the imaging plane in slices 6 – 10 (f – j).

8.d.iv Discussion

For the first time, this work has demonstrated the application of B2B-RMC in a small group of patients. While no clear coronary disease was identified, the results obtained were not inconsistent with the descriptions of disease given in the patients' referral letters. In the case of patients 2 and 3 the appearance of the vessel wall (figures 8.13 and 8.15) is highly suggestive of the stenoses described in the referral letters. Future studies

should make use of the images from the x-ray contrast angiography studies or other coronary imaging procedures performed clinically in each of these patients but which were not available for this study without additional ethics approval.

The B2B-RMC 3D spiral acquisition for cross-sectional coronary vessel wall imaging was successful in four of the five patients imaged. The failed acquisition was performed in the only patient where the LAD was imaged and the failure was due to insufficient SNR. In future, improved dedicated cardiac receive coils and higher field strengths should improve this. In-plane imaging of the RCA vessel wall using the 3D spiral technique with B2B-RMC was also successfully performed in one of the patients.

B2B-RMC performed well in this patient cohort despite a much greater range of diaphragm motion than in normal subjects (mean range of displacements 41 ± 13 mm compared to 19 ± 6 mm in the healthy subjects studied in chapter 6), resulting in a high respiratory efficiency ($96.2 \pm 4.2\%$). However, in future studies, image quality may be improved by using a diaphragmatic navigator to eliminate more of the very large respiratory displacements with a corresponding small loss of respiratory efficiency. B2B-RMC was not compared to navigator gating or any other respiratory motion compensation techniques in this small study. The duration of an equivalent navigator gated 3D spiral coronary vessel wall acquisition with the large respiratory displacements and frequent respiratory drift demonstrated by patients is likely to be prohibitive. Furthermore, the performance of B2B-RMC 3D spiral imaging for coronary vessel wall imaging compared to navigator gated techniques was demonstrated in previous chapters (in a phantom in chapter 4 and *in-vivo* in chapter 6).

In conclusion, 3D spiral with B2B-RMC has been successfully used to image the RCA vessel wall in a small patient cohort with confirmed coronary artery disease. The imaging of patients is more challenging than healthy subjects but results were not inconsistent with the patterns of disease expected.

9. Discussion

There is a current lack of non-invasive techniques which can reliably and reproducibly obtain images of the coronary vessel wall. MR coronary vessel wall imaging has considerable potential, but is a challenging technique due to the motion of the arteries with the cardiac and respiratory cycles. While breath-holding has been used to suspend respiratory motion, this limits the acquisition duration, and therefore the imaging resolution. Alternatively, high resolution 3D studies have been performed with navigator gating, but this results in low respiratory efficiencies and considerable numbers of failed acquisitions. Despite this, very little published work has so far considered respiratory motion in MR coronary vessel wall imaging. The work described in this thesis is based on a highly efficient technique for respiratory motion correction (B2B-RMC), which is well suited to cross-sectional coronary vessel wall imaging with 3D spiral acquisitions (Keegan et al., 2007). B2B-RMC has a respiratory efficiency close to 100% which allows high resolution 3D imaging of the vessel wall in a fixed and clinically reasonable acquisition time. This thesis describes the further development of this technique and investigations into the performance, reproducibility and reliability performed in a variety of phantom and *in-vivo* applications.

9.a Summary of findings

Developments to the B2B-RMC and associated high resolution 3D spiral acquisition (described in chapter 3) focused on improving both the performance of the respiratory motion correction provided by B2B-RMC and the quality of the high resolution 3D spiral vessel wall images. The resolution of the low resolution fat images was increased without lengthening the low resolution acquisition window, in order to improve the performance of the motion correction. Navigator gating was introduced to the B2B-RMC acquisitions to eliminate data acquired at very extreme respiratory positions where the respiratory motion of the heart is likely to be non-rigid (yet maintaining >99% respiratory efficiency). A number of reconstruction, processing and analysis tools were also developed, including techniques for evaluation of the ROIs used in localizing B2B-RMC. Developments to the high resolution acquisition for coronary vessel wall imaging included increasing in-plane resolution to 0.7 x 0.7mm and increasing the FOV for reliable SNR at the higher resolution. Artefacts caused by the non-rigid relationship between the motion of the heart and chest wall were also considered, along with methods of minimising these artefacts via careful positioning of the dark blood reinversion slab and navigator.

The design, construction, testing and use of an MR compatible respiratory motion phantom with associated realistic coronary artery and coronary vessel wall test objects was described in chapter 4. This provided a means to test the performance of B2B-RMC in response to tightly controlled parameters. The performance of B2B-RMC in correcting for sinusoidal and physiological respiratory motion was evaluated, which highlighted the degradation of the motion correction with increased respiratory amplitude or decreased respiratory period. B2B-RMC was found to outperform navigator gating with a 5mm window for a range of physiological respiratory traces obtained from healthy subjects. Further studies considered the effect of resolution and SNR of the low resolution data on the final quality of the reconstructed high resolution images. While both decreasing SNR and resolution result in decreasing quality of the corrected images, the magnitude of the degradation was much less for the reductions in SNR considered here. As a result, future improvements in the resolution of the low resolution images may be obtained at the expense of SNR to improve respiratory motion correction performance. However, additional tests are required to confirm that the performance of B2B-RMC is similarly invariant to an equivalent loss of SNR in the *in-vivo* low resolution data.

In-vivo studies in chapters 5 and 6 compared 3D spiral imaging with B2B-RMC to navigator gated techniques. In both cases B2B-RMC was significantly and substantially more efficient than navigator gating ($99.5 \pm 0.5\%$ vs. $44.0 \pm 8.9\%$ in chapter 5 and $99.6 \pm 1.2\%$ vs. $39.0 \pm 7.5\%$ in chapter 6 for B2B-RMC vs. navigator gating respectively). In addition, the variability of the respiratory efficiency when using B2B-RMC is low, meaning that, in contrast to navigator gating, the acquisition duration can be accurately predicted.

In chapter 5, respiratory motion correction using B2B-RMC was, for the first time *in-vivo*, compared to navigator gating with a 5mm window using in-plane MR coronary angiography of the RCA. Despite the inherently different contrast between the 3D spiral images acquired with B2B-RMC and the T2-prep bSSFP images acquired with navigator gating, proximal and mid vessel sharpness and mid vessel diameter were not significantly different between techniques. As expected, the motion of the proximal and distal RCA could not be simultaneously corrected with B2B-RMC due to local differences in respiratory motion of the heart. However, a rudimentary combination of the datasets corrected for proximal and distal respiratory motion resulted in B2B-RMC images which were sharp along the vessel length.

Chapter 6 presents a major comparison of the performance and reproducibility of MR coronary vessel wall imaging techniques including 80 coronary vessel wall acquisitions. 3D spiral imaging with B2B-RMC was compared to both 2D TSE and 2D spiral imaging with navigator gating. B2B-RMC 3D spiral acquisitions were performed with both 1RR and 2RR gating allowing the first direct comparison between these two cardiac gating regimes in coronary vessel wall imaging. 2D TSE acquisitions resulted in the greatest number of high quality images, but were also most likely to fail, largely due to cardiac motion. The short acquisition window of the spiral techniques resulted in very few failed acquisitions. The reduced SNR and robustness to variations in RR-interval associated with 1RR gating resulted in unreliable image quality and should be avoided, despite the improved imaging efficiency. This chapter also presented the first comparison of

coronary vessel wall thickness obtained using different MR vessel wall imaging techniques, together with an assessment of their reproducibility. There was no significant difference in wall thickness between techniques and reproducibility was excellent for B2B-RMC 3D spiral imaging using 2RR gating and good for all the other techniques. While the B2B-RMC 3D spiral techniques were more time consuming, the imaging efficiency – assessed as acquisition duration per slice – was much improved over the 2D navigator gated techniques. This resulted in greater vessel coverage with multiple thin contiguous slices in a reasonable timescale. Overall, of the techniques assessed, 3D spiral imaging with B2B-RMC and 2RR gating is the preferred technique for imaging the coronary vessel wall.

The B2B-RMC 3D spiral technique was used to study ageing of the coronary vessel wall in chapter 7. While the cohort was too small for separate analysis of male and female data, when combined, the average coronary vessel wall thickness and the proportion of the total vessel area that is vessel wall (presented as the W/OW ratio) were shown to increase with subject age. This was the first time that non-invasive imaging (MR or otherwise) has demonstrated coronary vessel wall thickening with age in healthy subjects. Also, the total vessel area (lumen + vessel wall) increased significantly with vessel wall thickness while the lumen area remained constant, which is consistent with outward (Glagov) remodelling of the coronary vessel wall.

A number of other coronary vessel wall applications of B2B-RMC 3D spiral imaging were presented in chapter 8. The first B2B-RMC cross-sectional images of the LAD vessel wall were successfully acquired and in-plane images of both the RCA and LAD vessel wall were also obtained using this technique. Subsequently, a new method for increasing the overall imaging efficiency of coronary vessel wall imaging while maintaining SNR was demonstrated. This technique simultaneously targets the left and right coronary arteries in alternate cardiac cycles with independent correction for respiratory motion using B2B-RMC. Further work is required to assess the robustness of this technique to changes in RR-interval. Finally, the first results of MR coronary vessel wall imaging using 3D spiral acquisitions with B2B-RMC in a small group of patients with known coronary artery disease were presented.

9.b Limitations

There are a number of limitations to the B2B-RMC 3D spiral technique. In chapter 4 the respiratory motion phantom was used to demonstrate that B2B-RMC is able to produce high quality images from ungated data and the performance of B2B-RMC exceeds that of navigator gating with a 5mm window. However, quantitative assessment of these images showed that B2B-RMC images are not equivalent to images of stationary phantom. Not all motion can be fully corrected, including non-rigid motion (*in-vivo*) and motion during and between the high and low resolution acquisitions. The phantom work also demonstrated problems that can arise when tracking motion in the through-plane direction. While the low resolution images were reconstructed to 0.5 x 0.5mm pixels with a 260 x 260mm FOV in the in-plane direction, the reconstructed resolution was 1.5mm with a slab thickness of 24mm in the through-plane direction. Future

studies should consider increasing the reconstructed resolution in the through-plane direction. In addition, anatomy with only subtle differences in shape between slices is difficult to track through-plane at the low resolutions used in the fat selective images. The limited slab thickness and the similarity of the target anatomy in the through-plane direction for cross-sectional coronary imaging result in a lower precision and greater error in the corrections obtained in this direction. The magnitude of the through-plane component of respiratory motion is dependent on the amplitude of respiratory motion and on the orientation of the imaging plane, both of which are highly subject-specific. In a review of the B2B-RMC displacements obtained for the ten subjects imaged in the initial studies of chapter 6, the mean of the maximum amount of motion per subject in the through-plane direction that was detected using B2B-RMC was, 5.1 ± 2.8 mm (range 1.9 – 10.5 mm). In the phantom studies using the coronary vessel wall test object (chapter 4), 4.5 mm of through-plane motion (15 mm sinusoid) was fully corrected for, while 7.5 mm (25 mm sinusoid) was insufficiently tracked. As a result, future studies should consider gating acquisitions to limit the through-plane motion at the expense of a small loss in respiratory efficiency. While, as discussed above, 4.5 mm of through-plane motion has been successfully corrected in phantom studies undergoing sinusoidal motion, this would be a conservative estimate for the amount of through-plane motion that can be corrected *in-vivo*. As shown in chapter 4, sinusoidal motion is more difficult to correct than physiological respiratory motion and the through-plane distribution of epicardial fat *in-vivo* is less homogeneous than that simulated using the coronary artery test objects constructed in chapter 4. Consequently, the amount of through plane motion that may be corrected is likely to be larger and indeed, all 10 initial studies in chapter 6 produced image quality sufficient for vessel wall thickness measurement after B2B-RMC.

In chapter 4 B2B-RMC was directly compared with gating motion to a 5 mm window in otherwise identical imaging sequences, using the respiratory motion phantom following physiological respiratory traces. *In-vivo*, B2B-RMC 3D spiral imaging was compared to commonly used navigator gated techniques for MR coronary angiography (chapter 5) and coronary vessel wall imaging (chapters 6). Both study designs would have benefited from the inclusion of an additional acquisition (navigator gated 3D spiral imaging) for direct comparison of respiratory motion correction techniques using otherwise identical imaging sequences. However, this was not possible due to the long and unpredictable acquisition durations which result from navigator gating.

A further limitation is that the large majority of the work presented here was applied to cross-sectional imaging of the RCA vessel wall in healthy subjects. While the left coronary artery system is less mobile, it is located deeper within the body, which results in lower SNR and the volume of surrounding epicardial fat is lower, potentially making B2B-RMC more difficult. Despite this, the LAD was successfully imaged with B2B-RMC in several healthy subjects. In a small group of patients with confirmed coronary artery disease, the RCA vessel wall was successfully imaged. However, in the single patient where LAD vessel wall imaging was attempted, it was unsuccessful. The increased size of this patient, his high heart rate and the large range of respiratory motion (diaphragm range 45 mm) combined to result in poor SNR.

9.c Further work

9.c.i Processing

All reconstruction and processing has, as yet, been performed offline due to its complexity and the required computational time. The majority of the images presented here were corrected and reconstructed on multi-core workstations with large amounts of RAM (most recently a workstation with eight Intel Xeon 2.4GHz CPU cores and 12 GB of RAM running a 64-bit Linux operating system). Even with basic parallelization of the NSPCC, a full correlation of 300 low resolution volumes can take several hours. In future, however, iterative peak finding techniques, highly parallelized cross-correlation using graphical processing units or multi-resolution template matching may be used to reduce processing time or even perform on-the-fly B2B-RMC.

9.c.ii Improved left coronary artery and in-plane vessel wall imaging

As discussed in section 9.b, left coronary artery vessel wall imaging is more challenging due to the deeper location of these arteries, which results in reduced SNR. In future studies however, SNR will be improved by imaging at 3T and by using dedicated cardiac receive coils, which typically make use of 32 receive channels. While in-plane MR coronary angiography and in-plane coronary vessel wall imaging was successfully performed, the non-rigid respiratory motion of the heart means that future in-plane studies should consider using non-rigid motion correction. The larger spatial extent of the anatomy of interest in in-plane imaging also means that the image quality of the high resolution spiral acquisitions is likely to benefit from B_0 field map corrections and correction for errors in the actual spiral trajectories (Delattre et al., 2010).

9.c.iii Parallel imaging and compressed sensing

Recently, there has been much interest in parallel imaging (Larkman and Nunes, 2007) and compressed sensing techniques (Lustig et al., 2007) for increasing overall imaging efficiency. The loss of SNR associated with parallel imaging renders it unsuitable for use in high resolution coronary vessel wall imaging, although it may enable valuable increases in the resolution of the low resolution data. However, the sparseness of the high resolution coronary vessel wall images presented in this work mean that compressed sensing may be a useful future strategy for reducing acquisition durations or for further increases in image resolution.

9.c.iv Clinical studies

As yet, no published *in-vivo* study has compared MR coronary vessel wall imaging to intravascular imaging of coronary artery disease. A comparison of vessel wall thickening in patients with coronary artery disease using B2B-RMC 3D spiral imaging and IVUS and/or histology would, therefore seem pertinent. Subsequently, longitudinal studies of coronary artery disease progression in response to therapy, changes in lifestyle or ageing will be possible with this technique.

The implications of this work extend beyond atherosclerotic disease; the effects of other diseases on the coronary vessel wall, such as Kawasaki disease (Greil et al., 2007b), may also be evaluated using the B2B-RMC 3D spiral technique. Furthermore, B2B-RMC is not limited to 3D spiral imaging; sequence modifications could replace the high resolution spiral readouts with bSSFP segments and T2-prep, for use in MR coronary angiography. Basic modifications to the existing sequence would permit T1 weighted imaging of the coronary vessel wall for use with or without contrast agent in differentiating plaque types (see section 1.e.ii.6). Neither is B2B-RMC limited to coronary artery imaging; these same modifications to the dark blood preparation with the addition of non-rigid motion correction capabilities could be used for 3D late gadolinium enhanced myocardial imaging. All of these alternative applications would benefit from the reliable, highly efficient respiratory motion compensation provided by B2B-RMC.

9.d Conclusion

In conclusion, 3D spiral imaging with B2B-RMC is an effective, reliable and reproducible technique for MR coronary vessel wall imaging when used with 2RR gating. B2B-RMC can effectively correct respiratory motion with respiratory efficiency close to 100% and is well suited to cross-sectional coronary vessel wall imaging. Small changes in normal vessel walls have been demonstrated and imaging was demonstrated in a small patient cohort. As a result of these developments 3D spiral imaging with B2B-RMC may, in future, be used in assessing the progression or regression of coronary atherosclerotic plaque with time or in response to therapy.

References

1985. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. *N Engl J Med*, 312, 932-6.
2000. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*, 894, i-xii, 1-253.
2003. *Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction*, London, National Institute for Clinical Excellence.
2004. Hypertension: management of hypertension in adults in primary care. *Evidence-based Clinical Practice Guidelines*. National Institute for Clinical Excellence (NICE).
- ABD-ELMONIEM, K. Z., WEISS, R. G. & STUBER, M. 2010. Phase-sensitive black-blood coronary vessel wall imaging. *Magn Reson Med*, 63, 1021-30.
- ACHENBACH, S., ROPERS, D., HOFFMANN, U., MACNEILL, B., BAUM, U., POHLE, K., BRADY, T. J., POMERANTSEV, E., LUDWIG, J., FLACHSKAMPF, F. A., WICKY, S., JANG, I. K. & DANIEL, W. G. 2004. Assessment of coronary remodeling in stenotic and nonstenotic coronary atherosclerotic lesions by multidetector spiral computed tomography. *J Am Coll Cardiol*, 43, 842-7.
- AGATSTON, A. S., JANOWITZ, W. R., HILDNER, F. J., ZUSMER, N. R., VIAMONTE, M., JR. & DETRANO, R. 1990. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*, 15, 827-32.
- AIME, S., CABELLA, C., COLOMBATTO, S., GENINATTI CRICH, S., GIANOLIO, E. & MAGGIONI, F. 2002. Insights into the use of paramagnetic Gd(III) complexes in MR-molecular imaging investigations. *J Magn Reson Imaging*, 16, 394-406.
- AL-KWIFI, O., STAINSBY, J., FOLTZ, W. D., SUSSMAN, M. S., HUANG, Y. & WRIGHT, G. A. 2006. Characterizing coronary motion and its effect on MR coronary angiography--initial experience. *J Magn Reson Imaging*, 24, 842--850.
- ALETRAS, A. H., DING, S., BALABAN, R. S. & WEN, H. 1999. DENSE: displacement encoding with stimulated echoes in cardiac functional MRI. *J Magn Reson*, 137, 247--252.
- ALFIDI, R. J., HAAGA, J. R., EL-YOUSEF, S. J., BRYAN, P. J., FLETCHER, B. D., LIPUMA, J. P., MORRISON, S. C., KAUFMAN, B., RICHEY, J. B., HINSHAW, W. S., KRAMER, D. M., YEUNG, H. N., COHEN, A. M., BUTLER, H. E., AMENT, A. E. & LIEBERMAN, J. M. 1982. Preliminary experimental results in humans and animals with a superconducting, whole-body, nuclear magnetic resonance scanner. *Radiology*, 143, 175--181.
- ARAD, Y., SPADARO, L. A., GOODMAN, K., NEWSTEIN, D. & GUERCI, A. D. 2000. Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol*, 36, 1253-60.
- ARAI, A. E., GAITHER, C. C., EPSTEIN, F. H., BALABAN, R. S. & WOLFF, S. D. 1999. Myocardial velocity gradient imaging by phase contrast MRI with application to regional function in myocardial ischemia. *Magn Reson Med*, 42, 98--109.
- ARMOUR, J. A., PACE, J. B. & RANDALL, W. C. 1970. Interrelationship of architecture and function of the right ventricle. *Am J Physiol*, 218, 174--179.
- ASCHOFF, A. J., SULMAN, A., MARTINEZ, M., DUERK, J. L., RESNICK, M. I., MACLENNAN, G. T. & LEWIN, J. S. 2001. Perfusion-modulated MR imaging-guided radiofrequency ablation of the kidney in a porcine model. *AJR Am J Roentgenol*, 177, 151--158.
- ASTRUP, A. S., TARNOW, L., ROSSING, P., PIETRASZEK, L., RIIS HANSEN, P. & PARVING, H. H. 2005. Improved prognosis in type 1 diabetic patients with nephropathy: a prospective follow-up study. *Kidney Int*, 68, 1250-7.

- ATKINSON, D. J. & EDELMAN, R. R. 1991. Cineangiography of the heart in a single breath hold with a segmented turboFLASH sequence. *Radiology*, 178, 357-60.
- AUSTEN, W. G., EDWARDS, J. E., FRYE, R. L., GENSINI, G. G., GOTT, V. L., GRIFFITH, L. S., MCGOON, D. C., MURPHY, M. L. & ROE, B. B. 1975. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation*, 51, 5-40.
- AXEL, L. & DOUGHERTY, L. 1989a. Heart wall motion: improved method of spatial modulation of magnetization for MR imaging. *Radiology*, 172, 349--350.
- AXEL, L. & DOUGHERTY, L. 1989b. MR imaging of motion with spatial modulation of magnetization. *Radiology*, 171, 841--845.
- AXEL, L., GONÇALVES, R. C. & BLOOMGARDEN, D. 1992. Regional heart wall motion: two-dimensional analysis and functional imaging with MR imaging. *Radiology*, 183, 745--750.
- AZHARI, H., WEISS, J. L., ROGERS, W. J., SIU, C. O., ZERHOUNI, E. A. & SHAPIRO, E. P. 1993. Noninvasive quantification of principal strains in normal canine hearts using tagged MRI images in 3-D. *Am J Physiol*, 264, H205--H216.
- BAILES, D. R., GILDERDALE, D. J., BYDDER, G. M., COLLINS, A. G. & FIRMIN, D. N. 1985. Respiratory ordered phase encoding (ROPE): a method for reducing respiratory motion artefacts in MR imaging. *J Comput Assist Tomogr*, 9, 835-838.
- BANSMANN, P. M., PRIEST, A. N., MUELLERLEILE, K., STORK, A., LUND, G. K., KAUL, M. G. & ADAM, G. 2007. MRI of the Coronary Vessel Wall at 3 T: Comparison of Radial and Cartesian k-Space Sampling. *Am. J. Roentgenol*, 188, 70-74.
- BAROLDI, G., BIGI, R. & CORTIGIANI, L. 2004. Ultrasound imaging versus morphopathology in cardiovascular diseases. Coronary atherosclerotic plaque. *Cardiovasc Ultrasound*, 2, 29.
- BARRETT, K. E. & GANONG, W. F. R. O. M. P. 2010. Ganong's review of medical physiology. 23rd ed. / Kim Barrett ... [et al.]. ed. New York: McGraw-Hill Medical.
- BASTARRIKA, G., LEE, Y. S., HUDA, W., RUZSICS, B., COSTELLO, P. & SCHOEPPF, U. J. 2009. CT of coronary artery disease. *Radiology*, 253, 317-38.
- BATCHELOR, P. G., ATKINSON, D., IRARRAZAVAL, P., HILL, D. L., HAJNAL, J. & LARKMAN, D. 2005. Matrix description of general motion correction applied to multishot images. *Magn Reson Med*, 54, 1273-80.
- BATSI, J. A. & LOPEZ-JIMENEZ, F. 2010. Cardiovascular risk assessment--from individual risk prediction to estimation of global risk and change in risk in the population. *BMC Med*, 8, 29.
- BECKER, C. R., KNEZ, A., OHNESORGE, B., SCHOEPPF, U. J. & REISER, M. F. 2000. Imaging of noncalcified coronary plaques using helical CT with retrospective ECG gating. *AJR Am J Roentgenol*, 175, 423-4.
- BERNE, R. M. & LEVY, M. N. 1988. *Physiology*. St. Louis, Mosby.
- BI, X., DESHPANDE, V., CARR, J. & LI, D. 2006. Coronary artery magnetic resonance angiography (MRA): a comparison between the whole-heart and volume-targeted methods using a T2-prepared SSFP sequence. *J Cardiovasc Magn Reson*, 8, 703-7.
- BIDAUT, L. M. & VALLÉE, J. P. 2001. Automated registration of dynamic MR images for the quantification of myocardial perfusion. *J Magn Reson Imaging*, 13, 648-655.
- BILD, D. E., BLUEMKE, D. A., BURKE, G. L., DETRANO, R., DIEZ ROUX, A. V., FOLSOM, A. R., GREENLAND, P., JACOB, D. R., JR., KRONMAL, R., LIU, K., NELSON, J. C., O'LEARY, D., SAAD, M. F., SHEA, S., SZKLO, M. & TRACY, R. P. 2002. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol*, 156, 871-81.
- BLAND, J. M. & ALTMAN, D. G. 1986. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*, 1, 307--310.
- BLEEKER-ROVERS, C. P., DE SEVAUX, R. G., VAN HAMERSVELT, H. W., CORSTENS, F. H. & OYEN, W. J. 2003. Diagnosis of renal and hepatic cyst infections by 18-F-fluorodeoxyglucose positron emission tomography in autosomal dominant polycystic kidney disease. *Am J Kidney Dis*, 41, E18-21.
- BORNERT, P., ALDEFELD, B. & NEHRKE, K. 2001a. Improved 3D spiral imaging for coronary MR angiography. *Magn Reson Med*, 45, 172-5.
- BORNERT, P., STUBER, M., BOTNAR, R. M., KISSINGER, K. V., KOKEN, P., SPUNTRUP, E. & MANNING, W. J. 2001b. Direct comparison of 3D spiral vs. Cartesian gradient-echo coronary magnetic resonance angiography. *Magn Reson Med*, 46, 789-94.

- BOTNAR, R. M., BUECKER, A., KIM, W. Y., VIOHL, I., GÜNTHER, R. W. & SPUNTRUP, E. 2003a. Initial experiences with in vivo intravascular coronary vessel wall imaging. *J Magn Reson Imaging*, 17, 615--619.
- BOTNAR, R. M., BUECKER, A., WIETHOFF, A. J., PARSONS, E. C., JR., KATOH, M., KATSIMAGLIS, G., WEISSKOFF, R. M., LAUFFER, R. B., GRAHAM, P. B., GUNTHER, R. W., MANNING, W. J. & SPUNTRUP, E. 2004a. In vivo magnetic resonance imaging of coronary thrombosis using a fibrin-binding molecular magnetic resonance contrast agent. *Circulation*, 110, 1463-6.
- BOTNAR, R. M., KIM, W. Y., BÖRNERT, P., STUBER, M., SPUNTRUP, E. & MANNING, W. J. 2001. 3D coronary vessel wall imaging utilizing a local inversion technique with spiral image acquisition. *Magn Reson Med*, 46, 848--854.
- BOTNAR, R. M., PEREZ, A. S., WITTE, S., WIETHOFF, A. J., LAREDO, J., HAMILTON, J., QUIST, W., PARSONS, E. C., JR., VAIDYA, A., KOLODZIEJ, A., BARRETT, J. A., GRAHAM, P. B., WEISSKOFF, R. M., MANNING, W. J. & JOHNSTONE, M. T. 2004b. In vivo molecular imaging of acute and subacute thrombosis using a fibrin-binding magnetic resonance imaging contrast agent. *Circulation*, 109, 2023-9.
- BOTNAR, R. M., STUBER, M., DANIAS, P. G., KISSINGER, K. V. & MANNING, W. J. 1999. Improved coronary artery definition with T2-weighted, free-breathing, three-dimensional coronary MRA. *Circulation*, 99, 3139--3148.
- BOTNAR, R. M., STUBER, M., KISSINGER, K. V., KIM, W. Y., SPUNTRUP, E. & MANNING, W. J. 2000a. Noninvasive coronary vessel wall and plaque imaging with magnetic resonance imaging. *Circulation*, 102, 2582--2587.
- BOTNAR, R. M., STUBER, M., KISSINGER, K. V. & MANNING, W. J. 2000b. Free-breathing 3D coronary MRA: the impact of "isotropic" image resolution. *J Magn Reson Imaging*, 11, 389--393.
- BOTNAR, R. M., STUBER, M., LAMERICH, R., SMINK, J., FISCHER, S. E., HARVEY, P. & MANNING, W. J. 2003b. Initial experiences with in vivo right coronary artery human MR vessel wall imaging at 3 tesla. *J Cardiovasc Magn Reson*, 5, 589--594.
- BOUMA, B. E., YUN, S. H., VAKOC, B. J., SUTER, M. J. & TEARNEY, G. J. 2009. Fourier-domain optical coherence tomography: recent advances toward clinical utility. *Curr Opin Biotechnol*, 20, 111-8.
- BOYD, D. P. & LIPTON, M. J. 1983. Cardiac computed tomography. *Proceedings of the IEEE*, 71, 298-307.
- BRAU, A. C. S. & BRITTAI, J. H. 2006. Generalized self-navigated motion detection technique: Preliminary investigation in abdominal imaging. *Magn Reson Med*, 55, 263-270.
- BREZINSKI, M. E., TEARNEY, G. J., BOUMA, B. E., IZATT, J. A., HEE, M. R., SWANSON, E. A., SOUTHERN, J. F. & FUJIMOTO, J. G. 1996. Optical coherence tomography for optical biopsy. Properties and demonstration of vascular pathology. *Circulation*, 93, 1206-13.
- BRILEY-SAEBO, K. C., MULDER, W. J., MANI, V., HYAFIL, F., AMIRBEKIAN, V., AGUINALDO, J. G., FISHER, E. A. & FAYAD, Z. A. 2007. Magnetic resonance imaging of vulnerable atherosclerotic plaques: current imaging strategies and molecular imaging probes. *J Magn Reson Imaging*, 26, 460-79.
- BRITTAI, J. H., HU, B. S., WRIGHT, G. A., MEYER, C. H., MACOVSKI, A. & NISHIMURA, D. G. 1995. Coronary angiography with magnetization-prepared T2 contrast. *Magn Reson Med*, 33, 689--696.
- BRUCE, R. A., BLACKMON, J. R., JONES, J. W. & STRAIT, G. 1963. Exercising Testing in Adult Normal Subjects and Cardiac Patients. *Pediatrics*, 32, SUPPL 742-56.
- BUDOFF, M. J., GEORGIOU, D., BRODY, A., AGATSTON, A. S., KENNEDY, J., WOLFKIEL, C., STANFORD, W., SHIELDS, P., LEWIS, R. J., JANOWITZ, W. R., RICH, S. & BRUNDAGE, B. H. 1996. Ultrafast computed tomography as a diagnostic modality in the detection of coronary artery disease: a multicenter study. *Circulation*, 93, 898-904.
- BUECKER, A., SPUNTRUP, E., RUEBBEN, A. & GUNTHER, R. W. 2002. Artifact-Free In-Stent Lumen Visualization by Standard Magnetic Resonance Angiography Using a New Metallic Magnetic Resonance Imaging Stent. *Circulation*, 105, 1772-1775.
- BUEHRER, M., CURCIC, J., BOESIGER, P. & KOZERKE, S. 2008. Prospective self-gating for simultaneous compensation of cardiac and respiratory motion. *Magn Reson Med*, 60, 683-90.
- BUSCHMAN, H. P., MARPLE, E. T., WACH, M. L., BENNETT, B., SCHUT, T. C., BRUINING, H. A., BRUSCHKE, A. V., VAN DER LAARSE, A. & PUPPELS, G. J. 2000. In vivo determination of the molecular composition of artery wall by intravascular Raman spectroscopy. *Anal Chem*, 72, 3771-5.
- CADEMARTIRI, F., MAFFEI, E., PALUMBO, A., CARRABBA, N., ARDISSINO, D., MOLLET, N., KRESTIN, G. & DE FEYTER, P. 2008. Multi-slice CT coronary angiography for the detection of in-stent restenosis. *Current Cardiovascular Imaging Reports*, 1, 119-124.

- CALLISTER, T. Q., COOIL, B., RAYA, S. P., LIPPOLIS, N. J., RUSSO, D. J. & RAGGI, P. 1998. Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method. *Radiology*, 208, 807-14.
- CARO, C. G. 2009. Discovery of the role of wall shear in atherosclerosis. *Arterioscler Thromb Vasc Biol*, 29, 158-61.
- CARO, C. G., FITZ-GERALD, J. M. & SCHROTER, R. C. 1969. Arterial wall shear and distribution of early atheroma in man. *Nature*, 223, 1159-60.
- CHANDLER, A. G., PINDER, R. J., NETSCH, T., SCHNABEL, J. A., HAWKES, D. J., HILL, D. L. G. & RAZAVI, R. 2008. Correction of misaligned slices in multi-slice cardiovascular magnetic resonance using slice-to-volume registration. *J Cardiovasc Magn Reson*, 10, 13.
- CHANG, S., CHAM, M. D., HU, S. & WANG, Y. 2008. 3-T Navigator Parallel-Imaging Coronary MR Angiography: Targeted-Volume Versus Whole-Heart Acquisition. *Am. J. Roentgenol*, 191, 38-42.
- CHAU, A. H., MOTZ, J. T., GARDECKI, J. A., WAXMAN, S., BOUMA, B. E. & TEARNEY, G. J. 2008. Fingerprint and high-wavenumber Raman spectroscopy in a human-swine coronary xenograft in vivo. *J Biomed Opt*, 13, 040501.
- CHEN, W., VUCIC, E., LEUPOLD, E., MULDER, W. J., CORMODE, D. P., BRILEY-SAEBO, K. C., BARAZZA, A., FISHER, E. A., DATHE, M. & FAYAD, Z. A. 2008. Incorporation of an apoE-derived lipopeptide in high-density lipoprotein MRI contrast agents for enhanced imaging of macrophages in atherosclerosis. *Contrast Media Mol Imaging*, 3, 233-42.
- CHOMA, M., SARUNIC, M., YANG, C. & IZATT, J. 2003. Sensitivity advantage of swept source and Fourier domain optical coherence tomography. *Opt Express*, 11, 2183-9.
- CHOUDHURY, R. P. & FISHER, E. A. 2009. Molecular imaging in atherosclerosis, thrombosis, and vascular inflammation. *Arterioscler Thromb Vasc Biol*, 29, 983-91.
- CONSTANTINIDES, C. D., ATALAR, E. & MCVEIGH, E. R. 1997. Signal-to-noise measurements in magnitude images from NMR phased arrays. *Magn Reson Med*, 38, 852-7.
- CORRADI, D., MAESTRI, R., CALLEGARI, S., PASTORI, P., GOLDONI, M., LUONG, T. V. & BORDI, C. 2004. The ventricular epicardial fat is related to the myocardial mass in normal, ischemic and hypertrophic hearts. *Cardiovasc Pathol*, 13, 313-6.
- CROWE, M. E., LARSON, A. C., ZHANG, Q., CARR, J., WHITE, R. D., LI, D. & SIMONETTI, O. P. 2004. Automated rectilinear self-gated cardiac cine imaging. *Magn Reson Med*, 52, 782-788.
- CUNNINGHAM, C. H., ARAI, T., YANG, P. C., MCCONNELL, M. V., PAULY, J. M. & CONOLLY, S. M. 2005. Positive contrast magnetic resonance imaging of cells labeled with magnetic nanoparticles. *Magn Reson Med*, 53, 999-1005.
- DALBY, M., BOUZAMONDO, A., LECHAT, P. & MONTALESCOT, G. 2003. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. *Circulation*, 108, 1809-14.
- DALBY, M., KHARBANDA, R., GHIMIRE, G., SPIRO, J., MOORE, P., ROUGHTON, M., LANE, R., AL-OBAIDI, M., TEOH, M., HUTCHISON, E., WHITBREAD, M., FOUNTAIN, D., GROCOTT-MASON, R., MITCHELL, A., MASON, M. & ILSLEY, C. 2009. Achieving routine sub 30 minute door-to-balloon times in a high volume 24/7 primary angioplasty center with autonomous ambulance diagnosis and immediate catheter laboratory access. *Am Heart J*, 158, 829-35.
- DANIAS, P. G., MCCONNELL, M. V., KHASGIWALA, V. C., CHUANG, M. L., EDELMAN, R. R. & MANNING, W. J. 1997. Prospective navigator correction of image position for coronary MR angiography. *Radiology*, 203, 733-736.
- DANIAS, P. G., STUBER, M., BOTNAR, R. M., KISSINGER, K. V., CHUANG, M. L. & MANNING, W. J. 1998. Navigator assessment of breath-hold duration: impact of supplemental oxygen and hyperventilation. *AJR Am J Roentgenol*, 171, 395-397.
- DANIAS, P. G., STUBER, M., BOTNAR, R. M., KISSINGER, K. V., EDELMAN, R. R. & MANNING, W. J. 1999. Relationship between motion of coronary arteries and diaphragm during free breathing: lessons from real-time MR imaging. *AJR Am J Roentgenol*, 172, 1061-1065.
- DAVIES, J. R., RUDD, J. H., WEISSBERG, P. L. & NARULA, J. 2006. Radionuclide imaging for the detection of inflammation in vulnerable plaques. *J Am Coll Cardiol*, 47, C57-68.
- DAWBER, T. R., MEADORS, G. F. & MOORE, F. E., JR. 1951. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health Nations Health*, 41, 279-81.

- DE GRAAF, F. R., SCHUIJF, J. D., DELGADO, V., VAN VELZEN, J. E., KROFT, L. J., DE ROOS, A., JUKEMA, J. W., VAN DER WALL, E. E. & BAX, J. J. 2010. Clinical application of CT coronary angiography: state of the art. *Heart Lung Circ*, 19, 107-16.
- DE KORTE, C. L., PASTERKAMP, G., VAN DER STEEN, A. F., WOUTMAN, H. A. & BOM, N. 2000. Characterization of plaque components with intravascular ultrasound elastography in human femoral and coronary arteries in vitro. *Circulation*, 102, 617-23.
- DE KORTE, C. L., SIEREVOGEL, M. J., MASTIK, F., STRIJDER, C., SCHAAR, J. A., VELEMA, E., PASTERKAMP, G., SERRUYS, P. W. & VAN DER STEEN, A. F. 2002. Identification of atherosclerotic plaque components with intravascular ultrasound elastography in vivo: a Yucatan pig study. *Circulation*, 105, 1627-30.
- DE LA PENA, E., NGUYEN, P. K., NAYAK, K. S., YANG, P. C., ROSENTHAL, D. N., HU, B. S., PAULY, J. M. & MCCONNELLU, M. V. 2006. Real-time color-flow CMR in adults with congenital heart disease. *J Cardiovasc Magn Reson*, 8, 809-815.
- DELATTRE, B. M., HEIDEMANN, R. M., CROWE, L. A., VALLEE, J. P. & HYACINTHE, J. N. 2010. Spiral demystified. *Magn Reson Imaging*, 28, 862-81.
- DENSLOW, S. & BUCKLES, D. S. 1993. Pulse oximetry-gated acquisition of cardiac MR images in patients with congenital cardiac abnormalities. *AJR Am J Roentgenol*, 160, 831-833.
- DESAI, M. Y., LAI, S., BARMET, C., WEISS, R. G. & STUBER, M. 2005. Reproducibility of 3D free-breathing magnetic resonance coronary vessel wall imaging. *Eur Heart J*, 26, 2320-2324.
- DESHPANDE, N., NEEDLES, A. & WILLMANN, J. K. 2010. Molecular ultrasound imaging: current status and future directions. *Clinical Radiology*, 65, 567-581.
- DESHPANDE, V. S., KRISHNAM, M. S., RUEHM, S. G., FINN, J. P. & LAUB, G. A. Year. Non-contrast MR angiography of the heart and great vessels using SSFP with nonselective excitation. In: the 14th International Society for Magnetic Resonance in Medicine, 2006 Seattle, WA. International Society for Magnetic Resonance in Medicine, 383.
- DESHPANDE, V. S., SHEA, S. M., LAUB, G., SIMONETTI, O. P., FINN, J. P. & LI, D. 2001a. 3D magnetization-prepared true-FISP: a new technique for imaging coronary arteries. *Magn Reson Med*, 46, 494-502.
- DESHPANDE, V. S., WIELOPOLSKI, P. A., SHEA, S. M., CARR, J., ZHENG, J. & LI, D. 2001b. Coronary artery imaging using contrast-enhanced 3D segmented EPI. *J Magn Reson Imaging*, 13, 676-81.
- DESJARDINS, B. & KAZEROONI, E. A. 2004. ECG-gated cardiac CT. *AJR Am J Roentgenol*, 182, 993-1010.
- DEWAN, M., HAGER, G. D. & LORENZ, C. H. 2008. Image-based coronary tracking and beat-to-beat motion compensation: feasibility for improving coronary MR angiography. *Magn Reson Med*, 60, 604-15.
- DODGE, J. T., JR., BROWN, B. G., BOLSON, E. L. & DODGE, H. T. 1992. Lumen diameter of normal human coronary arteries. Influence of age, sex, anatomic variation, and left ventricular hypertrophy or dilation. *Circulation*, 86, 232-46.
- DU, Y. P., SARANATHAN, M. & FOO, T. K. 2004. An accurate, robust, and computationally efficient navigator algorithm for measuring diaphragm positions. *J Cardiovasc Magn Reson*, 6, 483-490.
- DUERINCKX, A. & ATKINSON, D. P. 1997. Coronary MR angiography during peak-systole: work in progress. *J Magn Reson Imaging*, 7, 979-986.
- DUNPHY, M. P., FREIMAN, A., LARSON, S. M. & STRAUSS, H. W. 2005. Association of vascular 18F-FDG uptake with vascular calcification. *J Nucl Med*, 46, 1278-84.
- EARLS, J. P. 2009. How to use a prospective gated technique for cardiac CT. *Journal of Cardiovascular Computed Tomography*, 3, 45-51.
- EDELMAN, R. R., CHIEN, D. & KIM, D. 1991a. Fast selective black blood MR imaging. *Radiology*, 181, 655-660.
- EDELMAN, R. R., MANNING, W. J., BURSTEIN, D. & PAULIN, S. 1991b. Coronary arteries: breath-hold MR angiography. *Radiology*, 181, 641-643.
- EDELMAN, R. R., WALLNER, B., SINGER, A., ATKINSON, D. J. & SAINI, S. 1990. Segmented turboFLASH: method for breath-hold MR imaging of the liver with flexible contrast. *Radiology*, 177, 515-21.
- EDELMAN, R. R., WIELOPOLSKI, P. & SCHMITT, F. 1994. Echo-planar MR imaging. *Radiology*, 192, 600-612.
- EHMAN, R. L. & FELMLEE, J. P. 1989. Adaptive technique for high-definition MR imaging of moving structures. *Radiology*, 173, 255-263.
- EHMAN, R. L., MCNAMARA, M. T., PALLACK, M., HRICAK, H. & HIGGINS, C. B. 1984. Magnetic resonance imaging with respiratory gating: techniques and advantages. *AJR Am J Roentgenol*, 143, 1175-1182.
- ERBEL, R. 1991. Transesophageal echocardiography. New window to coronary arteries and coronary blood flow. *Circulation*, 83, 339-41.

- ERDOGMUS, D., YAN, R., LARSSON, E. G., PRINCIPE, J. C. & FITZSIMMONS, J. R. 2004. Image construction methods for phased array magnetic resonance imaging. *J Magn Reson Imaging*, 20, 306--314.
- FAYAD, Z. A., FUSTER, V., FALLON, J. T., JAYASUNDERA, T., WORTHLEY, S. G., HELFT, G., AGUINALDO, J. G., BADIMON, J. J. & SHARMA, S. K. 2000. Noninvasive in vivo human coronary artery lumen and wall imaging using black-blood magnetic resonance imaging. *Circulation*, 102, 506--510.
- FEINBERG, D. A., GIESE, D., BONGERS, D. A., RAMANNA, S., ZAITSEV, M., MARKL, M. & GUNTHER, M. 2010. Hybrid ultrasound MRI for improved cardiac imaging and real-time respiration control. *Magn Reson Med*, 63, 290-6.
- FEINBERG, D. A., ROFSKY, N. M. & JOHNSON, G. 1995. Multiple breath-hold averaging (MBA) method for increased SNR in abdominal MRI. *Magn Reson Med*, 34, 905-909.
- FELBLINGER, J. & BOESCH, C. 1997. Amplitude demodulation of the electrocardiogram signal (ECG) for respiration monitoring and compensation during MR examinations. *Magn Reson Med*, 38, 129-136.
- FERCHER, A. F., HITZENBERGER, C. K., KAMP, G. & EL-ZAIAT, S. Y. 1995. Measurement of intraocular distances by backscattering spectral interferometry. *Optics Communications*, 117, 43-48.
- FERNANDEZ-FRIERA, L., GARCIA-ALVAREZ, A., BAGHERIANNEJAD-ESFAHANI, F., MALICK, W., MIRELIS, J. G., SAWIT, S. T., FUSTER, V., SANZ, J., GARCIA, M. J. & HERMANN, L. K. 2011. Diagnostic value of coronary artery calcium scoring in low-intermediate risk patients evaluated in the emergency department for acute coronary syndrome. *Am J Cardiol*, 107, 17-23.
- FERNANDEZ, B., OSTER, J., LOHEZIC, M., MANDRY, D., PIETQUIN, O., VUISOZ, P. A. & FELBLINGER, J. 2010. Adaptive black blood fast spin echo for end-systolic rest cardiac imaging. *Magn Reson Med*, 64, 1760-71.
- FISCHER, R. W., BOTNAR, R. M., NEHRKE, K., BOESIGER, P., MANNING, W. J. & PETERS, D. C. 2006. Analysis of residual coronary artery motion for breath hold and navigator approaches using real-time coronary MRI. *Magn Reson Med*, 55, 612--618.
- FISCHER, S. E., WICKLINE, S. A. & LORENZ, C. H. 1999. Novel real-time R-wave detection algorithm based on the vectorcardiogram for accurate gated magnetic resonance acquisitions. *Magn Reson Med*, 42, 361-370.
- FLECKENSTEIN, J. L., ARCHER, B. T., BARKER, B. A., VAUGHAN, J. T., PARKEY, R. W. & PESHOCK, R. M. 1991. Fast short-tau inversion-recovery MR imaging. *Radiology*, 179, 499--504.
- FLOHR, T. G., MCCOLLOUGH, C. H., BRUDER, H., PETERSILKA, M., GRUBER, K., SUSS, C., GRASRUCK, M., STIERSTORFER, K., KRAUSS, B., RAUPACH, R., PRIMAK, A. N., KUTTNER, A., ACHENBACH, S., BECKER, C., KOPP, A. & OHNESORGE, B. M. 2006. First performance evaluation of a dual-source CT (DSCT) system. *Eur Radiol*, 16, 256-68.
- FLOHR, T. G. & OHNESORGE, B. M. 2008. Imaging of the heart with computed tomography. *Basic Res Cardiol*, 103, 161-73.
- FRANCONE, M., BUCCIARELLI-DUCCI, C., CARBONE, I., CANALI, E., SCARDALA, R., CALABRESE, F. A., SARDELLA, G., MANCONE, M., CATALANO, C., FEDELE, F., PASSARIELLO, R., BOGAERT, J. & AGATI, L. 2009. Impact of primary coronary angioplasty delay on myocardial salvage, infarct size, and microvascular damage in patients with ST-segment elevation myocardial infarction: insight from cardiovascular magnetic resonance. *J Am Coll Cardiol*, 54, 2145-53.
- FRAUENRATH, T., HEZEL, F., RENZ, W., D'ORTH TDE, G., DIERINGER, M., VON KNOBELSDORFF-BRENKENHOFF, F., PROTHMANN, M., MENDER, J. S. & NIENDORF, T. 2010. Acoustic cardiac triggering: a practical solution for synchronization and gating of cardiovascular magnetic resonance at 7 Tesla. *J Cardiovasc Magn Reson*, 12, 67.
- FUSTER, V. 2008. Hurst's the heart. 12th ed. ed. New York ; London: McGraw-Hill Medical.
- FUSTER, V., MORENO, P. R., FAYAD, Z. A., CORTI, R. & BADIMON, J. J. 2005. Atherothrombosis and high-risk plaque: part I: evolving concepts. *J Am Coll Cardiol*, 46, 937-54.
- GARG, S. & SERRUYS, P. W. 2010. Coronary stents: looking forward. *J Am Coll Cardiol*, 56, S43-78.
- GATEHOUSE, P. D., KEEGAN, J., YANG, G. Z., MOHIADDIN, R. H. & FIRMIN, D. N. 2001. Tracking local volume 3D-echo-planar coronary artery imaging. *Magn Reson Med*, 46, 1031--1036.
- GE, J., ERBEL, R., GERBER, T., GORGE, G., KOCH, L., HAUDE, M. & MEYER, J. 1994. Intravascular ultrasound imaging of angiographically normal coronary arteries: a prospective study in vivo. *Br Heart J*, 71, 572-8.
- GERRETSEN, S. C., KOOL, M. E., KESSELS, A. G., SCHALLA, S., KATOH, M., VAN DER GEEST, R. J., MANNING, W. J., WALTENBERGER, J., VAN ENGELSHOVEN, J. M., BOTNAR, R. M. & LEINER, T. 2010a. Visualization of

- coronary wall atherosclerosis in asymptomatic subjects and patients with coronary artery disease using magnetic resonance imaging. *PLoS One*, 5.
- GERRETSEN, S. C., WANG, J., MAKI, J. H., JAARMA, C., HERZKA, D. A., CHU, B., YARNYKH, V. L., YUAN, C. & LEINER, T. 2010b. Reproducible coronary vessel wall imaging at 3T using improved Motion Sensitized Driven Equilibrium (iMSDE). *Proc ISMRM, 18th Annual Meeting, Stockholm, Sweden*, 665.
- GHARIB, A. M., HERZKA, D. A., USTUN, A. O., DESAI, M. Y., LOCKLIN, J., PETTIGREW, R. I. & STUBER, M. 2007. Coronary MR angiography at 3T during diastole and systole. *J Magn Reson Imaging*, 26, 921-6.
- GIBSON, C. M., CANNON, C. P., DALEY, W. L., DODGE, J. T., JR., ALEXANDER, B., JR., MARBLE, S. J., MCCABE, C. H., RAYMOND, L., FORTIN, T., POOLE, W. K. & BRAUNWALD, E. 1996. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation*, 93, 879-88.
- GLAGOV, S., WEISENBERG, E., ZARINS, C. K., STANKUNAVICIUS, R. & KOLETTIS, G. J. 1987. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med*, 316, 1371-5.
- GOLDFARB, J. W. & EDELMAN, R. R. 1998. Coronary arteries: breath-hold, gadolinium-enhanced, three-dimensional MR angiography. *Radiology*, 206, 830-4.
- GOLDSTEIN, J. L., KITA, T. & BROWN, M. S. 1983. Defective lipoprotein receptors and atherosclerosis. Lessons from an animal counterpart of familial hypercholesterolemia. *N Engl J Med*, 309, 288-96.
- GRADUS-PIZLO, I., BIGELOW, B., MAHOMED, Y., SAWADA, S. G., RIEGER, K. & FEIGENBAUM, H. 2003. Left anterior descending coronary artery wall thickness measured by high-frequency transthoracic and epicardial echocardiography includes adventitia. *Am J Cardiol*, 91, 27-32.
- GRADUS-PIZLO, I., SAWADA, S. G., WRIGHT, D., SEGAR, D. S. & FEIGENBAUM, H. 2001. Detection of subclinical coronary atherosclerosis using two-dimensional, high-resolution transthoracic echocardiography. *J Am Coll Cardiol*, 37, 1422-9.
- GREENLAND, P., BONOW, R. O., BRUNDAGE, B. H., BUDOFF, M. J., EISENBERG, M. J., GRUNDY, S. M., LAUER, M. S., POST, W. S., RAGGI, P., REDBERG, R. F., RODGERS, G. P., SHAW, L. J., TAYLOR, A. J. & WEINTRAUB, W. S. 2007. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol*, 49, 378-402.
- GREIL, G. F., DESAI, M. Y., FENCHEL, M., MILLER, S., PETTIGREW, R. I., SIEVERDING, L. & STUBER, M. 2007a. Reproducibility of free-breathing cardiovascular magnetic resonance coronary angiography. *J Cardiovasc Magn Reson*, 9, 49--56.
- GREIL, G. F., SEEGER, A., MILLER, S., CLAUSSEN, C. D., HOFBECK, M., BOTNAR, R. M. & SIEVERDING, L. 2007b. Coronary magnetic resonance angiography and vessel wall imaging in children with Kawasaki disease. *Pediatr Radiol*, 37, 666--673.
- GREIL, G. F., STUBER, M., BOTNAR, R. M., KISSINGER, K. V., GEVA, T., NEWBURGER, J. W., MANNING, W. J. & POWELL, A. J. 2002. Coronary magnetic resonance angiography in adolescents and young adults with kawasaki disease. *Circulation*, 105, 908--911.
- GROBNER, T. 2006. Gadolinium--a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant*.
- GROSSMAN, P. M., GURM, H. S., MCNAMARA, R., LALONDE, T., CHANGEZI, H., SHARE, D., SMITH, D. E., CHETCUTI, S. J. & MOSCUCCI, M. 2009. Percutaneous coronary intervention complications and guide catheter size: bigger is not better. *JACC Cardiovasc Interv*, 2, 636-44.
- GUTTMAN, M. A., PRINCE, J. L. & MCVEIGH, E. R. 1994. Tag and contour detection in tagged MR images of the left ventricle. *IEEE Trans Med Imaging*, 13, 74--88.
- HAACKE, E. M. & PATRICK, J. L. 1986. Reducing motion artifacts in two-dimensional Fourier transform imaging. *Magn Reson Imaging*, 4, 359-376.
- HABER, I., METAXAS, D. N., GEVA, T. & AXEL, L. 2005. Three-dimensional systolic kinematics of the right ventricle. *Am J Physiol Heart Circ Physiol*, 289, H1826-H1833.
- HACKENBROCH, M., NEHRKE, K., GIESEKE, J., MEYER, C., TIEMANN, K., LITT, H., DEWALD, O., NAEHLE, C. P., SCHILD, H. & SOMMER, T. 2005. 3D motion adapted gating (3D MAG): a new navigator technique for accelerated acquisition of free breathing navigator gated 3D coronary MR-angiography. *Eur Radiol*, 15, 1598-1606.

- HAFFNER, S. M., LEHTO, S., RONNEMAA, T., PYORALA, K. & LAAKSO, M. 1998. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*, 339, 229-34.
- HARDY, C. J. & CLINE, H. E. 1989. Broadband nuclear magnetic resonance pulses with two-dimensional spatial selectivity. *Journal of Applied Physics*, 66, 1513-1516.
- HARDY, C. J., SARANATHAN, M., ZHU, Y. & DARROW, R. D. 2000. Coronary angiography by real-time MRI with adaptive averaging. *Magn Reson Med*, 44, 940-946.
- HARDY, C. J., ZHAO, L., ZONG, X., SARANATHAN, M. & YUCEL, E. K. 2003. Coronary MR angiography: respiratory motion correction with BACSPIN. *J Magn Reson Imaging*, 17, 170-176.
- HAUSLEITER, J., MEYER, T., HERMANN, F., HADAMITZKY, M., KREBS, M., GERBER, T. C., MCCOLLOUGH, C., MARTINOFF, S., KASTRATI, A., SCHOMIG, A. & ACHENBACH, S. 2009. Estimated radiation dose associated with cardiac CT angiography. *JAMA*, 301, 500-7.
- HAZIROLAN, T., GUPTA, S. N., MOHAMED, M. A. & BLUEMKE, D. A. 2005. Reproducibility of black-blood coronary vessel wall MR imaging. *J Cardiovasc Magn Reson*, 7, 409-413.
- HEINLE, S. K., NOBLIN, J., GOREE-BEST, P., MELLO, A., RAVAD, G., MULL, S., MAMMEN, P. & GRAYBURN, P. A. 2000. Assessment of myocardial perfusion by harmonic power Doppler imaging at rest and during adenosine stress: comparison with (99m)Tc-sestamibi SPECT imaging. *Circulation*, 102, 55-60.
- HENDEL, R. C., BERMAN, D. S., CULLOM, S. J., FOLLANSBEE, W., HELLER, G. V., KIAT, H., GROCH, M. W. & MAHMARIAN, J. J. 1999. Multicenter clinical trial to evaluate the efficacy of correction for photon attenuation and scatter in SPECT myocardial perfusion imaging. *Circulation*, 99, 2742-9.
- HENNIG, J., SCHNEIDER, B., PESCHL, S., MARKL, M., KRAUSE, T. & LAUBENBERGER, J. 1998. 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, 868-877.
- HERMILLER, J. B., BULLER, C. E., TENAGLIA, A. N., KISSLO, K. B., PHILLIPS, H. R., BASHORE, T. M., STACK, R. S. & DAVIDSON, C. J. 1993. Unrecognized left main coronary artery disease in patients undergoing interventional procedures. *Am J Cardiol*, 71, 173-6.
- HESS, A., ANDRONESI, O. C., TISDALL, M. D., SORENSEN, A. G., VAN DER KOUWE, A. J. & MEINTJES, E. M. 2010. Motion artefact correction in spectroscopic imaging using an EPI navigator and reacquisition. *Proc ISMRM, 18th Annual Meeting, Stockholm, Sweden*, 3308.
- HESS, A., TISDALL, M. D., MEINTJES, E. M. & VAN DER KOUWE, A. J. 2009. Real-Time Motion Corrected MRS using EPI Navigators. *Proc ISMRM, 17th Annual Meeting, Honolulu, Hawai'i, USA*, 4646.
- HIGGINS, C. B., BYRD, B. F., MCNAMARA, M. T., LANZER, P., LIPTON, M. J., BOTVINICK, E., SCHILLER, N. B., CROOKS, L. E. & KAUFMAN, L. 1985. Magnetic resonance imaging of the heart: a review of the experience in 172 subjects. *Radiology*, 155, 671-679.
- HILL, J. & TIMMIS, A. 2002. Exercise tolerance testing. *BMJ*, 324, 1084-7.
- HIRO, T., LEUNG, C. Y., DE GUZMAN, S., CAIOZZO, V. J., FARVID, A. R., KARIMI, H., HELFANT, R. H. & TOBIS, J. M. 1997. Are soft echoes really soft? Intravascular ultrasound assessment of mechanical properties in human atherosclerotic tissue. *Am Heart J*, 133, 1-7.
- HIRSCH, J. A. & BISHOP, B. 1981. Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate. *Am J Physiol*, 241, H620-H629.
- HOCHMAN, J. S., SLEEPER, L. A., WEBB, J. G., DZAVIK, V., BULLER, C. E., AYLWARD, P., COL, J. & WHITE, H. D. 2006. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *JAMA*, 295, 2511-5.
- HOCHMAN, J. S., SLEEPER, L. A., WEBB, J. G., SANBORN, T. A., WHITE, H. D., TALLEY, J. D., BULLER, C. E., JACOBS, A. K., SLATER, J. N., COL, J., MCKINLAY, S. M. & LEJEMTEL, T. H. 1999. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med*, 341, 625-34.
- HOFFMAN, E. A. & RITMAN, E. L. 1985. Invariant total heart volume in the intact thorax. *Am J Physiol*, 249, H883-H890.
- HOFMAN, M. B., WICKLINE, S. A. & LORENZ, C. H. 1998. Quantification of in-plane motion of the coronary arteries during the cardiac cycle: implications for acquisition window duration for MR flow quantification. *J Magn Reson Imaging*, 8, 568-576.

- HOLLAND, A. E., GOLDFARB, J. W. & EDELMAN, R. R. 1998. Diaphragmatic and cardiac motion during suspended breathing: preliminary experience and implications for breath-hold MR imaging. *Radiology*, 209, 483-489.
- HOPKINS, P. N. & WILLIAMS, R. R. 1989. Human genetics and coronary heart disease: a public health perspective. *Annu Rev Nutr*, 9, 303-45.
- HORE, P. J. 1983. Solvent suppression in fourier transform nuclear magnetic resonance. *Journal of Magnetic Resonance (1969)*, 55, 283-300.
- HORIGUCHI, J., KIGUCHI, M., FUJIOKA, C., ARIE, R., SHEN, Y., SUNASAKA, K., KITAGAWA, T., YAMAMOTO, H. & ITO, K. 2008. Variability of repeated coronary artery calcium scoring and radiation Dose on 64- and 16-slice computed tomography by prospective electrocardiographically-triggered axial and retrospective electrocardiographically-gated spiral computed tomography: a phantom study. *Acad Radiol*, 15, 958-65.
- HSIAO, E. M., RYBICKI, F. J. & STEIGNER, M. 2010. CT coronary angiography: 256-slice and 320-detector row scanners. *Curr Cardiol Rep*, 12, 68-75.
- HU, P., CHUANG, M. L., NGO, L. H., STOECK, C. T., PETERS, D. C., KISSINGER, K. V., GODDU, B., GOEPFERT, L. A., MANNING, W. J. & NEZAFAT, R. 2010. Coronary MR imaging: effect of timing and dose of isosorbide dinitrate administration. *Radiology*, 254, 401-9.
- HUBER, M. E., KOZERKE, S., PRUESSMANN, K. P., SMINK, J. & BOESIGER, P. 2004. Sensitivity-encoded coronary MRA at 3T. *Magn Reson Med*, 52, 221-7.
- HUNG, J., CHAITMAN, B. R., LAM, J., LESPERANCE, J., DUPRAS, G., FINES, P. & BOURASSA, M. G. 1984. Noninvasive diagnostic test choices for the evaluation of coronary artery disease in women: a multivariate comparison of cardiac fluoroscopy, exercise electrocardiography and exercise thallium myocardial perfusion scintigraphy. *J Am Coll Cardiol*, 4, 8-16.
- HUTCHINS, G. D., SCHWAIGER, M., ROSENSPIRE, K. C., KRIVOKAPICH, J., SCHELBERT, H. & KUHL, D. E. 1990. Noninvasive quantification of regional blood flow in the human heart using N-13 ammonia and dynamic positron emission tomographic imaging. *J Am Coll Cardiol*, 15, 1032-42.
- IACOBELLIS, G., CORRADI, D. & SHARMA, A. M. 2005. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. *Nat Clin Pract Cardiovasc Med*, 2, 536-43.
- IBRAHIM, T., MAKOWSKI, M. R., JANKAUSKAS, A., MAINTZ, D., KARCH, M., SCHACHOFF, S., MANNING, W. J., SCHOMIG, A., SCHWAIGER, M. & BOTNAR, R. M. 2009. Serial contrast-enhanced cardiac magnetic resonance imaging demonstrates regression of hyperenhancement within the coronary artery wall in patients after acute myocardial infarction. *JACC Cardiovasc Imaging*, 2, 580-8.
- INNES, J. A., CORT, S. C. D., KOX, W. & GUZ, A. 1993. Within-breath modulation of left ventricular function during normal breathing and positive-pressure ventilation in man. *J Physiol*, 460, 487-502.
- ISHIBASHI, F., AZIZ, K., ABELA, G. S. & WAXMAN, S. 2006. Update on coronary angiography: review of a 20-year experience and potential application for detection of vulnerable plaque. *J Interv Cardiol*, 19, 17-25.
- IULIANO, L., SIGNORE, A., VALLABAJOSULA, S., COLAVITA, A. R., CAMASTRA, C., RONGA, G., ALESSANDRI, C., SBARIGIA, E., FIORANI, P. & VIOLI, F. 1996. Preparation and biodistribution of 99m technetium labelled oxidized LDL in man. *Atherosclerosis*, 126, 131-41.
- JACKSON, J. I., MEYER, C. H., NISHIMURA, D. G. & MACOVSKI, A. 1991. Selection of a convolution function for Fourier inversion using gridding [computerised tomography application]. *IEEE Trans Med Imaging*, 10, 473-8.
- JAHNKE, C., NEHRKE, K., PAETSCH, I., SCHNACKENBURG, B., GEBKER, R., FLECK, E. & NAGEL, E. 2007. Improved bulk myocardial motion suppression for navigator-gated coronary magnetic resonance imaging. *J Magn Reson Imaging*, 26, 780-786.
- JAHNKE, C., PAETSCH, I., ACHENBACH, S., SCHNACKENBURG, B., GEBKER, R., FLECK, E. & NAGEL, E. 2006. Coronary MR imaging: breath-hold capability and patterns, coronary artery rest periods, and beta-blocker use. *Radiology*, 239, 71-78.
- JAHNKE, C., PAETSCH, I., NEHRKE, K., SCHNACKENBURG, B., BORNSTEDT, A., GEBKER, R., FLECK, E. & NAGEL, E. 2005a. A new approach for rapid assessment of the cardiac rest period for coronary MRA. *J Cardiovasc Magn Reson*, 7, 395-399.
- JAHNKE, C., PAETSCH, I., NEHRKE, K., SCHNACKENBURG, B., GEBKER, R., FLECK, E. & NAGEL, E. 2005b. Rapid and complete coronary arterial tree visualization with magnetic resonance imaging: feasibility and diagnostic performance. *Eur Heart J*, 26, 2313-2319.

- JAHNKE, C., PAETSCH, I., SCHNACKENBURG, B., GEBKER, R., KÖHLER, U., BORNSTEDT, A., FLECK, E. & NAGEL, E. 2004. Comparison of radial and Cartesian imaging techniques for MR coronary angiography. *J Cardiovasc Magn Reson*, 6, 865--875.
- JAKOBS, T. F., BECKER, C. R., OHNESORGE, B., FLOHR, T., SUESS, C., SCHOEPPF, U. J. & REISER, M. F. 2002. Multislice helical CT of the heart with retrospective ECG gating: reduction of radiation exposure by ECG-controlled tube current modulation. *Eur Radiol*, 12, 1081-6.
- JANG, I. K., BOUMA, B. E., KANG, D. H., PARK, S. J., PARK, S. W., SEUNG, K. B., CHOI, K. B., SHISHKOV, M., SCHLENDORF, K., POMERANTSEV, E., HOUSER, S. L., ARETZ, H. T. & TEARNEY, G. J. 2002. Visualization of coronary atherosclerotic plaques in patients using optical coherence tomography: comparison with intravascular ultrasound. *J Am Coll Cardiol*, 39, 604-9.
- JHOOTI, P., GATEHOUSE, P. D., KEEGAN, J., BUNCE, N. H., TAYLOR, A. M. & FIRMIN, D. N. 2000. Phase ordering with automatic window selection (PAWS): a novel motion-resistant technique for 3D coronary imaging. *Magn Reson Med*, 43, 470--480.
- JHOOTI, P., KEEGAN, J. & FIRMIN, D. N. 2010. A fully automatic and highly efficient navigator gating technique for high-resolution free-breathing acquisitions: Continuously adaptive windowing strategy. *Magn Reson Med*, 64, 1015-26.
- JHOOTI, P., KEEGAN, J., GATEHOUSE, P. D., COLLINS, S., ROWE, A., TAYLOR, A. M. & FIRMIN, D. N. 1999. 3D coronary artery imaging with phase reordering for improved scan efficiency. *Magn Reson Med*, 41, 555--562.
- JHOOTI, P., WIESMANN, F., TAYLOR, A. M., GATEHOUSE, P. D., YANG, G. Z., KEEGAN, J., PENNELL, D. J. & FIRMIN, D. N. 1998. Hybrid ordered phase encoding (HOPE): an improved approach for respiratory artifact reduction. *J Magn Reson Imaging*, 8, 968-980.
- JOHNSON, K. R., PATEL, S. J., WHIGHAM, A., HAKIM, A., PETTIGREW, R. I. & OSHINSKI, J. N. 2004. Three-dimensional, time-resolved motion of the coronary arteries. *J Cardiovasc Magn Reson*, 6, 663-73.
- JUDKINS, M. P. 1967. Selective Coronary Arteriography. *Radiology*, 89, 815-824.
- JUNG, B., FÖLL, D., BÖTTLER, P., PETERSEN, S., HENNIG, J. & MARKL, M. 2006. Detailed analysis of myocardial motion in volunteers and patients using high-temporal-resolution MR tissue phase mapping. *J Magn Reson Imaging*, 24, 1033--1039.
- JUNG, B., SCHNEIDER, B., MARKL, M., SAURBIER, B., GEIBEL, A. & HENNIG, J. 2004. Measurement of left ventricular velocities: phase contrast MRI velocity mapping versus tissue-doppler-ultrasound in healthy volunteers. *J Cardiovasc Magn Reson*, 6, 777--783.
- KADAH, Y. M., ABAZA, A. A., FAHMY, A. S., YOUSSEF, A.-B. M., HEBERLEIN, K. & HU, X. P. 2004. Floating navigator echo (FNAV) for in-plane 2D translational motion estimation. *Magn Reson Med*, 51, 403--407.
- KAJIYA, F., MATSUOKA, S., OGASAWARA, Y., HIRAMATSU, O., KANAZAWA, S., WADA, Y., TADAOKA, S., TSUJIOKA, K., FUJIWARA, T. & ZAMIR, M. 1993. Velocity profiles and phasic flow patterns in the non-stenotic human left anterior descending coronary artery during cardiac surgery. *Cardiovasc Res*, 27, 845-50.
- KAPLAN, G. A. & KEIL, J. E. 1993. Socioeconomic factors and cardiovascular disease: a review of the literature. *Circulation*, 88, 1973-98.
- KARWATOWSKI, S. P., BRECKER, S. J., YANG, G. Z., FIRMIN, D. N., SUTTON, M. S. J. & UNDERWOOD, S. R. 1996. A comparison of left ventricular myocardial velocity in diastole measured by magnetic resonance and left ventricular filling measured by Doppler echocardiography. *Eur Heart J*, 17, 795--802.
- KARWATOWSKI, S. P., MOHIADDIN, R., YANG, G. Z., FIRMIN, D. N., SUTTON, M. S., UNDERWOOD, S. R. & LONGMORE, D. B. 1994. Assessment of regional left ventricular long-axis motion with MR velocity mapping in healthy subjects. *J Magn Reson Imaging*, 4, 151-155.
- KATO, S., KITAGAWA, K., ISHIDA, N., ISHIDA, M., NAGATA, M., ICHIKAWA, Y., KATAHIRA, K., MATSUMOTO, Y., SEO, K., OCHIAi, R., KOBAYASHI, Y. & SAKUMA, H. 2010. Assessment of coronary artery disease using magnetic resonance coronary angiography: a national multicenter trial. *J Am Coll Cardiol*, 56, 983-91.
- KATOH, M., SPUNTRUP, E., BARMET, C. & STUBER, M. 2008. Local re-inversion coronary MR angiography: arterial spin-labeling without the need for subtraction. *J Magn Reson Imaging*, 27, 913-7.
- KATOH, M., SPUNTRUP, E., BUECKER, A., MANNING, W. J., GÜNTHER, R. W. & BOTNAR, R. M. 2006a. MR coronary vessel wall imaging: comparison between radial and spiral k-space sampling. *J Magn Reson Imaging*, 23, 757--762.

- KATOH, M., SPUNTRUP, E., BUECKER, A., SCHAEFFTER, T., STUBER, M., GÜNTHER, R. W. & BOTNAR, R. M. 2006b. MRI of coronary vessel walls using radial k-space sampling and steady-state free precession imaging. *AJR Am J Roentgenol*, 186, S401--S406.
- KATOH, M., SPUNTRUP, E., STUBER, M., BUECKER, A., MANNING, W. J., GÜNTHER, R. W. & BOTNAR, R. M. 2009. Flow Targeted 3D Steady-State Free-Precession Coronary MR Angiography: Comparison of Three Different Imaging Approaches. *Investigative Radiology*, 44, 757-762.
- KAUFMANN, B. A. 2009. Ultrasound molecular imaging of atherosclerosis. *Cardiovasc Res*, 83, 617-25.
- KAUL, M. G., STORK, A., BANSMANN, P. M., NOLTE-ERNSTING, C., LUND, G. K., WEBER, C. & ADAM, G. 2004. Evaluation of balanced steady-state free precession (TrueFISP) and K-space segmented gradient echo sequences for 3D coronary MR angiography with navigator gating at 3 Tesla. *Rofo*, 176, 1560-5.
- KAWAKAMI, K., MURASE, K., KUMASHIRO, M., KAWAKAMI, A., TANKI, N., YAMAZAKI, Y., TABUCHI, T., NAGAYAMA, M. & WATANABE, Y. 2004. Automatic motion correction for quantification of myocardial perfusion with dynamic magnetic resonance imaging. *Magn Reson Med Sci*, 3, 105-117.
- KAWASAKI, M., TAKATSU, H., NODA, T., SANO, K., ITO, Y., HAYAKAWA, K., TSUCHIYA, K., ARAI, M., NISHIGAKI, K., TAKEMURA, G., MINATOUGHU, S., FUJIWARA, T. & FUJIWARA, H. 2002. In vivo quantitative tissue characterization of human coronary arterial plaques by use of integrated backscatter intravascular ultrasound and comparison with angioscopic findings. *Circulation*, 105, 2487-92.
- KAWASAKI, T., KOGA, S., KOGA, N., NOGUCHI, T., TANAKA, H., KOGA, H., SERIKAWA, T., ORITA, Y., IKEDA, S., MITO, T., GOTO, Y., SHINTANI, Y., TANAKA, A. & FUKUYAMA, T. 2009. Characterization of hyperintense plaque with noncontrast T(1)-weighted cardiac magnetic resonance coronary plaque imaging: comparison with multislice computed tomography and intravascular ultrasound. *JACC Cardiovasc Imaging*, 2, 720-8.
- KEEGAN, J., GATEHOUSE, P., YANG, G.-Z. & FIRMIN, D. 2002. Coronary artery motion with the respiratory cycle during breath-holding and free-breathing: implications for slice-followed coronary artery imaging. *Magn Reson Med*, 47, 476-481.
- KEEGAN, J., GATEHOUSE, P. D., PRASAD, S. K. & FIRMIN, D. N. 2006. Improved turbo spin-echo imaging of the heart with motion-tracking. *J Magn Reson Imaging*, 24, 563-570.
- KEEGAN, J., GATEHOUSE, P. D., YANG, G.-Z. & FIRMIN, D. N. 2007. Non-model-based correction of respiratory motion using beat-to-beat 3D spiral fat-selective imaging. *J Magn Reson Imaging*, 26, 624--629.
- KEEGAN, J., HORKAEW, P., BUCHANAN, T. J., SMART, T. S., YANG, G.-Z. & FIRMIN, D. N. 2004. Intra- and interstudy reproducibility of coronary artery diameter measurements in magnetic resonance coronary angiography. *J Magn Reson Imaging*, 20, 160--166.
- KEENAN, N. G., LOCCA, D., VARGHESE, A., ROUGHTON, M., GATEHOUSE, P. D., HOOPER, J., FIRMIN, D. N. & PENNELL, D. J. 2009. Magnetic resonance of carotid artery ageing in healthy subjects. *Atherosclerosis*, 205, 168-73.
- KELLMAN, P., CHEFD'HOTEL, C., LORENZ, C. H., MANCINI, C., ARAI, A. E. & MCVEIGH, E. R. 2008. Fully automatic, retrospective enhancement of real-time acquired cardiac cine MR images using image-based navigators and respiratory motion-corrected averaging. *Magn Reson Med*, 59, 771--778.
- KENNY, A., WISBEY, C. R. & SHAPIRO, L. M. 1994. Measurement of left anterior descending coronary artery flow velocities by transthoracic Doppler ultrasound. *Am J Cardiol*, 73, 1021-2.
- KIETSELAER, B. L., REUTELINGSPERGER, C. P., HEIDENDAL, G. A., DAEMEN, M. J., MESS, W. H., HOFSTRA, L. & NARULA, J. 2004. Noninvasive detection of plaque instability with use of radiolabeled annexin A5 in patients with carotid-artery atherosclerosis. *N Engl J Med*, 350, 1472-3.
- KIM, W. S., MUN, C. W., KIM, D. J. & CHO, Z. H. 1990. Extraction of cardiac and respiratory motion cycles by use of projection data and its applications to NMR imaging. *Magn Reson Med*, 13, 25-37.
- KIM, W. Y., ASTRUP, A. S., STUBER, M., TARNOW, L., FALK, E., BOTNAR, R. M., SIMONSEN, C., PIETRASZEK, L., HANSEN, P. R., MANNING, W. J., ANDERSEN, N. T. & PARVING, H.-H. 2007. Subclinical coronary and aortic atherosclerosis detected by magnetic resonance imaging in type 1 diabetes with and without diabetic nephropathy. *Circulation*, 115, 228--235.
- KIM, W. Y., DANIAS, P. G., STUBER, M., FLAMM, S. D., PLEIN, S., NAGEL, E., LANGERAK, S. E., WEBER, O. M., PEDERSEN, E. M., SCHMIDT, M., BOTNAR, R. M. & MANNING, W. J. 2001a. Coronary magnetic resonance angiography for the detection of coronary stenoses. *N Engl J Med*, 345, 1863--1869.
- KIM, W. Y., STUBER, M., BÖRNERT, P., KISSINGER, K. V., MANNING, W. J. & BOTNAR, R. M. 2002. Three-dimensional black-blood cardiac magnetic resonance coronary vessel wall imaging detects positive

- arterial remodeling in patients with nonsignificant coronary artery disease. *Circulation*, 106, 296--299.
- KIM, W. Y., STUBER, M., KISSINGER, K. V., ANDERSEN, N. T., MANNING, W. J. & BOTNAR, R. M. 2001b. Impact of bulk cardiac motion on right coronary MR angiography and vessel wall imaging. *J Magn Reson Imaging*, 14, 383--390.
- KIPS, J. G., SEGERS, P. & VAN BORTEL, L. M. 2008. Identifying the vulnerable plaque: A review of invasive and non-invasive imaging modalities. *Artery Research*, 2, 21-34.
- KLEIN, C., GEBKER, R., KOKOCINSKI, T., DREYSSE, S., SCHNACKENBURG, B., FLECK, E. & NAGEL, E. 2008. Combined magnetic resonance coronary artery imaging, myocardial perfusion and late gadolinium enhancement in patients with suspected coronary artery disease. *J Cardiovasc Magn Reson*, 10, 45.
- KNEZ, A., BECKER, A., LEBER, A., WHITE, C., BECKER, C. R., REISER, M. F., STEINBECK, G. & BOEKSTEGERS, P. 2004. Relation of coronary calcium scores by electron beam tomography to obstructive disease in 2,115 symptomatic patients. *Am J Cardiol*, 93, 1150-2.
- KOKTZOGLU, I., SIMONETTI, O. & LI, D. 2005. Coronary artery wall imaging: initial experience at 3 Tesla. *J Magn Reson Imaging*, 21, 128--132.
- KOLODIE, F. D., PETROV, A., VIRMANI, R., NARULA, N., VERJANS, J. W., WEBER, D. K., HARTUNG, D., STEINMETZ, N., VANDERHEYDEN, J. L., VANNAN, M. A., GOLD, H. K., REUTELINGSPERGER, C. P., HOFSTRA, L. & NARULA, J. 2003. Targeting of apoptotic macrophages and experimental atheroma with radiolabeled annexin V: a technique with potential for noninvasive imaging of vulnerable plaque. *Circulation*, 108, 3134-9.
- KONIG, A. & KLAUSS, V. 2007. Virtual histology. *Heart*, 93, 977-82.
- KOOI, M. E., CAPPENDIJK, V. C., CLEUTJENS, K. B. J. M., KESSELS, A. G. H., KITSLAAR, P. J. E. H. M., BORBERS, M., FREDERIK, P. M., DAEMEN, M. J. A. P. & VAN ENGELSHOVEN, J. M. A. 2003. Accumulation of Ultrasmall Superparamagnetic Particles of Iron Oxide in Human Atherosclerotic Plaques Can Be Detected by In Vivo Magnetic Resonance Imaging. *Circulation*, 107, 2453-2458.
- KORIN, H. W., FELMLEE, J. P., EHMAN, R. L. & RIEDERER, S. J. 1990. Adaptive technique for three-dimensional MR imaging of moving structures. *Radiology*, 177, 217-221.
- KRAITCHMAN, D. L., YOUNG, A. A., CHANG, C. N. & AXEL, L. 1995. Semi-automatic tracking of myocardial motion in MR tagged images. *IEEE Trans Med Imaging*, 14, 422--433.
- KUBO, T., IMANISHI, T., TAKARADA, S., KUROI, A., UENO, S., YAMANO, T., TANIMOTO, T., MATSUO, Y., MASHO, T., KITABATA, H., TSUDA, K., TOMOBUCHI, Y. & AKASAKA, T. 2007. Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angiography. *J Am Coll Cardiol*, 50, 933-9.
- KUMAR, S. & GOLDFOG, D. 1994. Automatic tracking of SPAMM grid and the estimation of deformation parameters from cardiac MR images. *IEEE Trans Med Imaging*, 13, 122--132.
- KUMAR, V., ABBAS, A. K., FAUSTO, N., ROBBINS, S. L. & COTRAN, R. S. R. P. B. O. D. 2005. *Robbins and Cotran pathologic basis of disease*, Philadelphia, Pa. ; [London], Elsevier Saunders.
- KVITTING, J.-P. E., EBBERS, T., ENGVALL, J., SUTHERLAND, G. R., WRANNE, B. & WIGSTRÖM, L. 2004. Three-directional myocardial motion assessed using 3D phase contrast MRI. *J Cardiovasc Magn Reson*, 6, 627--636.
- LAGEMAAT, M. W., HENNIGSSON, M., STUBER, M., WIETHOFF, A. J. & BOTNAR, R. M. 2009. High-resolution 3D Coronary Vessel Wall Imaging Using Spiral Image Acquisition at 3T. *Proc ISMRM, 17th Annual Meeting, Honolulu, Hawai'i, USA*, 1.
- LAI, P., BI, X., JERECIC, R. & LI, D. 2009. A respiratory self-gating technique with 3D-translation compensation for free-breathing whole-heart coronary MRA. *Magn Reson Med*, 62, 731-8.
- LAI, P., LARSON, A. C., BI, X., JERECIC, R. & LI, D. 2008. A dual-projection respiratory self-gating technique for whole-heart coronary MRA. *J Magn Reson Imaging*, 28, 612--620.
- LANDIS, J. R. & KOCH, G. G. 1977. The measurement of observer agreement for categorical data. *Biometrics*, 33, 159-74.
- LANGE, H. W. & VON BOETTICHER, H. 2006. Randomized comparison of operator radiation exposure during coronary angiography and intervention by radial or femoral approach. *Catheter Cardiovasc Interv*, 67, 12-6.
- LANGER, H. F., HAUBNER, R., PICHLER, B. J. & GAWAZ, M. 2008. Radionuclide Imaging: A Molecular Key to the Atherosclerotic Plaque. *J Am Coll Cardiol*, 52, 1-12.

- LANGRECK, H., SCHNACKENBURG, B., NEHRKE, K., BOERNERT, P., WAHL, A., PAETSCH, I., BORNSTEDT, A., FLECK, E. & NAGELI, E. 2005. MR coronary artery imaging with 3D motion adapted gating (MAG) in comparison to a standard prospective navigator technique. *J Cardiovasc Magn Reson*, 7, 793--797.
- LANZER, P., BOTVINICK, E. H., SCHILLER, N. B., CROOKS, L. E., ARAKAWA, M., KAUFMAN, L., DAVIS, P. L., HERFKENS, R., LIPTON, M. J. & HIGGINS, C. B. 1984. Cardiac imaging using gated magnetic resonance. *Radiology*, 150, 121--127.
- LARKMAN, D. J. & NUNES, R. G. 2007. Parallel magnetic resonance imaging. *Phys Med Biol*, 52, R15--R55.
- LARSON, A. C., KELLMAN, P., ARAI, A., HIRSCH, G. A., MCVEIGH, E., LI, D. & SIMONETTI, O. P. 2005. Preliminary investigation of respiratory self-gating for free-breathing segmented cine MRI. *Magn Reson Med*, 53, 159-168.
- LARSON, A. C., SIMONETTI, O. P. & LI, D. 2002. Coronary MRA with 3D undersampled projection reconstruction TrueFISP. *Magn Reson Med*, 48, 594-601.
- LARSON, A. C., WHITE, R. D., LAUB, G., MCVEIGH, E. R., LI, D. & SIMONETTI, O. P. 2004. Self-gated cardiac cine MRI. *Magn Reson Med*, 51, 93-102.
- LEBER, A. W., BECKER, A., KNEZ, A., VON ZIEGLER, F., SIROL, M., NIKOLAOU, K., OHNESORGE, B., FAYAD, Z. A., BECKER, C. R., REISER, M., STEINBECK, G. & BOEKSTEGERS, P. 2006. Accuracy of 64-slice computed tomography to classify and quantify plaque volumes in the proximal coronary system: a comparative study using intravascular ultrasound. *J Am Coll Cardiol*, 47, 672-7.
- LEBER, A. W., KNEZ, A., WHITE, C. W., BECKER, A., VON ZIEGLER, F., MUEHLING, O., BECKER, C., REISER, M., STEINBECK, G. & BOEKSTEGERS, P. 2003. Composition of coronary atherosclerotic plaques in patients with acute myocardial infarction and stable angina pectoris determined by contrast-enhanced multislice computed tomography. *Am J Cardiol*, 91, 714-8.
- LEDESMA-CARBAYO, M. J., KELLMAN, P., ARAI, A. E. & MCVEIGH, E. R. 2007. Motion corrected free-breathing delayed-enhancement imaging of myocardial infarction using nonrigid registration. *J Magn Reson Imaging*, 26, 184--190.
- LEE, H. L., SHANKARANARAYANAN, A., POHOST, G. M. & NAYAK, K. S. 2010. Improved coronary MR angiography using wideband steady state free precession at 3 tesla with sub-millimeter resolution. *J Magn Reson Imaging*, 31, 1224-9.
- LEE, K. W. & PANTING, J. 2006. Current status of non-invasive coronary angiography for the diagnosis of coronary artery stenosis. *The British Journal of Cardiology (Acute & Interventional Cardiology)*, 13, 8.
- LEIGHTON, R. F., NELSON, A. D., ANDREWS, L. T. & GUPTA, M. 1983. Regional sequential motion in the normal left ventricle: nonuniform apical motion. *Cathet Cardiovasc Diagn*, 9, 129--136.
- LEINER, T., KATSIMAGLIS, G., YEH, E. N., KISSINGER, K. V., VAN YPEREN, G., EGGERS, H., MANNING, W. J. & BOTNAR, R. M. 2005. Correction for heart rate variability improves coronary magnetic resonance angiography. *J Magn Reson Imaging*, 22, 577--582.
- LI, D., CARR, J. C., SHEA, S. M., ZHENG, J., DESHPANDE, V. S., WIELOPOLSKI, P. A. & FINN, J. P. 2001. Coronary arteries: magnetization-prepared contrast-enhanced three-dimensional volume-targeted breath-hold MR angiography. *Radiology*, 219, 270--277.
- LI, D., DOLAN, R. P., WALOVITCH, R. C. & LAUFFER, R. B. 1998. Three-dimensional MRI of coronary arteries using an intravascular contrast agent. *Magn Reson Med*, 39, 1014--1018.
- LI, D., KAUSHIKKAR, S., HAACKE, E. M., WOODARD, P. K., DHAWALE, P. J., KROEKER, R. M., LAUB, G., KUGINUKI, Y. & GUTIERREZ, F. R. 1996. Coronary arteries: three-dimensional MR imaging with retrospective respiratory gating. *Radiology*, 201, 857-863.
- LI, D., PASCHAL, C. B., HAACKE, E. M. & ADLER, L. P. 1993. Coronary arteries: three-dimensional MR imaging with fat saturation and magnetization transfer contrast. *Radiology*, 187, 401-6.
- LIANG, H. D. & BLOMLEY, M. J. 2003. The role of ultrasound in molecular imaging. *Br J Radiol*, 76 Spec No 2, S140-50.
- LIBBY, P. 2002. Atherosclerosis: the new view. *Sci Am*, 286, 46--55.
- LIBBY, P., NAHRENDORF, M. & WEISSLEDER, R. 2010. Molecular imaging of atherosclerosis: a progress report. *Tex Heart Inst J*, 37, 324-7.
- LIPTON, M. J., HIGGINS, C. B., FARMER, D. & BOYD, D. P. 1984. Cardiac imaging with a high-speed Cine-CT Scanner: preliminary results. *Radiology*, 152, 579-82.
- LIU, X., BI, X., HUANG, J., JERECIC, R., CARR, J. & LI, D. 2008. Contrast-enhanced whole-heart coronary magnetic resonance angiography at 3.0 T: comparison with steady-state free precession technique at 1.5 T. *Invest Radiol*, 43, 663-8.

- LIU, Y. L., RIEDERER, S. J., ROSSMAN, P. J., GRIMM, R. C., DEBBINS, J. P. & EHMAN, R. L. 1993. A monitoring, feedback, and triggering system for reproducible breath-hold MR imaging. *Magn Reson Med*, 30, 507-511.
- LOOK, D. C. & LOCKER, D. R. 1970. Time Saving in Measurement of NMR and EPR Relaxation Times. *Rev Sci Instrum*, 41, 2.
- LU, B., MAO, S. S., ZHUANG, N., BAKHSHESHI, H., YAMAMOTO, H., TAKASU, J., LIU, S. C. & BUDOFF, M. J. 2001. Coronary artery motion during the cardiac cycle and optimal ECG triggering for coronary artery imaging. *Invest Radiol*, 36, 250-6.
- LUSTIG, M., DONOHO, D. & PAULY, J. M. 2007. Sparse MRI: The application of compressed sensing for rapid MR imaging. *Magn Reson Med*, 58, 1182-95.
- MACEDO, R., CHEN, S., LAI, S., SHEA, S., MALAYERI, A. A., SZKLO, M., LIMA, J. A. C. & BLUEMKE, D. A. 2008. MRI detects increased coronary wall thickness in asymptomatic individuals: the multi-ethnic study of atherosclerosis (MESA). *J Magn Reson Imaging*, 28, 1108--1115.
- MACGOWAN, C. K., KELLENBERGER, C. J., DETSKY, J. S., ROMAN, K. & YOO, S.-J. 2005. Real-time Fourier velocity encoding: an in vivo evaluation. *J Magn Reson Imaging*, 21, 297--304.
- MACLENNAN, R. N. 1993. Interrater Reliability with SPSS for Windows 5.0. *The American Statistician*, 47, 5.
- MAINTZ, D., AEPFELBACHER, F. C., KISSINGER, K. V., BOTNAR, R. M., DANIAS, P. G., HEINDEL, W., MANNING, W. J. & STUBER, M. 2004. Coronary MR angiography: comparison of quantitative and qualitative data from four techniques. *AJR Am J Roentgenol*, 182, 515--521.
- MAINTZ, D., OZGUN, M., HOFFMEIER, A., FISCHBACH, R., KIM, W. Y., STUBER, M., MANNING, W. J., HEINDEL, W. & BOTNAR, R. M. 2006. Selective coronary artery plaque visualization and differentiation by contrast-enhanced inversion prepared MRI. *Eur Heart J*, 27, 1732-6.
- MAINTZ, D., OZGUN, M., HOFFMEIER, A., QUANTE, M., FISCHBACH, R., MANNING, W. J., HEINDEL, W. & BOTNAR, R. M. 2007. Whole-heart coronary magnetic resonance angiography: value for the detection of coronary artery stenoses in comparison to multislice computed tomography angiography. *Acta Radiol*, 48, 967-73.
- MAKI, J. H., PRINCE, M. R., LONDY, F. J. & CHENEVERT, T. L. 1996. The effects of time varying intravascular signal intensity and k-space acquisition order on three-dimensional MR angiography image quality. *J Magn Reson Imaging*, 6, 642--651.
- MAKOWSKI, M. R., WIETHOFF, A. J., JANSEN, C. H. & BOTNAR, R. M. 2009. Molecular imaging with targeted contrast agents. *Top Magn Reson Imaging*, 20, 247-59.
- MALAYERI, A. A., MACEDO, R., LI, D., CHEN, S., BAHRAMI, H., LAI, S., LIMA, J. A. C. & BLUEMKE, D. A. 2009. Coronary vessel wall evaluation by magnetic resonance imaging in the multi-ethnic study of atherosclerosis: determinants of image quality. *J Comput Assist Tomogr*, 33, 1--7.
- MANI, V., BRILEY-SAEBO, K. C., ITSKOVICH, V. V., SAMBER, D. D. & FAYAD, Z. A. 2006. Gradient echo acquisition for superparamagnetic particles with positive contrast (GRASP): sequence characterization in membrane and glass superparamagnetic iron oxide phantoms at 1.5T and 3T. *Magn Reson Med*, 55, 126-35.
- MANI, V., ITSKOVICH, V. V., SZIMTENINGS, M., AGUINALDO, J. G., SAMBER, D. D., MIZSEL, G. & FAYAD, Z. A. 2004. Rapid extended coverage simultaneous multisection black-blood vessel wall MR imaging. *Radiology*, 232, 281-8.
- MANKE, D., NEHRKE, K. & BÖRNERT, P. 2003. Novel prospective respiratory motion correction approach for free-breathing coronary MR angiography using a patient-adapted affine motion model. *Magn Reson Med*, 50, 122-131.
- MANKE, D., NEHRKE, K., BÖRNERT, P., RÖSCH, P. & DÖSSEL, O. 2002a. Respiratory motion in coronary magnetic resonance angiography: a comparison of different motion models. *J Magn Reson Imaging*, 15, 661--671.
- MANKE, D., RÖSCH, P., NEHRKE, K., BÖRNERT, P. & DÖSSEL, O. 2002b. Model evaluation and calibration for prospective respiratory motion correction in coronary MR angiography based on 3-D image registration. *IEEE Trans Med Imaging*, 21, 1132--1141.
- MANNING, W. J. 2006. Cardiovascular magnetic resonance imaging. *Clin Cardiol*, 29, I34-48.
- MANNING, W. J., LI, W., BOYLE, N. G. & EDELMAN, R. R. 1993. Fat-suppressed breath-hold magnetic resonance coronary angiography. *Circulation*, 87, 94-104.
- MAO, S., LU, B., OUDIZ, R. J., BAKHSHESHI, H., LIU, S. C. & BUDOFF, M. J. 2000. Coronary artery motion in electron beam tomography. *J Comput Assist Tomogr*, 24, 253-8.

- MARCKMANN, P., SKOV, L., ROSSEN, K., DUPONT, A., DAMHOLT, M. B., HEAF, J. G. & THOMSEN, H. S. 2006. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol*, 17, 2359-62.
- MARKL, M., SCHNEIDER, B., HENNIG, J., PESCHL, S., WINTERER, J., KRAUSE, T. & LAUBENBERGER, J. 1999. Cardiac phase contrast gradient echo MRI: measurement of myocardial wall motion in healthy volunteers and patients. *Int J Card Imaging*, 15, 441-452.
- MARKS, B., MITCHELL, D. G. & SIMELARO, J. P. 1997. Breath-holding in healthy and pulmonary-compromised populations: effects of hyperventilation and oxygen inspiration. *J Magn Reson Imaging*, 7, 595-597.
- MATSUNAGA, E., TAKAYA, N., YOKOYAMA, T., AKIMOTO, Y., MIYAUCHI, K. & DAIDA, H. 2009. Relationship between coronary artery wall thickness measured by 64-slice multidetector computed tomography and cardiovascular risk factors. *Circ J*, 73, 681-5.
- MCALPINE, W. A. 1975. *Heart and coronary arteries : an anatomical atlas for clinical diagnosis, radiological investigation, and surgical treatment*, Berlin, Springer.
- MCCARTHY, R. M., SHEA, S. M., DESHPANDE, V. S., GREEN, J. D., PERELES, F. S., CARR, J. C., FINN, J. P. & LI, D. 2003. Coronary MR angiography: true FISP imaging improved by prolonging breath holds with preoxygenation in healthy volunteers. *Radiology*, 227, 283-288.
- MCCONNELL, M. V., KHASGIWALA, V. C., SAVORD, B. J., CHEN, M. H., CHUANG, M. L., EDELMAN, R. R. & MANNING, W. J. 1997a. Comparison of respiratory suppression methods and navigator locations for MR coronary angiography. *AJR Am J Roentgenol*, 168, 1369-1375.
- MCCONNELL, M. V., KHASGIWALA, V. C., SAVORD, B. J., CHEN, M. H., CHUANG, M. L., EDELMAN, R. R. & MANNING, W. J. 1997b. Prospective adaptive navigator correction for breath-hold MR coronary angiography. *Magn Reson Med*, 37, 148-152.
- MCLEISH, K., HILL, D. L. G., ATKINSON, D., BLACKALL, J. M. & RAZAVI, R. 2002. A study of the motion and deformation of the heart due to respiration. *IEEE Trans Med Imaging*, 21, 1142-1150.
- MCLEISH, K., KOZERKE, S., CRUM, W. R. & HILL, D. L. G. 2004. Free-breathing radial acquisitions of the heart. *Magn Reson Med*, 52, 1127-1135.
- METZ, S., BEER, A. J., SETTLES, M., PELISEK, J., BOTNAR, R. M., RUMMENY, E. J. & HEIDER, P. 2010. Characterization of carotid artery plaques with USPIO-enhanced MRI: assessment of inflammation and vascularity as in vivo imaging biomarkers for plaque vulnerability. *Int J Cardiovasc Imaging*.
- MEYER, C., HU, B. S., MACOVSKI, A. & NISHIMURA, D. G. 1998. Coronary vessel wall imaging. *Proc ISMRM, 6th Annual Meeting, Sydney, Australia*, 1, 1.
- MEYER, C. H., HU, B. S., NISHIMURA, D. G. & MACOVSKI, A. 1992. Fast spiral coronary artery imaging. *Magn Reson Med*, 28, 202-213.
- MEYER, C. H., PAULY, J. M., MACOVSKIAND, A. & NISHIMURA, D. G. 1990. Simultaneous spatial and spectral selective excitation. *Magnetic Resonance in Medicine*, 15, 287-304.
- MIAO, C., CHEN, S., MACEDO, R., LAI, S., LIU, K., LI, D., WASSERMAN, B. A., VOGEL-CLAUSSEN, J., LIMA, J. A. & BLUEMKE, D. A. 2009. Positive remodeling of the coronary arteries detected by magnetic resonance imaging in an asymptomatic population: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*, 53, 1708-15.
- MOORE, M. P., SPENCER, T., SALTER, D. M., KEARNEY, P. P., SHAW, T. R., STARKEY, I. R., FITZGERALD, P. J., ERBEL, R., LANGE, A., MCDICKEN, N. W., SUTHERLAND, G. R. & FOX, K. A. 1998. Characterisation of coronary atherosclerotic morphology by spectral analysis of radiofrequency signal: in vitro intravascular ultrasound study with histological and radiological validation. *Heart*, 79, 459-67.
- MOTOYAMA, S., KONDO, T., SARAI, M., SUGIURA, A., HARIGAYA, H., SATO, T., INOUE, K., OKUMURA, M., ISHII, J., ANNO, H., VIRMANI, R., OZAKI, Y., HISHIDA, H. & NARULA, J. 2007. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol*, 50, 319-26.
- MOTZ, J. T., FITZMAURICE, M., MILLER, A., GANDHI, S. J., HAKA, A. S., GALINDO, L. H., DASARI, R. R., KRAMER, J. R. & FELD, M. S. 2006. In vivo Raman spectral pathology of human atherosclerosis and vulnerable plaque. *J Biomed Opt*, 11, 021003.
- MOWATT, G., COOK, J. A., HILLIS, G. S., WALKER, S., FRASER, C., JIA, X. & WAUGH, N. 2008. 64-Slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: systematic review and meta-analysis. *Heart*, 94, 1386-93.

- NAGEL, E., BORNSTEDT, A., SCHNACKENBURG, B., HUG, J., OSWALD, H. & FLECK, E. 1999. Optimization of realtime adaptive navigator correction for 3D magnetic resonance coronary angiography. *Magn Reson Med*, 42, 408-411.
- NAGHAVI, M., LIBBY, P., FALK, E., CASSCELLS, S. W., LITOVSKY, S., RUMBERGER, J., BADIMON, J. J., STEFANADIS, C., MORENO, P., PASTERKAMP, G., FAYAD, Z., STONE, P. H., WAXMAN, S., RAGGI, P., MADJID, M., ZARRABI, A., BURKE, A., YUAN, C., FITZGERALD, P. J., SISCOVICK, D. S., DE KORTE, C. L., AIKAWA, M., AIRAKSINEN, K. E., ASSMANN, G., BECKER, C. R., CHESEBRO, J. H., FARB, A., GALIS, Z. S., JACKSON, C., JANG, I. K., KOENIG, W., LODDER, R. A., MARCH, K., DEMIROVIC, J., NAVAB, M., PRIORI, S. G., REKHTER, M. D., BAHR, R., GRUNDY, S. M., MEHRAN, R., COLOMBO, A., BOERWINKLE, E., BALLANTYNE, C., INSULL, W., JR., SCHWARTZ, R. S., VOGEL, R., SERRUYS, P. W., HANSSON, G. K., FAXON, D. P., KAUL, S., DREXLER, H., GREENLAND, P., MULLER, J. E., VIRMANI, R., RIDKER, P. M., ZIPES, D. P., SHAH, P. K. & WILLERSON, J. T. 2003a. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. *Circulation*, 108, 1772-8.
- NAGHAVI, M., LIBBY, P., FALK, E., CASSCELLS, S. W., LITOVSKY, S., RUMBERGER, J., BADIMON, J. J., STEFANADIS, C., MORENO, P., PASTERKAMP, G., FAYAD, Z., STONE, P. H., WAXMAN, S., RAGGI, P., MADJID, M., ZARRABI, A., BURKE, A., YUAN, C., FITZGERALD, P. J., SISCOVICK, D. S., DE KORTE, C. L., AIKAWA, M., JUHANI AIRAKSINEN, K. E., ASSMANN, G., BECKER, C. R., CHESEBRO, J. H., FARB, A., GALIS, Z. S., JACKSON, C., JANG, I. K., KOENIG, W., LODDER, R. A., MARCH, K., DEMIROVIC, J., NAVAB, M., PRIORI, S. G., REKHTER, M. D., BAHR, R., GRUNDY, S. M., MEHRAN, R., COLOMBO, A., BOERWINKLE, E., BALLANTYNE, C., INSULL, W., JR., SCHWARTZ, R. S., VOGEL, R., SERRUYS, P. W., HANSSON, G. K., FAXON, D. P., KAUL, S., DREXLER, H., GREENLAND, P., MULLER, J. E., VIRMANI, R., RIDKER, P. M., ZIPES, D. P., SHAH, P. K. & WILLERSON, J. T. 2003b. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation*, 108, 1664-72.
- NAHRENDORF, M., JAFFER, F. A., KELLY, K. A., SOSNOVIK, D. E., AIKAWA, E., LIBBY, P. & WEISSLEDER, R. 2006. Noninvasive vascular cell adhesion molecule-1 imaging identifies inflammatory activation of cells in atherosclerosis. *Circulation*, 114, 1504-11.
- NAIR, A., KUBAN, B. D., TUZCU, E. M., SCHOENHAGEN, P., NISSEN, S. E. & VINCE, D. G. 2002. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. *Circulation*, 106, 2200-6.
- NAYAK, K. S., LEE, H. L., HARGREAVES, B. A. & HU, B. S. 2007. Wideband SSFP: alternating repetition time balanced steady state free precession with increased band spacing. *Magn Reson Med*, 58, 931-8.
- NAYAK, K. S., PAULY, J. M., KERR, A. B., HU, B. S. & NISHIMURA, D. G. 2000. Real-time color flow MRI. *Magn Reson Med*, 43, 251-258.
- NEHRKE, K. & BÖRNERT, P. 2005. Prospective correction of affine motion for arbitrary MR sequences on a clinical scanner. *Magn Reson Med*, 54, 1130-1138.
- NEHRKE, K., BÖRNERT, P., MANKE, D. & BÖCK, J. C. 2001. Free-breathing cardiac MR imaging: study of implications of respiratory motion-initial results. *Radiology*, 220, 810-815.
- NEHRKE, K., BORNERT, P., MAZURKEWITZ, P., WINKELMANN, R. & GRASSLIN, I. 2006. Free-breathing whole-heart coronary MR angiography on a clinical scanner in four minutes. *J Magn Reson Imaging*, 23, 752-6.
- NGUYEN, T. D., NUVAL, A., MULUKUTLA, S. & WANG, Y. 2003. Direct monitoring of coronary artery motion with cardiac fat navigator echoes. *Magn Reson Med*, 50, 235-241.
- NGUYEN, T. D., SPINCEMAILLE, P., CHAM, M. D., WEINSAFT, J. W., PRINCE, M. R. & WANG, Y. 2008. Free-breathing 3D steady-state free precession coronary magnetic resonance angiography: Comparison of diaphragm and cardiac fat navigators. *J Magn Reson Imaging*, 28, 509-514.
- NGUYEN, T. D., SPINCEMAILLE, P., PRINCE, M. R. & WANG, Y. 2006. Cardiac fat navigator-gated steady-state free precession 3D magnetic resonance angiography of coronary arteries. *Magn Reson Med*, 56, 210-215.
- NISSEN, S. E., GURLEY, J. C., GRINES, C. L., BOOTH, D. C., MCCLURE, R., BERK, M., FISCHER, C. & DEMARIA, A. N. 1991. Intravascular ultrasound assessment of lumen size and wall morphology in normal subjects and patients with coronary artery disease. *Circulation*, 84, 1087-99.
- NISSEN, S. E., TUZCU, E. M., SCHOENHAGEN, P., BROWN, B. G., GANZ, P., VOGEL, R. A., CROWE, T., HOWARD, G., COOPER, C. J., BRODIE, B., GRINES, C. L. & DEMARIA, A. N. 2004. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA*, 291, 1071-80.

- NISSEN, S. E. & YOCK, P. 2001. Intravascular ultrasound: novel pathophysiological insights and current clinical applications. *Circulation*, 103, 604-16.
- NOBLE, N. M. I., BOUBERTAKH, R., RAZAVI, R. S. & HILL, D. L. G. 2005. Inter-breath-hold registration for the production of high resolution cardiac MR volumes. *Med Image Comput Comput Assist Interv Int Conf Med Image Comput Comput Assist Interv*, 8, 894-901.
- NOLL, D. C., NISHIMURA, D. G. & MACOVSKI, A. 1991. Homodyne detection in magnetic resonance imaging. *IEEE Trans Med Imaging*, 10, 154-63.
- ODILLE, F., CINDEA, N., MANDRY, D., PASQUIER, C., VUISSOZ, P. A. & FELBLINGER, J. 2008a. Generalized MRI reconstruction including elastic physiological motion and coil sensitivity encoding. *Magn Reson Med*, 59, 1401-11.
- ODILLE, F., PASQUIER, C., ABACHERLI, R., VUISSOZ, P. A., ZIENTARA, G. P. & FELBLINGER, J. 2007. Noise cancellation signal processing method and computer system for improved real-time electrocardiogram artifact correction during MRI data acquisition. *IEEE Trans Biomed Eng*, 54, 630-40.
- ODILLE, F., URIBE, S., BATCHELOR, P. G., PRIETO, C., SCHAEFFTER, T. & ATKINSON, D. 2010. Model-based reconstruction for cardiac cine MRI without ECG or breath holding. *Magn Reson Med*, 63, 1247-57.
- ODILLE, F., VUISSOZ, P. A., MARIE, P. Y. & FELBLINGER, J. 2008b. Generalized reconstruction by inversion of coupled systems (GRICS) applied to free-breathing MRI. *Magn Reson Med*, 60, 146-57.
- OEMRAWISINGH, P. V., MINTZ, G. S., SCHALIJ, M. J., ZWINDERMAN, A. H., JUKEMA, J. W. & WALL, E. E. V. D. 2003. Intravascular Ultrasound Guidance Improves Angiographic and Clinical Outcome of Stent Implantation for Long Coronary Artery Stenoses: Final Results of a Randomized Comparison With Angiographic Guidance (TULIP Study). *Circulation*, 107, 62-67.
- OSHINSKI, J. N., HOFLAND, L., DIXON, W. T. & PETTIGREW, R. I. 1998. Magnetic resonance coronary angiography using navigator echo gated real-time slice following. *Int J Card Imaging*, 14, 191-199.
- OSHINSKI, J. N., HOFLAND, L., MUKUNDAN, S., DIXON, W. T., PARKS, W. J. & PETTIGREW, R. I. 1996. Two-dimensional coronary MR angiography without breath holding. *Radiology*, 201, 737-743.
- OSMAN, N. F., KERWIN, W. S., MCVEIGH, E. R. & PRINCE, J. L. 1999. Cardiac motion tracking using CINE harmonic phase (HARP) magnetic resonance imaging. *Magn Reson Med*, 42, 1048-1060.
- OZOLANTA, I., TETERE, G., PURINYA, B. & KASYANOV, V. 1998. Changes in the mechanical properties, biochemical contents and wall structure of the human coronary arteries with age and sex. *Med Eng Phys*, 20, 523-33.
- PAGE, E., FOZZARD, H. A. & SOLARO, R. J. 2002. *Handbook of Physiology: Section 2 - The Cardiovascular system: Volume 1: The Heart*, Oxford University Press.
- PARKER, D. L., GOODRICH, K. C., MASIKER, M., TSURUDA, J. S. & KATZMAN, G. L. 2002. Improved efficiency in double-inversion fast spin-echo imaging. *Magn Reson Med*, 47, 1017-21.
- PAT, G. T., PAULY, J. M., HU, B. S. & NISHIMURA, D. G. 1998. One-shot spatially resolved velocity imaging. *Magn Reson Med*, 40, 603-613.
- PATWARI, P., WEISSMAN, N. J., BOPPART, S. A., JESSER, C., STAMPER, D., FUJIMOTO, J. G. & BREZINSKI, M. E. 2000. Assessment of coronary plaque with optical coherence tomography and high-frequency ultrasound. *Am J Cardiol*, 85, 641-4.
- PAULIN, S., VON SCHULTHESS, G. K., FOSSEL, E. & KRAYENBUEHL, H. P. 1987. MR imaging of the aortic root and proximal coronary arteries. *Am. J. Roentgenol.*, 148, 665-670.
- PEEL, S. A., HUSSAIN, T., GREIL, G., SCHAEFFTER, T. & BOTNAR, R. M. 2010. Local inversion spiral coronary vessel wall imaging: A comparison between 1.5T and 3T. *Proc ISMRM, 18th Annual Meeting, Stockholm, Sweden*, 3672.
- PENNELL, D. J. 2010. Cardiovascular magnetic resonance. *Circulation*, 121, 692-705.
- PENNELL, D. J., KEEGAN, J., FIRMIN, D. N., GATEHOUSE, P. D., UNDERWOOD, S. R. & LONGMORE, D. B. 1993. Magnetic resonance imaging of coronary arteries: technique and preliminary results. *Br Heart J*, 70, 315-26.
- PEPINE, C. J. 1998. The effects of angiotensin-converting enzyme inhibition on endothelial dysfunction: potential role in myocardial ischemia. *Am J Cardiol*, 82, 23S-27S.
- PETERSEN, S. E., JUNG, B. A., WIESMANN, F., SELVANAYAGAM, J. B., FRANCIS, J. M., HENNIG, J., NEUBAUER, S. & ROBSON, M. D. 2006. Myocardial tissue phase mapping with cine phase-contrast mr imaging: regional wall motion analysis in healthy volunteers. *Radiology*, 238, 816-826.

- PETITJEAN, C., ROUGON, N. & CLUZEL, P. 2005. Assessment of myocardial function: a review of quantification methods and results using tagged MRI. *J Cardiovasc Magn Reson*, 7, 501-516.
- PICANO, E., SANTORO, G. & VANO, E. 2007. Sustainability in the cardiac cath lab. *Int J Cardiovasc Imaging*, 23, 143-7.
- PIPE, J. G. 1999. Motion correction with PROPELLER MRI: application to head motion and free-breathing cardiac imaging. *Magn Reson Med*, 42, 963--969.
- PIPE, J. G. & ZWART, N. 2006. Turboprop: improved PROPELLER imaging. *Magn Reson Med*, 55, 380-5.
- PIZZUTO, F., VOCI, P., MARIANO, E., PUDDU, P. E., CHIAVARI, P. A. & ROMEO, F. 2003. Noninvasive coronary flow reserve assessed by transthoracic coronary Doppler ultrasound in patients with left anterior descending coronary artery stents. *Am J Cardiol*, 91, 522-6.
- PLEIN, S., JONES, T. R., RIDGWAY, J. P. & SIVANANTHAN, M. U. 2003. Three-dimensional coronary MR angiography performed with subject-specific cardiac acquisition windows and motion-adapted respiratory gating. *AJR Am J Roentgenol*, 180, 505--512.
- POHOST, G. M. 2000. *Imaging in cardiovascular disease*, Philadelphia ; London, Lippincott Williams & Wilkins.
- POLZIN, J. A., KOROSSEC, F. R., WEDDING, K. L., GRIST, T. M., FRAYNE, R., PETERS, D. C. & MISTRETTA, C. A. 1996. Effects of through-plane myocardial motion on phase-difference and complex-difference measurements of absolute coronary artery flow. *J Magn Reson Imaging*, 6, 113--123.
- POST, J. C., VAN ROSSUM, A. C., BRONZWAER, J. G. F., DE COCK, C. C., HOFMAN, M. B. M., VALK, J. & VISSER, C. A. 1995. Magnetic Resonance Angiography of Anomalous Coronary Arteries : A New Gold Standard for Delineating the Proximal Course? *Circulation*, 92, 3163-3171.
- POULEUR, A.-C., LE POLAIN DE WAROUX, J.-B. T., KEFER, J., PASQUET, A. S., VANOVERSCHELDE, J.-L. & GERBER, B. L. 2008. Direct Comparison of Whole-Heart Navigator-Gated Magnetic Resonance Coronary Angiography and 40- and 64-Slice Multidetector Row Computed Tomography to Detect the Coronary Artery Stenosis in Patients Scheduled for Conventional Coronary Angiography / CLINICAL PERSPECTIVE. *Circulation: Cardiovascular Imaging*, 1, 114-121.
- PRIEST, A. N., BANSMANN, P. M., KAUL, M. G., STORK, A. & ADAM, G. 2005. Magnetic resonance imaging of the coronary vessel wall at 3 T using an obliquely oriented reinversion slab with adiabatic pulses. *Magn Reson Med*, 54, 1115-22.
- PRIEST, A. N., BANSMANN, P. M., MULLERLEILE, K. & ADAM, G. 2007. Coronary vessel-wall and lumen imaging using radial k-space acquisition with MRI at 3 Tesla. *Eur Radiol*, 17, 339-46.
- PRINCE, J. L. & MCVEIGH, E. R. 1992. Motion estimation from tagged MR image sequences. *IEEE Trans Med Imaging*, 11, 238--249.
- PRUESSMANN, K. P., WEIGER, M., BÖRNERT, P. & BOESIGER, P. 2001. Advances in sensitivity encoding with arbitrary k-space trajectories. *Magn Reson Med*, 46, 638--651.
- PRUESSMANN, K. P., WEIGER, M., SCHEIDEGGER, M. B. & BOESIGER, P. 1999. SENSE: sensitivity encoding for fast MRI. *Magn Reson Med*, 42, 952--962.
- RABKIN, S. W. 2007. Epicardial fat: properties, function and relationship to obesity. *Obesity Reviews*, 8, 253-261.
- RAFFLENBEUL, W., URTHALER, F., RUSSELL, R. O., LICHTLEN, P. & JAMES, T. N. 1980. Dilation of coronary artery stenoses after isosorbide dinitrate in man. *Br Heart J*, 43, 546-9.
- RAPER, A. J., RICHARDSON, D. W., KONTOS, H. A. & PATTERSON, J. L. 1967. Circulatory responses to breath holding in man. *J Appl Physiol*, 22, 201-206.
- RAZAVI, R., HILL, D. L., KEEVIL, S. F., MIQUEL, M. E., MUTHURANGU, V., HEGDE, S., RHODE, K., BARNETT, M., VAN VAALS, J., HAWKES, D. J. & BAKER, E. 2003. Cardiac catheterisation guided by MRI in children and adults with congenital heart disease. *Lancet*, 362, 1877-82.
- RIGO, F. 2005. Coronary flow reserve in stress-echo lab. From pathophysiologic toy to diagnostic tool. *Cardiovasc Ultrasound*, 3, 8.
- RIGO, F., MURER, B., OSSENA, G. & FAVARETTO, E. 2008. Transthoracic echocardiographic imaging of coronary arteries: tips, traps, and pitfalls. *Cardiovasc Ultrasound*, 6, 7.
- ROES, S. D., KOROSGLOU, G., SCHÄR, M., WESTENBERG, J. J., VAN OSCH, M. J. P., DE ROOS, A. & STUBER, M. 2008. Correction for heart rate variability during 3D whole heart MR coronary angiography. *J Magn Reson Imaging*, 27, 1046--1053.
- ROFSKY, N. M. 2008. Nephrogenic systemic fibrosis: considerations for the cardiologist. *JACC Cardiovasc Imaging*, 1, 457-9.

- ROMER, T. J., BRENNAN, J. F., 3RD, PUPPELS, G. J., ZWINDERMAN, A. H., VAN DUINEN, S. G., VAN DER LAARSE, A., VAN DER STEEN, A. F., BOM, N. A. & BRUSCHKE, A. V. 2000. Intravascular ultrasound combined with Raman spectroscopy to localize and quantify cholesterol and calcium salts in atherosclerotic coronary arteries. *Arterioscler Thromb Vasc Biol*, 20, 478-83.
- ROSENFELD, D., PANFIL, S. L. & ZUR, Y. 1997. Design of adiabatic pulses for fat-suppression using analytic solutions of the Bloch equation. *Magn Reson Med*, 37, 793-801.
- RUMBERGER, J. A., SHEEDY, P. F., 2ND, BREEN, J. F., FITZPATRICK, L. A. & SCHWARTZ, R. S. 1996. Electron beam computed tomography and coronary artery disease: scanning for coronary artery calcification. *Mayo Clin Proc*, 71, 369-77.
- RUMBERGER, J. A., SIMONS, D. B., FITZPATRICK, L. A., SHEEDY, P. F. & SCHWARTZ, R. S. 1995. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. *Circulation*, 92, 2157-62.
- RYAN, T. J., FAXON, D. P., GUNNAR, R. M., KENNEDY, J. W., KING, S. B., 3RD, LOOP, F. D., PETERSON, K. L., REEVES, T. J., WILLIAMS, D. O., WINTERS, W. L., JR. & ET AL. 1988. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). *Circulation*, 78, 486-502.
- RYBICKI, F. J., OTERO, H. J., STEIGNER, M. L., VOROBIOF, G., NALLAMSHETTY, L., MITSOURAS, D., ERSOY, H., MATHER, R. T., JUDY, P. F., CAI, T., COYNER, K., SCHULTZ, K., WHITMORE, A. G. & DI CARLI, M. F. 2008. Initial evaluation of coronary images from 320-detector row computed tomography. *Int J Cardiovasc Imaging*, 24, 535-46.
- SAAM, T., KERWIN, W. S., CHU, B., CAI, J., KAMPSCHULTE, A., HATSUKAMI, T. S., ZHAO, X. Q., POLISSAR, N. L., NERADILEK, B., YARNYKH, V. L., FLEMMING, K., HUSTON, J., 3RD, INSULL, W., JR., MORRISETT, J. D., RAND, S. D., DEMARCO, K. J. & YUAN, C. 2005. Sample size calculation for clinical trials using magnetic resonance imaging for the quantitative assessment of carotid atherosclerosis. *J Cardiovasc Magn Reson*, 7, 799-808.
- SACHS, T. S., MEYER, C. H., HU, B. S., KOHLI, J., NISHIMURA, D. G. & MACOVSKI, A. 1994. Real-time motion detection in spiral MRI using navigators. *Magn Reson Med*, 32, 639--645.
- SACHS, T. S., MEYER, C. H., IRARRAZABAL, P., HU, B. S., NISHIMURA, D. G. & MACOVSKI, A. 1995. The diminishing variance algorithm for real-time reduction of motion artifacts in MRI. *Magn Reson Med*, 34, 412-422.
- SACHS, T. S., MEYER, C. H., PAULY, J. M., HU, B. S., NISHIMURA, D. G. & MACOVSKI, A. 2000. The real-time interactive 3-D-DVA for robust coronary MRA. *IEEE Trans Med Imaging*, 19, 73-79.
- SAKUMA, H. 2007. Magnetic resonance imaging for ischemic heart disease. *J Magn Reson Imaging*, 26, 3-13.
- SAKUMA, H., ICHIKAWA, Y., CHINO, S., HIRANO, T., MAKINO, K. & TAKEDA, K. 2006. Detection of coronary artery stenosis with whole-heart coronary magnetic resonance angiography. *J Am Coll Cardiol*, 48, 1946-50.
- SAKUMA, H., ICHIKAWA, Y., SUZAWA, N., HIRANO, T., MAKINO, K., KOYAMA, N., CAUTEREN, M. V. & TAKEDA, K. 2005. Assessment of coronary arteries with total study time of less than 30 minutes by using whole-heart coronary MR angiography. *Radiology*, 237, 316--321.
- SAKUMA, H., KAWADA, N., KUBO, H., NISHIDE, Y., TAKANO, K., KATO, N. & TAKEDA, K. 2001. Effect of breath holding on blood flow measurement using fast velocity encoded cine MRI. *Magn Reson Med*, 45, 346-348.
- SAMDARSHI, T. E., NANDA, N. C., GATEWOOD, R. P., JR., BALLAL, R. S., CHANG, L. K., SINGH, H. P., NATH, H., KIRKLIN, J. K. & PACIFICO, A. D. 1992. Usefulness and limitations of transesophageal echocardiography in the assessment of proximal coronary artery stenosis. *J Am Coll Cardiol*, 19, 572-80.
- SANDBORG, M., FRANSSON, S. G. & PETTERSSON, H. 2004. Evaluation of patient-absorbed doses during coronary angiography and intervention by femoral and radial artery access. *Eur Radiol*, 14, 653-8.
- SANO, K., KAWASAKI, M., ISHIHARA, Y., OKUBO, M., TSUCHIYA, K., NISHIGAKI, K., ZHOU, X., MINATOUGHU, S., FUJITA, H. & FUJIWARA, H. 2006. Assessment of vulnerable plaques causing acute coronary syndrome using integrated backscatter intravascular ultrasound. *J Am Coll Cardiol*, 47, 734-41.
- SCARBOROUGH, P., BHATNAGAR, P., WICKRAMASINGHE, K., SMOLINA, K., MITCHELL, C. & RAYNER, M. 2010. *Coronary heart disease statistics 2010 edition*, London, British Heart Foundation.

- SCHAAR, J. A., DE KORTE, C. L., MASTIK, F., BALDEWSING, R., REGAR, E., DE FEYTER, P., SLAGER, C. J., VAN DER STEEN, A. F. & SERRUYS, P. W. 2003. Intravascular palpography for high-risk vulnerable plaque assessment. *Herz*, 28, 488-95.
- SCHAAR, J. A., MULLER, J. E., FALK, E., VIRMANI, R., FUSTER, V., SERRUYS, P. W., COLOMBO, A., STEFANADIS, C., WARD CASSCELLS, S., MORENO, P. R., MASERI, A. & VAN DER STEEN, A. F. 2004. Terminology for high-risk and vulnerable coronary artery plaques. Report of a meeting on the vulnerable plaque, June 17 and 18, 2003, Santorini, Greece. *Eur Heart J*, 25, 1077-82.
- SCHAAR, J. A., VAN DER STEEN, A. F., MASTIK, F., BALDEWSING, R. A. & SERRUYS, P. W. 2006. Intravascular palpography for vulnerable plaque assessment. *J Am Coll Cardiol*, 47, C86-91.
- SCHÄR, M., KIM, W. Y., STUBER, M., BOESIGER, P., MANNING, W. J. & BOTNAR, R. M. 2003. The impact of spatial resolution and respiratory motion on MR imaging of atherosclerotic plaque. *J Magn Reson Imaging*, 17, 538-544.
- SCHOENHAGEN, P., WHITE, R. D., NISSEN, S. E. & TUZCU, E. M. 2003. Coronary imaging: angiography shows the stenosis, but IVUS, CT, and MRI show the plaque. *Cleve Clin J Med*, 70, 713-9.
- SCHOEPF, U. J., ZWERNER, P. L., SAVINO, G., HERZOG, C., KERL, J. M. & COSTELLO, P. 2007. Coronary CT angiography. *Radiology*, 244, 48-63.
- SCHROEDER, S., KOPP, A. F., BAUMBACH, A., MEISNER, C., KUETTNER, A., GEORG, C., OHNESORGE, B., HERDEG, C., CLAUSSEN, C. D. & KARSCH, K. R. 2001. Noninvasive detection and evaluation of atherosclerotic coronary plaques with multislice computed tomography. *J Am Coll Cardiol*, 37, 1430-5.
- SCHUETZ, G. M., ZACHAROPOULOU, N. M., SCHLATTMANN, P. & DEWEY, M. 2010. Meta-analysis: noninvasive coronary angiography using computed tomography versus magnetic resonance imaging. *Ann Intern Med*, 152, 167-77.
- SCHULTZ, C. L., ALFIDI, R. J., NELSON, A. D., KOPIWODA, S. Y. & CLAMPITT, M. E. 1984. The effect of motion on two-dimensional Fourier transformation magnetic resonance images. *Radiology*, 152, 117-121.
- SCHWITTER, J. 2006. Myocardial perfusion. *J Magn Reson Imaging*, 24, 953-63.
- SCOTT, A. D., KEEGAN, J. & FIRMIN, D. N. 2009. Motion in cardiovascular MR imaging. *Radiology*, 250, 331-351.
- SCOTT, A. D., KEEGAN, J. & FIRMIN, D. N. 2010. Cardiac and respiratory motion in MRI of the heart. *RAD Magazine*, 36, 2.
- SCOTT, A. D., KEEGAN, J. & FIRMIN, D. N. 2011a. Beat-to-beat respiratory motion correction with near 100% efficiency: A quantitative assessment using high resolution coronary artery imaging. *Magnetic Resonance Imaging*, In Press.
- SCOTT, A. D., KEEGAN, J. & FIRMIN, D. N. 2011b. High-resolution 3D coronary vessel wall imaging with near 100% respiratory efficiency using epicardial fat tracking: reproducibility and comparison with standard methods. *J Magn Reson Imaging*, 33, 77-86.
- SEGRS, D., WEINBERG, P. & KRAMS, R. 2008. Atherosclerosis: cell biology and lipoproteins--shear stress and inflammation in plaque formation: new evidence. *Curr Opin Lipidol*, 19, 627-8.
- SERFATY, J. M., YANG, X., AKSIT, P., QUICK, H. H., SOLAIYAPPAN, M. & ATALAR, E. 2000. Toward MRI-guided coronary catheterization: visualization of guiding catheters, guidewires, and anatomy in real time. *J Magn Reson Imaging*, 12, 590-594.
- SHAW, P. X., HORKKO, S., TSIMIKAS, S., CHANG, M. K., PALINSKI, W., SILVERMAN, G. J., CHEN, P. P. & WITZTUM, J. L. 2001. Human-derived anti-oxidized LDL autoantibody blocks uptake of oxidized LDL by macrophages and localizes to atherosclerotic lesions in vivo. *Arterioscler Thromb Vasc Biol*, 21, 1333-9.
- SHEA, S. M., DESHPANDE, V. S., CHUNG, Y. C. & LI, D. 2002. Three-dimensional true-FISP imaging of the coronary arteries: improved contrast with T2-preparation. *J Magn Reson Imaging*, 15, 597-602.
- SHEA, S. M., KROEKER, R. M., DESHPANDE, V., LAUB, G., ZHENG, J., FINN, J. P. & LI, D. 2001. Coronary artery imaging: 3D segmented k-space data acquisition with multiple breath-holds and real-time slab following. *J Magn Reson Imaging*, 13, 301-307.
- SHEA, S. M., WANG, C., BI, X., MACEDO, R., BLUEMKE, D. A. & LORENZ, C. H. Year. Optimisation of coronary wall imaging. In: 15th scientific meeting of the International Society for Magnetic Resonance in Medicine, 2007 Berlin. International Society for Magnetic Resonance in Medicine, 2475.
- SHECHTER, G., OZTURK, C., RESAR, J. R. & MCVEIGH, E. R. 2004. Respiratory motion of the heart from free breathing coronary angiograms. *IEEE Trans Med Imaging*, 23, 1046-1056.

- SHECHTER, G., RESAR, J. R. & MCVEIGH, E. R. 2006. Displacement and velocity of the coronary arteries: cardiac and respiratory motion. *IEEE Trans Med Imaging*, 25, 369-75.
- SHMUELI, K., THOMAS, D. L. & ORDIDGE, R. J. 2007. Design, construction and evaluation of an anthropomorphic head phantom with realistic susceptibility artifacts. *J Magn Reson Imaging*, 26, 202-7.
- SIMONETTI, O. P., FINN, J. P., WHITE, R. D., LAUB, G. & HENRY, D. A. 1996. "Black blood" T2-weighted inversion-recovery MR imaging of the heart. *Radiology*, 199, 49-57.
- SINKUS, R. & BÖRNERT, P. 1999. Motion pattern adapted real-time respiratory gating. *Magn Reson Med*, 41, 148-155.
- SIRCAR, S. 2008. *Principles of medical physiology*, Stuttgart ; New York, Thieme.
- SIROL, M., ITSKOVICH, V. V., MANI, V., AGUINALDO, J. G., FALLON, J. T., MISSEWITZ, B., WEINMANN, H. J., FUSTER, V., TOUSSAINT, J. F. & FAYAD, Z. A. 2004. Lipid-rich atherosclerotic plaques detected by gadofluorine-enhanced in vivo magnetic resonance imaging. *Circulation*, 109, 2890-6.
- SKINNER, J. S., SMEETH, L., KENDALL, J. M., ADAMS, P. C. & TIMMIS, A. 2010. NICE guidance. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. *Heart*, 96, 974-8.
- SLAVIN, G. S., RIEDERER, S. J. & EHMAN, R. L. 1998. Two-dimensional multishot echo-planar coronary MR angiography. *Magn Reson Med*, 40, 883-9.
- SMALL, W. C., NELSON, R. C. & BERNARDINO, M. E. 1993. Dual contrast enhancement of both T1- and T2-weighted sequences using ultrasmall superparamagnetic iron oxide. *Magn Reson Imaging*, 11, 645-54.
- SODICKSON, D. K. & MANNING, W. J. 1997. Simultaneous acquisition of spatial harmonics (SMASH): fast imaging with radiofrequency coil arrays. *Magn Reson Med*, 38, 591-603.
- SOMMER, T., HACKENBROCH, M., HOFER, U., SCHMIEDEL, A., WILLINEK, W. A., FLACKE, S., GIESEKE, J., TRABER, F., FIMMERS, R., LITT, H. & SCHILD, H. 2005. Coronary MR angiography at 3.0 T versus that at 1.5 T: initial results in patients suspected of having coronary artery disease. *Radiology*, 234, 718-25.
- SONES, F. N., SHIREY, E. K., PROUDFIT, W. L. & WESTCOTT, R. N. 1959. Cine-Coronary Arteriography. *Circulation*, 89, 2.
- SONG, H. K., WRIGHT, A. C., WOLF, R. L. & WEHRLI, F. W. 2002. Multislice double inversion pulse sequence for efficient black-blood MRI. *Magn Reson Med*, 47, 616-20.
- SOSNOVIK, D. E., NAHRENDORF, M. & WEISSELEDER, R. 2008. Magnetic nanoparticles for MR imaging: agents, techniques and cardiovascular applications. *Basic Res Cardiol*, 103, 122-30.
- SOULEN, R. L. & HIGGINS, C. B. 1985. Magnetic resonance imaging of the cardiovascular system. *Magn Reson Annu*, 27--43.
- SPRAGGINS, T. A. 1990. Wireless retrospective gating: application to cine cardiac imaging. *Magn Reson Imaging*, 8, 675-681.
- SPUENTRUP, E. & BOTNAR, R. M. 2006. Coronary magnetic resonance imaging: visualization of the vessel lumen and the vessel wall and molecular imaging of arteriothrombosis. *Eur Radiol*, 16, 1--14.
- SPUENTRUP, E., BOTNAR, R. M., WIETHOFF, A. J., IBRAHIM, T., KELLE, S., KATOH, M., OZGUN, M., NAGEL, E., VYMAZAL, J., GRAHAM, P. B., GUNTHER, R. W. & MAINTZ, D. 2008. MR imaging of thrombi using EP-2104R, a fibrin-specific contrast agent: initial results in patients. *Eur Radiol*, 18, 1995-2005.
- SPUENTRUP, E., BUECKER, A., KARASSIMOS, E., GÜNTHER, R. W. & STUBER, M. 2002a. Navigator-gated and real-time motion corrected free-breathing MR Imaging of myocardial late enhancement. *Rofo*, 174, 562--567.
- SPUENTRUP, E., BUECKER, A., KATOH, M., WIETHOFF, A. J., PARSONS, E. C., JR., BOTNAR, R. M., WEISSKOFF, R. M., GRAHAM, P. B., MANNING, W. J. & GUNTHER, R. W. 2005a. Molecular magnetic resonance imaging of coronary thrombosis and pulmonary emboli with a novel fibrin-targeted contrast agent. *Circulation*, 111, 1377-82.
- SPUENTRUP, E., KATOH, M., BUECKER, A., FAUSTEN, B., WIETHOFF, A. J., WILDBERGER, J. E., HAAGE, P., PARSONS, E. C., JR., BOTNAR, R. M., GRAHAM, P. B., VETTELSCHOSS, M. & GUNTHER, R. W. 2007a. Molecular MR imaging of human thrombi in a swine model of pulmonary embolism using a fibrin-specific contrast agent. *Invest Radiol*, 42, 586-95.
- SPUENTRUP, E., KATOH, M., BUECKER, A., MANNING, W. J., SCHAEFFTER, T., NGUYEN, T. H., KUHL, H. P., STUBER, M., BOTNAR, R. M. & GUNTHER, R. W. 2004. Free-breathing 3D steady-state free precession

- coronary MR angiography with radial k-space sampling: comparison with cartesian k-space sampling and cartesian gradient-echo coronary MR angiography--pilot study. *Radiology*, 231, 581-6.
- SPUENTRUP, E., KATOH, M., WIETHOFF, A. J., BUECKER, A., BOTNAR, R. M., PARSONS, E. C. & GUENTHER, R. W. 2007b. Molecular coronary MR imaging of human thrombi using EP-2104R, a fibrin-targeted contrast agent: experimental study in a swine model. *Rofo*, 179, 1166-73.
- SPUENTRUP, E., MANNING, W. J., BOTNAR, R. M., KISSINGER, K. V. & STUBER, M. 2002b. Impact of navigator timing on free-breathing submillimeter 3D coronary magnetic resonance angiography. *Magn Reson Med*, 47, 196--201.
- SPUENTRUP, E., RUEBBEN, A., MAHNKEN, A., STUBER, M., KOLKER, C., NGUYEN, T. H., GUNTHER, R. W. & BUECKER, A. 2005b. Artifact-free coronary magnetic resonance angiography and coronary vessel wall imaging in the presence of a new, metallic, coronary magnetic resonance imaging stent. *Circulation*, 111, 1019-26.
- STARY, H. C. 2000. Natural history and histological classification of atherosclerotic lesions: an update. *Arterioscler Thromb Vasc Biol*, 20, 1177-8.
- STARY, H. C., CHANDLER, A. B., GLAGOV, S., GUYTON, J. R., INSULL, W., JR., ROSENFELD, M. E., SCHAFFER, S. A., SCHWARTZ, C. J., WAGNER, W. D. & WISSLER, R. W. 1994. A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation*, 89, 2462-78.
- STEGMANN, M. B., OLAFSDÓTTIR, H. & LARSSON, H. B. W. 2005. Unsupervised motion-compensation of multi-slice cardiac perfusion MRI. *Med Image Anal*, 9, 394--410.
- STEHNING, C., BÖRNERT, P., NEHRKE, K. & DÖSSEL, O. 2005a. Free breathing 3D balanced FFE coronary magnetic resonance angiography with prolonged cardiac acquisition windows and intra-RR motion correction. *Magn Reson Med*, 53, 719--723.
- STEHNING, C., BORNERT, P., NEHRKE, K., EGGERS, H. & DOSSEL, O. 2004. Fast isotropic volumetric coronary MR angiography using free-breathing 3D radial balanced FFE acquisition. *Magn Reson Med*, 52, 197-203.
- STEHNING, C., BÖRNERT, P., NEHRKE, K., EGGERS, H. & STUBER, M. 2005b. Free-breathing whole-heart coronary MRA with 3D radial SSFP and self-navigated image reconstruction. *Magn Reson Med*, 54, 476--480.
- STEIN, P. D., BEEMATH, A., KAYALI, F., SKAF, E., SANCHEZ, J. & OLSON, R. E. 2006. Multidetector computed tomography for the diagnosis of coronary artery disease: a systematic review. *Am J Med*, 119, 203-16.
- STEIN, P. D., YAEKOUB, A. Y., MATTA, F. & SOSTMAN, H. D. 2008. 64-slice CT for diagnosis of coronary artery disease: a systematic review. *Am J Med*, 121, 715-25.
- STEINER, R. E., BYDDER, G. M., SELWYN, A., DEANFIELD, J., LONGMORE, D. B., KLIPSTEN, R. H. & FIRMIN, D. 1983. Nuclear magnetic resonance imaging of the heart. Current status and future prospects. *Br Heart J*, 50, 202--208.
- STONE, G. W., HODGSON, J. M., ST GOAR, F. G., FREY, A., MUDRA, H., SHEEHAN, H. & LINNEMEIER, T. J. 1997. Improved procedural results of coronary angioplasty with intravascular ultrasound-guided balloon sizing: the CLOUT Pilot Trial. Clinical Outcomes With Ultrasound Trial (CLOUT) Investigators. *Circulation*, 95, 2044-52.
- STONE, G. W., MOSES, J. W., ELLIS, S. G., SCHOFER, J., DAWKINS, K. D., MORICE, M. C., COLOMBO, A., SCHAMPAERT, E., GRUBE, E., KIRTANE, A. J., CUTLIP, D. E., FAHY, M., POCOCK, S. J., MEHRAN, R. & LEON, M. B. 2007. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med*, 356, 998-1008.
- STUBER, M., BARMET, C., TANDRI, H., DESAI, M., BOESIGER, P. & MANNING, W. J. 2004. The use of a highly spatially selective radio frequency pulse for coronary vessel wall imaging. *J Cardiovasc Magn Reson*, 6, 2.
- STUBER, M., BÖRNERT, P., SPUENTRUP, E., BOTNAR, R. M. & MANNING, W. J. 2002a. Selective three-dimensional visualization of the coronary arterial lumen using arterial spin tagging. *Magn Reson Med*, 47, 322--329.
- STUBER, M., BOTNAR, R. M., DANIAS, P. G., KISSINGER, K. V. & MANNING, W. J. 1999a. Submillimeter three-dimensional coronary MR angiography with real-time navigator correction: comparison of navigator locations. *Radiology*, 212, 579-587.

- STUBER, M., BOTNAR, R. M., DANIAS, P. G., MCCONNELL, M. V., KISSINGER, K. V., YUCEL, E. K. & MANNING, W. J. 1999b. Contrast agent-enhanced, free-breathing, three-dimensional coronary magnetic resonance angiography. *J Magn Reson Imaging*, 10, 790-9.
- STUBER, M., BOTNAR, R. M., FISCHER, S. E., LAMERICH, R., SMINK, J., HARVEY, P. & MANNING, W. J. 2002b. Preliminary report on in vivo coronary MRA at 3 Tesla in humans. *Magn Reson Med*, 48, 425-9.
- STUBER, M., BOTNAR, R. M., SPUNTRUP, E., KISSINGER, K. V. & MANNING, W. J. 2001. Three-dimensional high-resolution fast spin-echo coronary magnetic resonance angiography. *Magn Reson Med*, 45, 206--211.
- STUBER, M., GILSON, W. D., SCHAR, M., KEDZIOREK, D. A., HOFMANN, L. V., SHAH, S., VONKEN, E. J., BULTE, J. W. & KRAITCHMAN, D. L. 2007. Positive contrast visualization of iron oxide-labeled stem cells using inversion-recovery with ON-resonant water suppression (IRON). *Magn Reson Med*, 58, 1072-7.
- STUBER, M. & WEISS, R. G. 2007. Coronary magnetic resonance angiography. *J Magn Reson Imaging*.
- SUBRAMANIAN, S., JAFFER, F. A. & TAWAKOL, A. 2010. Optical molecular imaging in atherosclerosis. *J Nucl Cardiol*, 17, 135-44.
- SUSSMAN, M. S., STAINSBY, J. A., ROBERT, N., MERCHANT, N. & WRIGHT, G. A. 2002. Variable-density adaptive imaging for high-resolution coronary artery MRI. *Magn Reson Med*, 48, 753-764.
- TAKEMURA, A., SUZUKI, A., INABA, R., SONOBE, T., TSUCHIYA, K., OMURO, M. & KORENAGA, T. 2007. Utility of coronary MR angiography in children with Kawasaki disease. *AJR Am J Roentgenol*, 188, W534-9.
- TAMHANE, A. A. & ARFANAKIS, K. 2009. Motion correction in periodically-rotated overlapping parallel lines with enhanced reconstruction (PROPELLER) and turboprop MRI. *Magn Reson Med*, 62, 174-82.
- TANAKA, A., KAWASAKI, T., NOGUCHI, T., KOGA, S., HIRAMATSU, Y., FUKUYAMA, T. & KOGA, N. 2009a. Hyperintense plaque with noncontrast T1-weighted magnetic resonance coronary plaque imaging leading to acute coronary syndrome. *Circulation*, 120, 2400-1.
- TANAKA, M., TOMIYASU, K., FUKUI, M., AKABAME, S., KOBAYASHI-TAKENAKA, Y., NAKANO, K., KADONO, M., HASEGAWA, G., ODA, Y. & NAKAMURA, N. 2009b. Evaluation of characteristics and degree of remodeling in coronary atherosclerotic lesions by 64-detector multislice computed tomography (MSCT). *Atherosclerosis*, 203, 436-41.
- TANAKA, S., MORI, M., KITAZAKI, K., NAKAHIRA, K., NAKATSUKA, H., MAEDA, Y., MADONO, H., NAITO, Y., SUGIMORI, Y. & INOUE, Y. 2009c. Visualization of coronary arterial wall based on maximum intensity fusion of whole-heart MR angiograms and water suppression SPIR 3D T(1) TFE images. *Magn Reson Med Sci*, 8, 55-63.
- TAYLOR, A. M., JHOOTI, P., KEEGAN, J., SIMONDS, A. K. & PENNELL, D. J. 1999a. Magnetic resonance navigator echo diaphragm monitoring in patients with suspected diaphragm paralysis. *J Magn Reson Imaging*, 9, 69-74.
- TAYLOR, A. M., JHOOTI, P., WIESMANN, F., KEEGAN, J., FIRMIN, D. N. & PENNELL, D. J. 1997. MR navigator-echo monitoring of temporal changes in diaphragm position: implications for MR coronary angiography. *J Magn Reson Imaging*, 7, 629--636.
- TAYLOR, A. M., KEEGAN, J., JHOOTI, P., FIRMIN, D. N. & PENNELL, D. J. 1999b. Calculation of a subject-specific adaptive motion-correction factor for improved real-time navigator echo-gated magnetic resonance coronary angiography. *J Cardiovasc Magn Reson*, 1, 131-138.
- TAYLOR, A. M., KEEGAN, J., JHOOTI, P., GATEHOUSE, P. D., FIRMIN, D. N. & PENNELL, D. J. 2000. A comparison between segmented k-space FLASH and interleaved spiral MR coronary angiography sequences. *J Magn Reson Imaging*, 11, 394-400.
- TEIRSTEIN, P. S., SCHATZ, R. A., DENARDO, S. J., JENSEN, E. E. & JOHNSON, A. D. 1995. Angiographic versus angiographic detection of thrombus during coronary interventional procedures. *Am J Cardiol*, 75, 1083-7.
- TERASHIMA, M., NGUYEN, P. K., RUBIN, G. D., MEYER, C. H., SHIMAKAWA, A., NISHIMURA, D. G., EHARA, S., IRIBARREN, C., COURTNEY, B. K., GO, A. S., HLATKY, M. A., FORTMANN, S. P. & MCCONNELL, M. V. 2010. Right Coronary Wall MRI in the Older Asymptomatic ADVANCE Cohort: Positive Remodeling and Associations with Type 2 Diabetes and Coronary Calcium. *J Cardiovasc Magn Reson*, 12, 75.
- THOMPSON, R. B. & MCVEIGH, E. R. 2006. Cardiorespiratory-resolved magnetic resonance imaging: measuring respiratory modulation of cardiac function. *Magn Reson Med*, 56, 1301-1310.
- THOMSEN, H. S. 2006. Nephrogenic systemic fibrosis: A serious late adverse reaction to gadodiamide. *Eur Radiol*, 16, 2619-21.

- TISDALL, M. D., HESS, A. & VAN DER KOUWE, A. J. 2009. MPRAGE Using EPI Navigators for Prospective Motion Correction. *Proc ISMRM, 18th Annual Meeting, Stockholm, Sweden*, 4656.
- TOPOL, E. J. & CALIFF, R. M. 2007. *Textbook of cardiovascular medicine*, Philadelphia, Pa. ; London, Lippincott Williams & Wilkins.
- TRIVEDI, R. A., JM, U. K.-I., GRAVES, M. J., CROSS, J. J., HORSLEY, J., GODDARD, M. J., SKEPPER, J. N., QUARTEY, G., WARBURTON, E., JOUBERT, I., WANG, L., KIRKPATRICK, P. J., BROWN, J. & GILLARD, J. H. 2004. In vivo detection of macrophages in human carotid atheroma: temporal dependence of ultrasmall superparamagnetic particles of iron oxide-enhanced MRI. *Stroke*, 35, 1631-5.
- TSIMIKAS, S., SHORTAL, B. P., WITZTUM, J. L. & PALINSKI, W. 2000. In Vivo Uptake of Radiolabeled MDA2, an Oxidation-Specific Monoclonal Antibody, Provides an Accurate Measure of Atherosclerotic Lesions Rich in Oxidized LDL and Is Highly Sensitive to Their Regression. *Arterioscler Thromb Vasc Biol*, 20, 689-697.
- UNITED NATIONS. SCIENTIFIC COMMITTEE ON THE EFFECTS OF ATOMIC RADIATION. 2008. *Sources and effects of ionizing radiation : United Nations Scientific Committee on the Effects of Atomic Radiation : UNSCEAR 2008 report to the General Assembly, with scientific annexes*, New York, United Nations.
- URIBE, S., MUTHURANGU, V., BOUBERTAKH, R., SCHAEFFTER, T., RAZAVI, R., HILL, D. L. G. & HANSEN, M. S. 2007. Whole-heart cine MRI using real-time respiratory self-gating. *Magn Reson Med*, 57, 606-613.
- VAN ELDEREN, S. G., VERSLUIS, M. J., WEBB, A. G., WESTENBERG, J. J., DOORNBOS, J., SMITH, N. B., DE ROOS, A. & STUBER, M. 2009. Initial results on in vivo human coronary MR angiography at 7 T. *Magn Reson Med*, 62, 1379-84.
- VAN ELDEREN, S. G., VERSLUIS, M. J., WESTENBERG, J. J., AGARWAL, H., SMITH, N. B., STUBER, M., DE ROOS, A. & WEBB, A. G. 2010. Right coronary MR angiography at 7 T: a direct quantitative and qualitative comparison with 3 T in young healthy volunteers. *Radiology*, 257, 254-9.
- VELICAN, D. & VELICAN, C. 1981. Comparative study on age-related changes and atherosclerotic involvement of the coronary arteries of male and female subjects up to 40 years of age. *Atherosclerosis*, 38, 39-50.
- VILLARREAL, F. J., LEGRICE, I., POPE, A. & SMAILL, B. 2005. The Architecture of the Heart: Myocyte Organization and the Cardiac Extracellular Matrix. *Interstitial Fibrosis in Heart Failure*. Springer New York.
- VIRMANI, R., KOLODIE, F. D., BURKE, A. P., FARB, A. & SCHWARTZ, S. M. 2000. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*, 20, 1262-75.
- VOCI, P., BILOTTA, F., CARETTA, Q., MERCANTI, C. & MARINO, B. 1995. Papillary muscle perfusion pattern. A hypothesis for ischemic papillary muscle dysfunction. *Circulation*, 91, 1714-8.
- VOCI, P., PIZZUTO, F., MARIANO, E., PUDDU, P. E., CHIAVARI, P. A. & ROMEO, F. 2002. Measurement of coronary flow reserve in the anterior and posterior descending coronary arteries by transthoracic Doppler ultrasound. *Am J Cardiol*, 90, 988-91.
- VOCI, P., PIZZUTO, F., MARIANO, E., PUDDU, P. E., SARDELLA, G. & ROMEO, F. 2003. Usefulness of coronary flow reserve measured by transthoracic coronary Doppler ultrasound to detect severe left anterior descending coronary artery stenosis. *Am J Cardiol*, 92, 1320-4.
- WADA, N., WATANABE, N., YAMAURA, Y., NEISHI, Y., KOYAMA, Y., KAWAMOTO, T., AKASAKA, T. & YOSHIDA, K. 2005. Comparison of high-frequency two-dimensional transthoracic echocardiography versus intravascular ultrasound for evaluation of the left anterior descending coronary artery. *Am J Cardiol*, 96, 1746-9.
- WANG, J., GERRETSEN, S. C., MAKI, J. H., HERZKA, D. A., CHU, B., YARNYKH, V. L., YUAN, C. & LEINER, T. 2009. Robust and time-efficient black blood coronary vessel wall imaging at 3T using iMSDE. *Proc ISMRM, 17th Annual Meeting, Honolulu, Hawai'i, USA*, 1.
- WANG, S. J., HU, B. S., MACOVSKI, A. & NISHIMURA, D. G. 1991. Coronary angiography using fast selective inversion recovery. *Magn Reson Med*, 18, 417-23.
- WANG, Y., CHRISTY, P. S., KOROSSEC, F. R., ALLEY, M. T., GRIST, T. M., POLZIN, J. A. & MISTRETTA, C. A. 1995a. Coronary MRI with a respiratory feedback monitor: the 2D imaging case. *Magn Reson Med*, 33, 116--121.
- WANG, Y. & EHMAN, R. L. 2000. Retrospective adaptive motion correction for navigator-gated 3D coronary MR angiography. *J Magn Reson Imaging*, 11, 208-214.
- WANG, Y., GRIMM, R. C., FELMLEE, J. P., RIEDERER, S. J. & EHMAN, R. L. 1996a. Algorithms for extracting motion information from navigator echoes. *Magn Reson Med*, 36, 117-123.

- WANG, Y., GRIST, T. M., KOROSSEC, F. R., CHRISTY, P. S., ALLEY, M. T., POLZIN, J. A. & MISTRETTA, C. A. 1995b. Respiratory blur in 3D coronary MR imaging. *Magn Reson Med*, 33, 541--548.
- WANG, Y., RIEDERER, S. J. & EHMAN, R. L. 1995c. Respiratory motion of the heart: kinematics and the implications for the spatial resolution in coronary imaging. *Magn Reson Med*, 33, 713--719.
- WANG, Y., ROSSMAN, P. J., GRIMM, R. C., RIEDERER, S. J. & EHMAN, R. L. 1996b. Navigator-echo-based real-time respiratory gating and triggering for reduction of respiration effects in three-dimensional coronary MR angiography. *Radiology*, 198, 55-60.
- WANG, Y., VIDAN, E. & BERGMAN, G. W. 1999. Cardiac motion of coronary arteries: variability in the rest period and implications for coronary MR angiography. *Radiology*, 213, 751-758.
- WANG, Y., WATTS, R., MITCHELL, I., NGUYEN, T. D., BEZANSON, J. W., BERGMAN, G. W. & PRINCE, M. R. 2001a. Coronary MR angiography: selection of acquisition window of minimal cardiac motion with electrocardiography-triggered navigator cardiac motion prescanning-initial results. *Radiology*, 218, 580-585.
- WANG, Y. X., HUSSAIN, S. M. & KRESTIN, G. P. 2001b. Superparamagnetic iron oxide contrast agents: physicochemical characteristics and applications in MR imaging. *Eur Radiol*, 11, 2319-31.
- WEBER, O. M., MARTIN, A. J. & HIGGINS, C. B. 2003. Whole-heart steady-state free precession coronary artery magnetic resonance angiography. *Magn Reson Med*, 50, 1223--1228.
- WEBER, O. M., PUJADAS, S., MARTIN, A. J. & HIGGINS, C. B. 2004. Free-breathing, three-dimensional coronary artery magnetic resonance angiography: comparison of sequences. *J Magn Reson Imaging*, 20, 395--402.
- WEIGER, M., BÖRNERT, P., PROKSA, R., SCHÄFFTER, T. & HAASE, A. 1997. Motion-adapted gating based on k-space weighting for reduction of respiratory motion artifacts. *Magn Reson Med*, 38, 322-333.
- WEINMANN, H. J., BRASCH, R. C., PRESS, W. R. & WESBEY, G. E. 1984. Characteristics of gadolinium-DTPA complex: a potential NMR contrast agent. *Am. J. Roentgenol*, 142, 619-624.
- WEISSLEDER, R., ELIZONDO, G., WITTENBERG, J., RABITO, C. A., BENGELE, H. H. & JOSEPHSON, L. 1990. Ultrasmall superparamagnetic iron oxide: characterization of a new class of contrast agents for MR imaging. *Radiology*, 175, 489-493.
- WEISSLEDER, R. & NTZIACHRISTOS, V. 2003. Shedding light onto live molecular targets. *Nat Med*, 9, 123-8.
- WEISSLER, A. M., HARRIS, W. S. & SCHOENFELD, C. D. 1968. Systolic time intervals in heart failure in man. *Circulation*, 37, 149-159.
- WEISSTEIN, E. W. 2011. *Fourier Transform* [Online]. <http://mathworld.wolfram.com/FourierTransform.html>. [Accessed 12th February 2011].
- WESSELY, R., BOTNAR, R. M., VORPAHL, M., SCHWAIGER, M., SCHOMIG, A. & IBRAHIM, T. 2007. Images in cardiovascular medicine. Subacute thrombotic occlusion and spontaneous recanalization of the right coronary artery after percutaneous coronary intervention for ST-elevation myocardial infarction visualized by coronary angiography and cardiac magnetic resonance imaging. *Circulation*, 116, e78-80.
- WEST, R., ELLIS, G. & BROOKS, N. 2006. Complications of diagnostic cardiac catheterisation: results from a confidential inquiry into cardiac catheter complications. *Heart*, 92, 810-4.
- WEXLER, L., BRUNDAGE, B., CROUSE, J., DETRANO, R., FUSTER, V., MADDAHI, J., RUMBERGER, J., STANFORD, W., WHITE, R. & TAUBERT, K. 1996. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association. Writing Group. *Circulation*, 94, 1175-92.
- WIELOPOLSKI, P. A., VAN GEUNS, R. J., DE FEYTER, P. J. & OUDKERK, M. 1998. Breath-hold coronary MR angiography with volume-targeted imaging. *Radiology*, 209, 209-19.
- WILSON, P. W., D'AGOSTINO, R. B., LEVY, D., BELANGER, A. M., SILBERSHATZ, H. & KANNEL, W. B. 1998. Prediction of coronary heart disease using risk factor categories. *Circulation*, 97, 1837-47.
- WILSON, R. F., HOLIDA, M. D. & WHITE, C. W. 1986. Quantitative angiographic morphology of coronary stenoses leading to myocardial infarction or unstable angina. *Circulation*, 73, 286-93.
- WINTER, P. M., NEUBAUER, A. M., CARUTHERS, S. D., HARRIS, T. D., ROBERTSON, J. D., WILLIAMS, T. A., SCHMIEDER, A. H., HU, G., ALLEN, J. S., LACY, E. K., ZHANG, H., WICKLINE, S. A. & LANZA, G. M. 2006. Endothelial $\alpha(v)\beta3$ integrin-targeted fumagillin nanoparticles inhibit angiogenesis in atherosclerosis. *Arterioscler Thromb Vasc Biol*, 26, 2103-9.

- WORTHLEY, S. G., HELFT, G., FAYAD, Z. A., FUSTER, V., RODRIGUEZ, O. J., ZAMAN, A. G. & BADIMON, J. J. 2001. Cardiac gated breath-hold black blood MRI of the coronary artery wall: an in vivo and ex vivo comparison. *Int J Cardiovasc Imaging*, 17, 195--201.
- XIE, J., LAI, P., BHAT, H. & LI, D. 2010. Whole-heart coronary magnetic resonance angiography at 3.0T using short-TR steady-state free precession, vastly undersampled isotropic projection reconstruction. *J Magn Reson Imaging*, 31, 1230-5.
- YANG, G. Z., BURGER, P., PANTING, J., GATEHOUSE, P. D., RUECKERT, D., PENNELL, D. J. & FIRMIN, D. N. 1998a. Motion and deformation tracking for short-axis echo-planar myocardial perfusion imaging. *Med Image Anal*, 2, 285-302.
- YANG, G. Z., GATEHOUSE, P. D., KEEGAN, J., MOHIADDIN, R. H. & FIRMIN, D. N. 1998b. Three-dimensional coronary MR angiography using zonal echo planar imaging. *Magn Reson Med*, 39, 833-842.
- YANG, P. C., KERR, A. B., LIU, A. C., LIANG, D. H., HARDY, C., MEYER, C. H., MACOVSKI, A., PAULY, J. M. & HU, B. S. 1998c. New real-time interactive cardiac magnetic resonance imaging system complements echocardiography. *J Am Coll Cardiol*, 32, 2049--2056.
- YEON, S. B., SABIR, A., CLOUSE, M., MARTINEZCLARK, P. O., PETERS, D. C., HAUSER, T. H., GIBSON, C. M., NEZAFAT, R., MAINTZ, D., MANNING, W. J. & BOTNAR, R. M. 2007. Delayed-enhancement cardiovascular magnetic resonance coronary artery wall imaging: comparison with multislice computed tomography and quantitative coronary angiography. *J Am Coll Cardiol*, 50, 441-7.
- YOUN, H. J. & FOSTER, E. 2000. Transesophageal echocardiography (TEE) in the evaluation of the coronary arteries. *Cardiol Clin*, 18, 833-48.
- YUN, S. H., TEARNEY, G. J., VAKOC, B. J., SHISHKOV, M., OH, W. Y., DESJARDINS, A. E., SUTER, M. J., CHAN, R. C., EVANS, J. A., JANG, I. K., NISHIOKA, N. S., DE BOER, J. F. & BOUMA, B. E. 2006. Comprehensive volumetric optical microscopy in vivo. *Nat Med*, 12, 1429-33.
- ZERHOUNI, E. A., PARISH, D. M., ROGERS, W. J., YANG, A. & SHAPIRO, E. P. 1988. Human heart: tagging with MR imaging-a method for noninvasive assessment of myocardial motion. *Radiology*, 169, 59-63.
- ZHANG, S., RAFIE, S., CHEN, Y., HILLENBRAND, C. M., WACKER, F. K., DUERK, J. L. & LEWIN, J. S. 2006. In vivo cardiovascular catheterization under real-time MRI guidance. *J Magn Reson Imaging*, 24, 914-7.
- ZUR, Y., STOKAR, S. & BENDEL, P. 1988. An analysis of fast imaging sequences with steady-state transverse magnetization refocusing. *Magn Reson Med*, 6, 175-93.
- ZWICKY, P., DANIEL, W. G., MUGGE, A. & LICHTLEN, P. R. 1988. Imaging of coronary arteries by color-coded transesophageal Doppler echocardiography. *Am J Cardiol*, 62, 639-40.

Appendix A: Publications arising

The published papers below (excluding the final paper – “Non-invasive detection of coronary artery wall thickening with age in healthy subjects using high resolution magnetic resonance imaging with beat-to-beat respiratory motion correction” which is *in press* at the time of publishing this thesis) are included in the supplementary material.

- Scott AD, Keegan J, Firmin D. Motion in cardiovascular MRI. *Radiology* 2009. 250; 331-351.
 - See section 1.c and chapter 2.
- Scott AD, Keegan J, Firmin D. Cardiac and respiratory motion in MRI of the heart. *Rad Magazine* March 2010.
- Scott AD, Keegan J, Firmin D. High resolution 3D magnetic resonance coronary vessel wall imaging with near 100% respiratory efficiency using epicardial fat tracking: reproducibility and comparison with standard methods. *Journal of Magnetic Resonance Imaging* 2011. 33; 77-86.
 - See chapter 6.
- Scott AD, Keegan J, Firmin D. Beat-to-beat respiratory motion correction with near 100% efficiency: A quantitative assessment using high resolution coronary artery imaging. *Magnetic Resonance Imaging* 2011. 29; 568-578.
 - See chapter 5.
- Scott AD, Keegan J, Mohiaddin RH, Firmin D. Non-invasive detection of coronary artery wall thickening with age in healthy subjects using high resolution magnetic resonance imaging with beat-to-beat respiratory motion correction. *Journal of Magnetic Resonance Imaging* 2011. In press.
 - See chapter 7.

Appendix B: Conference presentations and posters arising

Presentations

- Scott AD, Keegan J, Firmin D. High resolution 3D coronary vessel wall imaging with near 100% respiratory efficiency using epicardial fat tracking: Reproducibility and comparison with standard methods. ISMRM 2011, Montreal, Canada. Abstract 930.
 - See chapter 6.
- Scott AD, Keegan J, Firmin D. Reproducibility of coronary vessel wall imaging techniques. In: Proc Society of Cardiovascular Magnetic Resonance Imaging 2011, Nice.
 - See chapter 6.
- Scott AD, Keegan J, Mohiaddin RH, Firmin D. MRI detects coronary vessel wall thickening with age in healthy subjects. In: Proc Society of Cardiovascular Magnetic Resonance Imaging 2011, Nice.
 - See chapter 7.
- Scott AD, Keegan J, Firmin D. Development of a highly efficient and reproducible 3D technique for: Magnetic resonance coronary artery vessel wall imaging. National Heart and Lung Institute Postgraduate Research Day. Imperial College London 2010.
- Scott AD, Keegan J, Firmin D. Respiratory motion correction in coronary MR imaging using epicardial fat. In: Proc Bioengineering 08, London 2008. p 90.
- Scott AD, Keegan J, Firmin D. Non-model based respiratory motion correction in coronary vessel wall imaging. In: Proc Study and treatment of cardiovascular disease: devices and fluidics – UK Focus for Biomedical Engineering – The Royal Academy of Engineering, London 2008. p 27.

Posters

- Scott AD, Keegan J, Firmin D. Simultaneous left and right coronary artery wall imaging with highly efficient beat-to-beat respiratory motion correction. ISMRM 2011, Montreal, Canada. Abstract 1957.
 - See section 8.c.
- Scott AD, Keegan J, Mohiaddin RH, Firmin D. MR detects coronary vessel wall imaging with age in healthy subjects. ISMRM 2011, Montreal, Canada. Abstract 2676.
 - See section 7.
- Scott AD, Keegan J, Firmin D. Simultaneous 3D left and right coronary artery vessel wall imaging. In: Proc Society of Cardiovascular Magnetic Resonance Imaging 2011, Nice.
 - See section 8.c.
- Scott AD, Keegan J, Firmin D. High resolution 3D spiral coronary vessel wall imaging with >99% respiratory efficiency using beat to beat respiratory motion correction: quantitative comparison with navigator gated 2D spiral and turbo spin echo imaging. In: Proc ISMRM 2010, Stockholm, Sweden. Abstract 3383.
 - See chapter 6.
- Scott AD, Keegan J, Firmin D. High resolution, free-breathing coronary artery imaging with >99% respiratory efficiency: comparing beat to beat respiratory motion correction with navigator gating. In: Proc ISMRM 2010, Stockholm, Sweden. Abstract 3648.
 - See chapter 5.
- Scott AD, Keegan J, Firmin D. Beat-to-beat respiratory motion correction for coronary vessel wall imaging: a quantitative comparison with standard diaphragmatic navigator gating. In: Proc ISMRM Workshop on Current Concepts of Motion Correction for MRI & MRS 2010, Kitzbühel, Austria.
 - See chapter 6.
- Scott AD, Keegan J, Firmin D. High resolution, free-breathing coronary artery imaging with >99% respiratory efficiency. In: Proc Society of Cardiovascular Magnetic Resonance Imaging 2010, Phoenix. p 35.
 - See chapter 5.
- Scott AD, Keegan J, Firmin D. Design and validation of an accurate, reproducible and MR compatible respiratory motion phantom for use in coronary artery and general MR imaging. In: Proc ISMRM 2009, Honolulu. Abstract 2572.
 - See chapter 4.
- Scott AD, Keegan J, Firmin D. Beat-to-beat respiratory motion correction for coronary vessel wall imaging: a quantitative comparison with standard diaphragmatic navigator gating. The Philip Poole-Wilson Symposium, National Heart and Lung Institute. Imperial College London 2010.
 - See chapter 6.

- Scott AD, Keegan J, Firmin D. BREATHATRON: Design and validation of an accurate, reproducible and MR compatible respiratory motion phantom for use in coronary artery and general MR imaging. The Hounsfield Lecture, Imperial College, London 2009.
 - See chapter 4.
- Scott AD, Keegan J, Firmin D. Advances in respiratory motion correction using 3D spiral fat navigators: 3D coronary vessel wall imaging in less than 5 minutes. The Hounsfield Lecture, Imperial College, London 2009.
 - See chapter 3.
- Scott AD, Keegan J, Firmin D, The Optimum Gridding Algorithm for Multiple Interleaf Spiral Magnetic Resonance Imaging, The Hounsfield Lecture, Imperial College, London 2008. Poster.