Cardiovascular Magnetic Resonance Imaging Assessment of the Acute and Chronic Haemodynamics of Right Ventricular Pacing

Christopher Edward Debedick Saunderson

Submitted in accordance with the requirements for the degree of Doctor of Medicine (MD)

The University of Leeds

Faculty of Medicine and Health

Leeds Institute of Cardiovascular and Metabolic Medicine

March 2020

Intellectual Property and Publication Statements

The candidate confirms that the work is his own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

This copy has been supplied on the understanding that it is copyright material and that no quotation from the thesis may be published without proper acknowledgement

Publications arising from this work

Abstracts:

1. Saunderson CED, Gierula J, Paton MF, Brown LAE, Chew PG, Das A, Levelt E, Dall'Armellina E, Witte KK, Greenwood JP, Plein S, Swoboda PP. Assessment of acute haemodynamic effects of forced right ventricular pacing by cardiovascular magnetic resonance in patients with and without left ventricular scar. Oral presentation at SCMR 2019 Seattle February 2019.

2. Saunderson CED, Paton MF, Gierula J, Brown LAE, Chew PG, Das A, Craven TP, Jain M, Levelt E, Dall'Armellina E, Witte KK, Greenwood JP, Plein S, Swoboda PP. Prevalence and distribution of cardiac fibrosis in patients with atrioventricular block undergoing pacemaker implantation. Eur Heart J Cardiovasc Imaging Jun 2019, 20 (Suppl 2). Oral presentation at EuroCMR 2019 Venice May 2019.

3. Saunderson CED, Paton MF, Gierula J, Brown LAE, Das A, Chew PG, Craven TP, Kelly C, Witte KK, Greenwood JP, Plein S, Swoboda PP, Garg P. Feasibility and validation of four-dimensional flow cardiovascular magnetic resonance imaging in patients with MRI conditional pacemakers. Poster presentation at British Chapter ISMRN Sheffield September 2019.

4. Saunderson CED, Paton MF, Gierula J, Brown LAE, Chew PG, Das A, Craven TP, Koshy A, Levelt E, Dall'Armellina E, Witte KK, Greenwood JP, Plein S, Swoboda PP. Prevalence and distribution of cardiac fibrosis in patients with atrioventricular block undergoing pacemaker implantation. Poster presentation at HRC 2019 Birmingham October 2019.

Acknowledgements

The work in this thesis would not have been possible without the support of multiple other people. First and foremost I would like to express my appreciation to all my supervisors Dr Peter Swoboda, Professor Sven Plein and Professor John Greenwood. Their leadership and guidance throughout my time at Leeds has been fantastic and is certainly something I will try and replicate during my career. Particular thanks must go to Dr Swoboda without whom the publication of this thesis would never have been possible. His knowledge, enthusiasm and patience have kept me focused and motivated even in the most challenging times.

I have truly enjoyed my time working with the multi-disciplinary team in the University Of Leeds CMR Department. I have loved meeting and working with everyone in the department and forged many new friendships along the way. I would specifically like to thank my fellow colleagues Drs Brown, Chew, Sengupta, Craven, Das, Foley, Jain and Chowdhary for their help with analysis, recruitment and generally making it a fun place to work. Special thanks to my 'buddy' Dr Louise Brown for her help with statistics and always helping me to endure the more challenging periods of clinical research and Dr Sengupta for his proof reading services. Additional thanks go to former fellow Dr Garg whose tireless help with 4D flow analysis and interpretation has been second to none, a truly inspirational and enthusiastic academic. I must not forget to thank Maria Paton and John Gierula for the huge amount of support they gave me with endless things but especially for giving up their own precious academic time to facilitate my research. Finally I would like to thank the clinical team at Leeds General Infirmary for helping in the recruitment of patients to the study.

I am eternally grateful to the research nurses Petra, Hannah and Fiona for always going above and beyond to help with everything but not least writing ethics, assisting with recruitment and ensuring my patients always made it home safely. Furthermore none of this would have been possible without the expertise, patience and flexibility of the excellent radiographers and assistants within the department: Gavin, Margaret, Lisa, Debbie, Dave, Georgina, Caroline, Faz and Julian.

The greatest thanks of all go to the patients who participated in this research project who spared their precious time to help others and expand our knowledge in this field.

Lastly, I would like to acknowledge my parents for their constant encouragement and instilling me with a solid work ethic. In conjunction with my parents-in-law they have also provided hours of free childcare to enable me write up. My children Ethan and Olivia for always putting a smile on my face, teaching me to enjoy the moment and keeping this all-consuming thesis in perspective. Finally my wife Sally for literally everything she does for me, I don’t think any of this work would have been possible without her love and support.

Table of Contents

Intellectual Property and Publication Statements ii

Publications arising from this work..... iii

Acknowledgements iv

Table of Contents..... vi

List of Figures xi

List of Tables..... xiii

List of Equations..... xv

Abbreviations..... xvi

Abstract xx

Chapter 1 Cardiac magnetic resonance imaging in patients with cardiovascular implantable electronic devices: risks, safety and image optimisation .. 22

1.1 Potential hazards of imaging cardiovascular implanted electronic devices 23

1.1.1 Torque effect 23

1.1.2 Heating effect 23

1.1.3 Electromechanical effects..... 24

1.2 MRI conditional devices..... 25

1.3 Imaging Artefacts 33

1.4 Image optimisation in patients with CIEDs undergoing CMR 33

1.4.1 Pre-scan considerations 33

1.4.2 Imaging sequences 36

1.5 Conclusion 41

Chapter 2 Pacing Induced Cardiomyopathy: Pathophysiology, Treatment and the Role of Imaging..... 43

2.1 Introduction 43

2.2 Pathophysiology of adverse effects of RV pacing 44

2.2.1 Animal work evaluating RV pacing 45

2.2.2 Effects of RV pacing in humans..... 47

2.3 Incidence of Pacemaker Induced Cardiomyopathy..... 48

2.4 Risk factors for pacing-induced cardiomyopathy and development of heart failure 54

2.4.1 Pre-implantation factors..... 54

2.4.2 Post implantation factors 55

2.5 Prognosis of PICM 58

2.6 Therapeutic options for prevention or treatment of pacing-induced cardiomyopathy 59
2.6.1 Biventricular Pacing 59
2.6.2 Alternate pacing sites 65
2.6.3 Ventricular pacing avoidance algorithms 67
2.6.4 Medications 67
2.7 Current recommendations for physiological pacing 68
2.8 Role of imaging in identification and risk stratification of PICM 72
2.8.1 Echocardiography 72
2.8.2 Cardiovascular Magnetic Resonance 73
2.9 Conclusions 85
Chapter 3 Feasibility and validation of four-dimensional flow cardiovascular magnetic resonance imaging in pacemaker recipients 87
3.1 Abstract 87
3.2 Introduction 88
3.3 Methods 89
3.3.1 Study Population 89
3.3.2 Device Programming 89
3.3.3 Cardiovascular Magnetic Resonance 89
3.3.4 Image Acquisition 90
3.3.5 Image Analysis 90
3.3.6 Statistical analysis 92
3.4 Results 93
3.4.1 Patient Characteristics 93
3.4.2 Safety and device parameters 94
3.4.3 Baseline Cardiac MRI data 95
3.4.4 Image quality assessments 96
3.4.5 Tricuspid flow quantification - with/without inclusion of pacemaker lead artefact 98
3.4.6 Consistency of 4D Flow Derived Flow Volume Assessment 98
3.4.7 Comparison of Cine and 4D flow derived valvular stroke volumes 100
3.5 Discussion 104
3.5.1 Safety 104
3.5.2 Image Quality and Qualitative Assessment of Flow 104
3.5.3 Quantitative assessment of transvalvular flow 106
3.5.4 Clinical Applications 107
3.5.5 Possible Future Applications 107

3.5.6 Limitations 108
3.6 Conclusion 109
Chapter 4 Impact of myocardial fibrosis on ventricular performance during intrinsic atrioventricular conduction and forced right ventricular pacing 110
4.1 Abstract 110
4.2 Introduction 111
4.3 Methods 113
4.3.1 Study Population 113
4.3.2 Ethics Approval 117
4.3.3 Device Programming 117
4.3.4 Cardiovascular Magnetic Resonance 119
4.3.5 Image Acquisition 120
4.3.6 Image Analysis 121
4.3.7 Statistical analysis 128
4.4 Results 128
4.4.1 Demographic characteristics 128
4.4.2 Patient characteristics according to LGE status 132
4.4.3 Differences between AOO and DOO pacing modes 140
4.4.4 Absolute change between pacing modes according to LGE status 144
4.4.5 4D flow derived LV kinetic energy 147
4.4.6 Device parameters 151
4.5 Discussion 152
4.5.1 Influence of myocardial fibrosis on left ventricular volumes during forced RV pacing 152
4.5.2 Influence of myocardial fibrosis on right ventricular volumes during forced RV pacing 154
4.5.3 Effect of Pacing on Electromechanical Synchrony and Strain 155
4.5.4 Left Ventricular Kinetic Energy 156
4.5.5 Safety and feasibility 157
4.5.6 Limitations 157
4.5.7 Future implications 158
4.6 Conclusions 159
Chapter 5 Impact of myocardial fibrosis on long term ventricular remodelling in patients with atrioventricular block undergoing permanent pacemaker implantation 160
5.1 Abstract 160

5.2 Introduction 161
5.3 Methods 163
5.3.1 Study Design and Population 163
5.3.2 Primary Endpoint.....165
5.3.3 Ethics Approval 167
5.3.4 Device Programming.....167
5.3.5 Quality of Life assessment 168
5.3.6 Cardiovascular Magnetic Resonance 168
5.3.7 Image Acquisition.....169
5.3.8 Image Analysis.....170
5.3.9 Statistical analysis.....173
5.4 Results.....174
5.4.1 Baseline characteristics.....174
5.4.2 Baseline CMR data 177
5.4.3 Device and pacing characteristics 181
5.4.4 Electrocardiographic characteristics 186
5.4.5 Changes in CMR parameters between baseline and follow up....186
5.4.6 Contractility, dyssynchrony and strain 200
5.4.7 Predictors of change in LVESVi 202
5.4.8 Quality of life and NYHA Class.....204
5.4.9 Adverse events 206
5.4.10 Device parameters 207
5.5 Discussion.....209
5.5.1 Left Ventricular End-Systolic Volume after right ventricular pacing in patients with and without myocardial fibrosis.....210
5.5.2 Left ventricular volumes and function after right ventricular pacing in patients with myocardial fibrosis.....210
5.5.3 Left and right ventricular volumes after right ventricular pacing in entire cohort 211
5.5.4 Electromechanical dyssynchrony and left ventricular contractility after right ventricular pacing in patients with myocardial fibrosis.....213
5.5.5 Effect of distribution and burden of myocardial fibrosis on change in left ventricular volumes and function 214
5.5.6 NYHA Class, Quality of Life and Adverse events after pacemaker implantation.....215
5.5.7 Prevalence of myocardial fibrosis.....216
5.5.8 Feasibility of imaging in patients with bradycardia and permanent pacemakers 217

5.5.9 Device Safety 217
5.5.10 Limitations 217
5.5.11 Future implications 218
5.6 Conclusion 220
Chapter 6 Short and long term effects of right ventricular pacing in patients with myocardial fibrosis 221
6.1 Acute and chronic effect of right ventricular apical pacing in patients with myocardial fibrosis 222
6.1.1 Left Ventricular End-Systolic Volume 225
6.1.2 Left Ventricular End-Diastolic Volume 226
6.1.3 Discussion 227
6.2 Comparison to clinical trials evaluating RV pacing 229
6.2.1 Left Ventricular End-Systolic Volume 232
6.2.2 Left Ventricular End-Diastolic Volume 232
6.2.3 Left Ventricular Ejection Fraction 233
6.3 Impact of Research Findings 233
6.3.1 Limitations 234
6.3.2 Clinical Impact 235
6.3.3 Future implications 236
6.4 Conclusion 237
References 239
Appendix 260
Ethical approval, Patient information sheets and consent form for Chapters 3 and 4 260
Clinical and CMR parameters of patients excluded from analysis in Chapter 4 286
Ethical approval, Patient information sheets and consent form for Chapter 5 287

List of Figures

Figure 1-1: MR Item Safety Classification System 25

Figure 1-2: Effect of arm positioning on image quality at 1.5T.....35

Figure 1-3: Effect of cine imaging sequence on image quality in patients with ICDs. 38

Figure 1-4: T2 STIR acquisition in a patient with a pacemaker.....38

Figure 1-5: Mid ventricular short axis perfusion acquisitions in a patient with an ICD at 1.5T. 39

Figure 1-6: Late gadolinium enhancement images in a patient with an ICD....41

Figure 1-7: Suggested algorithm for CMR imaging in patients with CIEDs. 42

Figure 2-1: Proposed Mechanism of Pacing Induced Cardiomyopathy.....45

Figure 2-2: Strain traces of left ventricular walls during RV pacing. 46

Figure 2-3: Factors implicated in development of pacing induced cardiomyopathy and potential effect of upfront physiological pacing ...57

Figure 2-4: Proposed CMR scan protocol in patients with pacemakers and/or ICDs to evaluate mechanisms underlying PICM.....75

Figure 2-5: CMR images in patients with cardiac implantable electronic devices. 77

Figure 2-6: CMR Feature tracking images in a patient with a pacemaker.....79

Figure 2-7: Late Gadolinium Enhanced Images in patients with CIEDs.....81

Figure 2-8: Parametric mapping in a patient with a pacemaker. 83

Figure 3-1: Example of how valvular flow contours were segmented on the phase contrast multiplanar reconstruction.....92

Figure 3-2: Qualitative assessment of flow in the raw data prior to valvular plane reconstruction.....97

Figure 3-3: Scatter plots of aortic stroke volume (SV) against mitral and tricuspid SV for AOO and DOO pacing modes to investigate consistency between methods.....99

Figure 3-4: Bland Altman analysis for the assessment of aortic stroke volume (SV) against mitral and tricuspid SV for AOO and DOO pacing modes.100

Figure 3-5: Comparison of valvular flow to left ventricular short-axis cine stroke volume. 101

Figure 3-6: 4D flow velocity vectors. 105

Figure 4-1: Short axis cine images in patients with implantable cardioverter defibrillators. 114

Figure 4-2: Patient recruitment pathway 116

Figure 4-3: Study protocol 118

Figure 4-4: Vertical long axis SSFP acquisition in a patient with an implant cardioverter defibrillator.....119

Figure 4-5: Late gadolinium enhancement phase sensitive inversion recovery sequences in a patient with an ICD. 121

Figure 4-6: Short axis late gadolinium enhancement images in study patients. 123

Figure 4-7: Calculation of global longitudinal strain and time to peak strain using CMR feature tracking in a patient with a pacemaker. 125

Figure 4-8: Endocardial segmentation on left ventricular short axis stack in a patient with a pacemaker. 127

Figure 4-9: Global longitudinal strain in a patient with a pacemaker. 143

Figure 4-10: Time to peak radial strain in AOO and DOO pacing modes. 144

Figure 4-11: Change in left ventricular volumes between pacing modes. 145

Figure 4-12: Change in ventricular volumes between AOO and DOO pacing modes. 146

Figure 4-13: Scatterplot of change in LVESVi and QRS duration between AOO and DOO pacing modes. 147

Figure 5-1: Patient recruitment pathway 164

Figure 5-2: Study protocol. 166

Figure 5-3: Measurement of left atrial parameters at end-systolic phase of cardiac cycle. 171

Figure 5-4: Late gadolinium enhancement images in two orthogonal planes in study patients. 172

Figure 5-5: Distribution of late gadolinium enhancement. 178

Figure 5-6: Scatter plots of baseline LV volumes and heart rate. 181

Figure 5-7: Line graphs demonstrating changing in volumes and function before and 6 months after pacing. 190

Figure 5-8: Line graphs depicting change in left ventricular volume for each patient before and 6 months after pacing. 191

Figure 5-9: Scatter plots of baseline LGE mass and change in LVESVi from baseline to 6 months. 200

Figure 5-10: Feature tracking parameters before and 6 months after pacemaker implantation. 201

Figure 5-11: Change in NYHA Class. 206

Figure 6-1: Changes in Left Ventricular Volumes with initiation of Right Ventricular pacing. 223

Figure 6-2: Proposed mechanism for the pathophysiology underpinning the development of heart failure in those with myocardial fibrosis. 228

List of Tables

Table 1-1: Design changes to MR Conditional Devices 26

Table 1-2: Large Studies (>100 patients) evaluating safety of MR Conditional Devices 29

Table 1-3: Large Studies (>100 patients) evaluating safety of MR Non-Conditional Devices.....32

Table 2-1: Incidence of pacing-induced cardiomyopathy in studies of right ventricular pacing 52

Table 2-2: Randomised clinical trials comparing right ventricular pacing and biventricular pacing. 64

Table 2-3: Guideline recommendations for physiological pacing in patients requiring bradycardia support 70

Table 3-1: Clinical characteristics of patients recruited to study. 93

Table 3-2: Pacemaker and lead models in the study population. 94

Table 3-3: Comparison of device parameters before and immediately after the MRI examination. 95

Table 3-4: Baseline CMR parameters of patients in AOO pacing mode.....96

Table 3-5: Atrial pacing mode pairwise comparison of stroke volume by cine, aortic/mitral/tricuspid valves. 102

Table 3-6: Ventricular pacing mode pairwise comparison of stroke volume by cine, aortic/mitral/tricuspid valves. 103

Table 4-1: Baseline Characteristics of all patients and then separated dependant on absence or presence of late gadolinium enhancement .131

Table 4-2: Baseline device characteristics and ECG parameters in AOO and DOO pacing modes dependant on absence or presence of late gadolinium enhancement. 134

Table 4-3: Device and lead models in the study population. 136

Table 4-4: Baseline CMR data. 139

Table 4-5: CMR, contractility and QRS duration in AOO and DOO pacing modes in those with and without LGE. 142

Table 4-6: Baseline values for mapping of left ventricular kinetic energy in patients with and without late gadolinium enhancement. 149

Table 4-7: Left ventricular kinetic energy in AOO and DOO pacing modes in those with and without LGE. 150

Table 4-8: Comparison of device parameters before and immediately after the CMR examination 151

Table 5-1: Baseline Characteristics (whole cohort and then dependent on absence or presence of late gadolinium enhancement) 176

Table 5-2: Baseline CMR data of all patients and then separated dependant on absence or presence of late gadolinium enhancement 180

Table 5-3: Device implantation and follow up parameters of all patients and then separated based on absence or presence of late gadolinium enhancement 184

Table 5-4: Device and lead models in the study population 185

Table 5-5: Follow up electrocardiogram parameters of all patients and then separated dependant on absence or presence of late gadolinium enhancement..... 186

Table 5-6: CMR parameters of all patients pre and 6 months after pacemaker implantation..... 188

Table 5-7: Changes in CMR characteristics of patients with and without late gadolinium enhancement from baseline to follow up. 193

Table 5-8: Baseline Device, Electrocardiographic and CMR data of late gadolinium enhancement positive patients separated dependant on pattern of late gadolinium enhancement..... 196

Table 5-9: CMR parameters of all late gadolinium enhancement positive patients' pre and 6 months after pacemaker implantation according to the pattern of late gadolinium enhancement..... 198

Table 5-10: Univariate and multivariate analysis of percentage change in LVESVi..... 203

Table 5-11: Quality of life scores and NYHA Class for the entire study population at baseline and 6 month follow up..... 204

Table 5-12: Quality of life scores and NYHA Class stratified according to absence or presence of late gadolinium enhancement at baseline and 6 month follow up. 205

Table 5-13: Comparison of procedure related and clinical adverse events in patients with and without late gadolinium enhancement..... 207

Table 5-14: Comparison of device parameters before and immediately after the CMR examination..... 208

Table 5-15: Clinically significant changes in device parameters from pre and immediately post MRI. 209

Table 6-1: Changes in LV volumes and function in patients assigned to a right ventricular apical pacing in large clinical trials (>100 patients) and our study. 231

List of Equations

Equation 1: Calculation of Left Ventricular Ejection Fraction 54
Equation 2: Calculation of Left Ventricular Mass 91
Equation 3: Calculation of LV Contractility.....125
Equation 4: Calculation of Kinetic Energy 128
Equation 5 : Left atrial volume calculation. 170

Abbreviations

AAI	Atrial Demand Pacing
ACC	American College of Cardiology
AF	Atrial Fibrillation
AHA	American Heart Association
AOO	Asynchronous Atrial Pacing
AV	Atrioventricular
BiVP	Biventricular Pacing
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
bpm	beats per minute
CAD	Coronary Artery Disease
CCS	Canadian Cardiovascular Society
CI	Confidence Interval
CIED	Cardiovascular Implanted Electronic Device
CMR	Cardiovascular Magnetic Resonance
CRT	Cardiac Resynchronisation Therapy
CSPAMM	Complementary Spatial Modulation of Magnetisation
DDD	Dual Chamber Pacemaker
DOO	Asynchronous Dual Chamber Pacing
ECG	Electrocardiogram
ECV	Extracellular Volume Fraction
EDV	End Diastolic Volume
EMI	Electromagnetic Inference
EPI	Echo Planar Imaging
ESC	European Society of Cardiology
FDA	Food and Drug Administration

FFE	Fast Field Echo
FoV	Field of View
GLS	Global Longitudinal Strain
HARP	Harmonic Phase
HF	Heart Failure
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	Hazard Ratio
HRS	Heart Rhythm Society
ICD	Implantable Cardioverter Defibrillator
IPG	Implantable Pulse Generator
KE	Kinetic Energy
LBBB	Left Bundle Branch Block
LGE	Late Gadolinium Enhancement
LOA	Limit of Agreement
LV	Left Ventricle
LVEDD	Left Ventricular End-Diastolic Diameter
LVEDV	Left Ventricular End-Diastolic Volume
LVEDVi	Left Ventricular End-Diastolic Volume Index
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End-Systolic Volume
LVESVi	Left Ventricular End-Systolic Diameter Index
MDI	Mechanical Dyssynchrony Index
MOLLI	Modified Look-Locker Inversion recovery
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
PCT	Pacing Capture Threshold
PICM	Pacing-induced Cardiomyopathy

PIVD	Pacing-induced Left Ventricular Dysfunction
PM	Pacemaker
PSIR	Phase Sensitive Inversion Recovery
QoL	Quality of Life
RA	Right Atrial
RCT	Randomised Controlled Trial
RF	Radiofrequency
ROI	Region of Interest
RV	Right Ventricle
RVEDVi	Right Ventricular End-Diastolic Volume Index
RVEF	Right Ventricular Ejection Fraction
RVESVi	Right Ventricular End-Systolic Volume Index
RVOT	Right Ventricular Outflow Tract
RVP	Right Ventricular Pacing
SA	Short-axis
SBP	Systolic Blood Pressure
SENSE	Sensitivity Encoding
SGE	Spoiled Gradient Echo
SND	Sinus Node Disease
SNR	Signal to Noise Ratio
SPAMM	Spatial Modulation of Magnetization
SSFP	Steady State Free Precession
STE	Speckle Tracking Echocardiography
STIR	Short Tau Inversion Recovery
SV	Stroke Volume
T	Tesla
TDI	Tissue Doppler Imaging
TE	Echo Time

TI	Inversion Time
TR	Repetition Time
TTE	Transthoracic Echocardiogram
VAS	Visual Analogue Scale
VCG	Vectorcardiogram
VENC	Velocity Encoding
VOO	Asynchronous Ventricular Pacing
VVI	Ventricular demand pacing

Abstract

Introduction: Right ventricular (RV) pacing is recommended treatment for bradycardia and can normalise life expectancy and restore quality of life. Clinical trials have demonstrated that chronic RV apical pacing may be associated with an adverse prognosis and development of heart failure. Multi-parametric cardiovascular magnetic resonance (CMR) has several clinical and research applications and can quantitatively assess cardiac anatomy, function, intracardiac flow and myocardial tissue characteristics.

Aims: To assess 1.) the feasibility of 4D flow and validity of transvalvular flow quantification in pacemaker patients. 2.) haemodynamic response of intrinsic atrioventricular (AV) conduction and forced RV pacing in those with and without focal myocardial fibrosis. 3.) the hypothesis that long term RV pacing in presence of focal myocardial fibrosis leads to adverse cardiac remodelling.

Methods: Between November 2017 and August 2019, patients with MRI conditional devices were prospectively recruited from a single centre. Patients underwent multi-parametric CMR at 1.5 Tesla. Patients in Chapters 3 and 4 underwent CMR in two separate pacing modes during a single visit. Patients in Chapter 5 underwent CMR before and 6 months after pacemaker implantation.

Results:

1. Flow across aortic, mitral and tricuspid valves was consistent and reproducible in both pacing modes ($p>0.05$ for all).
2. A greater decline in left ventricular (LV) ejection fraction ($p=0.02$) was observed during forced RV pacing in patients with myocardial fibrosis compared to patients without fibrosis.
3. Patients with AV block and myocardial fibrosis undergoing pacemaker implantation have greater electromechanical dyssynchrony and a consequent increase in LV end systolic volume ($p=0.008$) at 6 months compared to those without fibrosis.

Conclusions: Right ventricular pacing in patients with myocardial fibrosis, compared to those without, leads to greater deterioration in cardiac function both immediately and after 6 months.

Chapter 1 Cardiac magnetic resonance imaging in patients with cardiovascular implantable electronic devices: risks, safety and image optimisation

Magnetic resonance imaging (MRI) is currently the imaging modality of choice in diagnosing many musculoskeletal, neurological and cardiovascular disorders. MRI offers unparalleled soft tissue resolution without the need for ionising radiation. In parallel with this the number of patients with cardiovascular implanted electronic devices (CIED) continues to expand with 555 pacemakers per million population implanted in England in 2016 (1). An estimated 50-75% of these individuals will have the need for an MRI during the lifetime of their device due to the prevalence of diseases such as cancer and stroke (2). Serious adverse effects related to scanning pacemakers have historically been reported, albeit rarely, including inhibition of pacing, asynchronous pacing, induction of ventricular fibrillation and even death (3). Given this, there is now a range of magnetic resonance (MR) conditional systems available since the first United States Food and Drug Administration (FDA) approved system in 2011. Unfortunately, patients with CIEDs continue to have limited access to MRI with only half of UK centres providing this service (4).

Cardiovascular magnetic resonance (CMR) provides accurate non-invasive assessment of coronary artery disease as well as offering unparalleled tissue characterisation for assessing myocardial viability and the aetiology of cardiomyopathies (5-7). Therefore CMR is now seen as a cost effective imaging technique for diagnosis and management of cardiovascular diseases and has developed an increasingly prominent role for the diagnosis, management and monitoring of patients with cardiovascular disease in European guidelines (8, 9). Patients with CIEDs have a high burden of concomitant cardiovascular conditions and greater awareness of adverse events, risks and technological advances in devices is needed in order to widen access to CMR for these individuals (10, 11).

1.1 Potential hazards of imaging cardiovascular implanted electronic devices

CIED systems are sophisticated tools for the management of brady- or tachyarrhythmias and are usually composed of cardiac leads attached to either an implantable pulse generator (IPG) or an implantable cardioverter defibrillator (ICD). Although MRI on the whole is a very safe imaging modality the generation of static and gradient magnetic fields and use of radiofrequency (RF) pulses have the potential to interact with CIEDs.

1.1.1 Torque effect

CIEDs contain ferromagnetic material which may be subject to force and torque induced by both static and gradient magnetic fields during MRI. These forces depend on the strength of the magnetic field, positioning within the field and the amount of ferromagnetic material and can potentially lead to movement of the IPG or leads (12). However modern IPGs appear safe with little force or torque effects demonstrated in 1.5 Tesla (T) scanners and pacing leads do not contain sufficient ferromagnetic material to cause movement (13, 14).

1.1.2 Heating effect

Radiofrequency pulses during an MRI can induce electrical fields within the body leading to the dissipation of RF energy into tissues (15). Pacing leads can act as ‘antennae’ during repeated RF pulses and concentrate electromagnetic energy at uninsulated points such as the lead tip and where local heating may cause tissue damage (16). Theoretically this can lead to changes in sensing and capture thresholds or even induction of arrhythmias (17). Factors such as lead design (length and diameter), the configuration of leads in the body and specific absorption rate can determine the potential for heating and the presence of abandoned or epicardial leads can further increase risk (16, 18, 19). Indeed one small study found an increase in serum troponin levels in 4 out of 114 patients with MR unconditional pacing systems at 1.5T which the authors postulated may have been due to MRI related myocardial tissue damage (20).

1.1.3 Electromechanical effects

1.1.3.1 Reed switch activation

Reed switches incorporated into non-conditional devices allow device programming by the placement of a magnet. The static magnetic field in MRI can have a variable effect on reed switch activity potentially leading to loss of pacing, inhibition of therapies in patients with ICDs or activation of an asynchronous pacing mode which can theoretically increase the risk of ventricular arrhythmias in those with an underlying rhythm (21).

1.1.3.2 Electrical reset

Electrical reset is the term used for the backup mode that a specific device reverts to as it nears battery depletion. The backup mode depends on the individual device manufacturer but for pacemakers is usually a VVI (ventricular demand pacing) mode with advanced functions disabled and in ICDs the tachyarrhythmia therapies may be deactivated (22). Electromagnetic inference (EMI) during an MRI examination can lead to electrical reset and this occurred in 6 of 1000 patients in the MagnaSafe registry of patients with non-conditional devices (23). Electrical reset can often not be reprogrammed, necessitating a procedural intervention to replace the device. Furthermore, during MRI RF pulses may be inappropriately interpreted as intrinsic electrical activity so changing from an asynchronous pacing mode to a demand pacing mode has potentially life-threatening consequences (24).

1.1.3.3 Inappropriate function

Electromagnetic interference in the MRI environment from rapidly changing magnetic fields gradients or RF pulses may lead to under or over sensing in the device which in turn may cause inhibition of necessary pacing or initiation of anti-tachycardia therapy in those with ICDs (24, 25). No reported cases of ICD therapies have been recorded in the MRI environment however this may be due to an inability of ICD capacitors to charge sufficiently in the static magnetic field. Furthermore gradient fields might be sufficient to capture the myocardium and induce arrhythmias (18, 26).

1.2 MRI conditional devices

All materials including implantable devices should be evaluated prior to an MRI to determine their safety in an MRI environment. In 2005 the MR task group of the American Society for Testing and Materials published the following classification system for the labelling of medical products (Figure 1-1) (27).

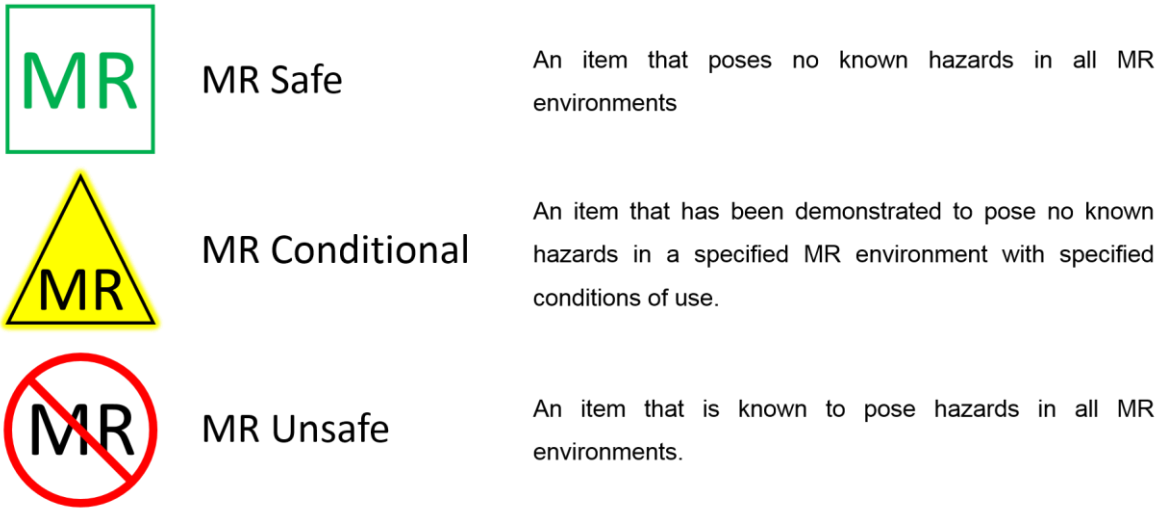


Figure 1-1: MR Item Safety Classification System

Originally the presence of an implanted pacemaker was deemed an absolute contraindication for MR imaging due to safety concerns; in particular reported fatal events worldwide (28). However, these events were often poorly documented and, in some circumstances, occurred when MRI staff were unaware of the presence of a pacemaker in a particular patient. Therefore manufacturer led research has focussed on the development of MRI conditional CIEDs that enable safe scanning of patients under certain scanning conditions, such as a specified field strength (i.e. 1.5T) or specific absorption rate limit [often <2 Watts per kilogram (W/kg)]. These restrictions are often manufacturer- and device-specific so careful assessment before undertaking MRI is essential. Manufacturers have also made alterations in both the hardware and software of devices in order to enhance reliability and performance in the MRI environment. Examples of hardware modifications and their intended effects can be seen in Table 1-1.

Modification	Purpose
Generator design	
Reduction in ferromagnetic content	Reduce torque and susceptibility artefacts
Replacement of reed switch with solid state technology (Hall Sensor)	Avoid unpredictable reed switch behaviour
Bandstop filter	Shield circuitry
Lead design	
Inner coil pitch redesigned to alter resonant frequency	Minimise lead heating and current induction
Lead diameter changed	Minimise lead heating and current induction
Bandstop filter at tip of lead	Shield circuitry

Table 1-1: Design changes to MR Conditional Devices

Software changes to MR conditional devices have included the introduction of 'MRI Safe' modes. These modes differ somewhat between manufacturers but are there to ensure safe scanning within the MRI environment by avoiding issues such as over-sensing and delivery of inappropriate therapies. In general this allows pacing in either an asynchronous mode or completely switches pacing off to prevent the interpretation of EMI as intrinsic rhythm and subsequent lack of pacing. Pacing outputs are often increased to reduce the risk of loss of capture and advanced functions are turned off, in particular the detection and delivery of therapies for tachyarrhythmias in patients with ICDs.

In 2011 the first MRI conditional CIED was approved by the FDA with a randomised controlled trial (RCT) demonstrating no MRI related complications with this device (29). Most modern devices are deemed MRI conditional and the safety of these devices when scanned under the correct conditions is now well established (Table 1-2). Furthermore large scale studies in patients without MRI conditional devices have shown that serious MRI related complications are very rare if patients are scanned in a controlled way in both thoracic and non-thoracic scans (Table 1-3). These studies have led to international societies publishing comprehensive guidelines to ensure the safe scanning of patients with and without MRI conditional CIEDs (22, 30). The growing body of evidence for

scanning conditional as well as non-conditional devices is of paramount importance as the necessity of providing MRI and CMR to these individuals is only likely to increase.

Reference	Year	Type of study	Number having MRI	Type of device	Field strength	Area imaged	Significant complications	Lead parameters
Wilkoff *et al.* (29)	2011	Multi centre RCT	258	PM	1.5T	Brain & lumbar spine	None	Minimal changes - similar to controls
Gimbel *et al.* (31)	2013	Multi centre RCT	177	PM	1.5T	Brain & cardiac	None	Minimal changes - similar to controls
Gold *et al.* (32)	2015	Multi centre RCT	175	ICD	1.5T	Brain, cardiac & cervical spine	None	Met inferiority with controls
Bailey *et al.* (33)	2015	Multi centre, prospective	226	PM	1.5T	Brain & lumbar spine	None	Freedom from changes in PCT and sensing in ≥99%.
Awad *et al.* (34)	2015	Multi centre, prospective	153	ICD	1.5T	Cardiac & thoracic spine	None	No change in ventricular PCT (>0.5V), one patient had a drop in R- wave sensing of >50% at 1 month
Shentar *et al.* (35)	2015	Multi centre RCT	177	PM	1.5T	Whole body	None	Minimal changes - similar to controls

Bailey *et al.* (36)	2016	Multi centre, prospective	216	PM	1.5T	Cardiac & thoracic spine	One (0.4%) pericardial effusion requiring lead reposition	Freedom from changes in PCT and sensing in ≥98%.
Ching *et al.* (37)	2017	Multi centre, prospective	140	PM	1.5T	Cardiac	None	No significant changes between groups
Williamson *et al.* (38)	2017	Prospective real world data	526	PM	1.5T	Whole body	None	Six (1%) MRI-related observations including AF and PCT increase

Table 1-2: Large Studies (>100 patients) evaluating safety of MR Conditional Devices

Abbreviations: AF: atrial fibrillation, ICD: implantable cardioverter defibrillator, MRI: Magnetic resonance imaging, PCT: pacing capture threshold, PM: pacemaker, RCT: randomised controlled trial, T: Tesla.

Reference	Year	Type of study	Number having MRI	Type of device	Field strength	Area imaged	Significant complications	Lead parameters
Strach *et al.* (39)	2010	Single centre, prospective	114	PM	0.2T	Whole body	None	No significant changes
Mollerus *et al.* (40)	2010	Single centre, prospective	103	CRT, ICD & PM	1.5T	Whole body	One (0.7%) partial electrical reset	PCT unchanged Lead sensing & impedances decreased significantly
Nazarian *et al.* (41)	2011	Single centre, prospective	438	PM & ICD	1.5T	Whole body	Three (0.7%) partial electrical resets	Small but significant differences but deemed not clinically important
Cohen *et al.* (42)	2012	Single centre, retrospective	109	CRT, ICD & PM	1.5T	Whole body	None	Small but significant differences but deemed not clinically important
Friedman *et al.* (43)	2013	Single centre, prospective	171	PM	1.5T	Whole body	None	Small but significant differences but deemed not clinically important

Muehling *et al.* (44)	2014	Single centre, prospective	356	PM	1.5T	Head	None	No significant changes
Higgins *et al.* (45)	2015	Single centre, prospective	198	PM	1.5T	Whole body	Nine (3.5%) partial electrical resets	N/A
Russo *et al.* (23)	2017	Multi centre Prospective registry	1246	ICD & PM	1.5T	Whole body excluding thoracic	Six (0.004%) partial electrical resets One ICD generator required immediate replacement Five cases of atrial arrhythmia	Large changes in device parameters occurred infrequently and did not cause adverse clinical events.
Nazarian *et al.* (46)	2017	Multi centre, prospective	1509	PM & ICD	1.5T	Whole body	Nine (0.4%) electrical resets – one required IPG replacement	Small but significant differences but deemed not clinically important
Mason *et al.* (47)	2017	Single centre, prospective	178	CRT, ICD & PM	1.5T	Whole body	None	No significant changes were noted.

Lupo *et al.* (48)	2018	Single centre, prospective	120	PM & ICD	1.5T	Whole body	None	Small but significant differences but deemed not clinically important

Table 1-3: Large Studies (>100 patients) evaluating safety of MR Non-Conditional Devices

Abbreviations: CRT: cardiac resynchronisation therapy, ICD: implantable cardioverter defibrillator, IPG: implantable pulse generator, MRI: Magnetic resonance imaging, PCT: pacing capture threshold, PM: pacemaker, RCT: randomised controlled trial, T: Tesla.

1.3 Imaging Artefacts

Cardiovascular magnetic resonance is a very safe and robust tool for assessment of cardiovascular diseases with diagnostic image quality obtained in 98% of patients in a large European cohort (8). The presence of CIEDs has the potential not only to impact MR safety but to create significant artefacts which can hinder image interpretation. The different magnetic susceptibilities of the metallic components of CIEDs compared to human tissue leads to distortions in the magnetic field, thus generating artefacts. Pacing leads, although they contain ferromagnetic materials, are thin and therefore create little artefact that does not impact significantly on image interpretation (49). The majority of imaging artefacts occur due to the presence of the IPG or ICD which is particularly pertinent in cardiac scanning where the device is in close proximity to the area of interest. Greater artefacts over the heart during CMR are associated with larger devices (i.e. ICDs), the proximity of the device to the heart, the imaging sequence used as well as field strength (49). The first consideration when contemplating CMR in those with CIEDs should be whether the clinical questions can be addressed sufficiently by another imaging modality. Clearly if the optimal investigation is CMR then a flexible approach to scanning these individuals is required in order to maximise image quality.

1.4 Image optimisation in patients with CIEDs undergoing CMR

1.4.1 Pre-scan considerations

The advent of MRI safe modes on device programmers has simplified programming prior to MRI. Selecting the correct pacing mode for the duration of the CMR is vital for safety but may also have the potential to impact image quality. Pacing modes that can be selected are generally asynchronous modes (Atrial:AOO / Dual chamber:DOO / Ventricular:VOO), which prevent inadvertent inhibition, or complete deactivation of pacing (ODO). Clearly, in those who are pacing dependent, an asynchronous mode with ventricular pacing is mandated. In the remainder of patients there is more flexibility in choice of mode. If safe, then patients should be scanned with pacing disabled to avoid the risk of the pacing mode competing with the intrinsic rhythm which in theory could lead to an R on T phenomenon within the scanner. Furthermore ventricular paced rhythms can induce ventricular dyssynchrony which can adversely impact on left ventricular ejection fraction (LVEF) so volumetric analysis undertaken may not accurately reflect cardiac function (50). In certain situations the initiation of asynchronous pacing modes

may improve the image quality obtained. CMR utilises a vectorcardiogram (VCG) to gate images and prevent distortion of images that may result from cardiac motion (51). Most imaging sequences are acquired over several cardiac cycles, so called segmented imaging, and the presence of arrhythmias (i.e. atrial fibrillation) and breath holding can impact on image quality (52). Some of these issues can be overcome with the use of real time or single shot imaging and arrhythmia rejection algorithms, although the latter may significantly increase the duration of breath holds which may prove to be difficult in patients with heart failure. Furthermore these techniques can lead to trade-offs in spatial resolution and may not capture the entire cardiac cycle if prospective VCG triggering is used. Therefore in those with atrial fibrillation, for example, the use of a ventricular pacing mode that sets a regular R-R interval may facilitate better image quality, through shorter breath holds and less image blurring. The caveat to this is that right ventricular (RV) pacing can induce alterations in left ventricular (LV) contraction and could potentially lead to underestimation of LVEF. Interestingly a minority of patients with devices may also develop MRI associated ectopy, which is another potential cause of image distortion, when programmed to back up pacing at 40 beats per minute (bpm) (25). Whether programming to a fixed ventricular pacing rate reduces the chances of this occurring is unknown.

The amount of artefact present over the heart depends in a large part on the distance from the IPG or ICD to the heart (49, 53, 54). Indeed less artefact was observed in those with higher body mass indices in one study possibly due to a greater distance between the device and the heart (49). In patients with left sided implants raising the arm over the head during the scan may reduce artefact over the heart by increasing the distance between area of interest and the device (Figure 1-2). However not all device manufacturers allow for positioning the arms over the head and it may adversely impact on patient comfort for the duration of the scan.

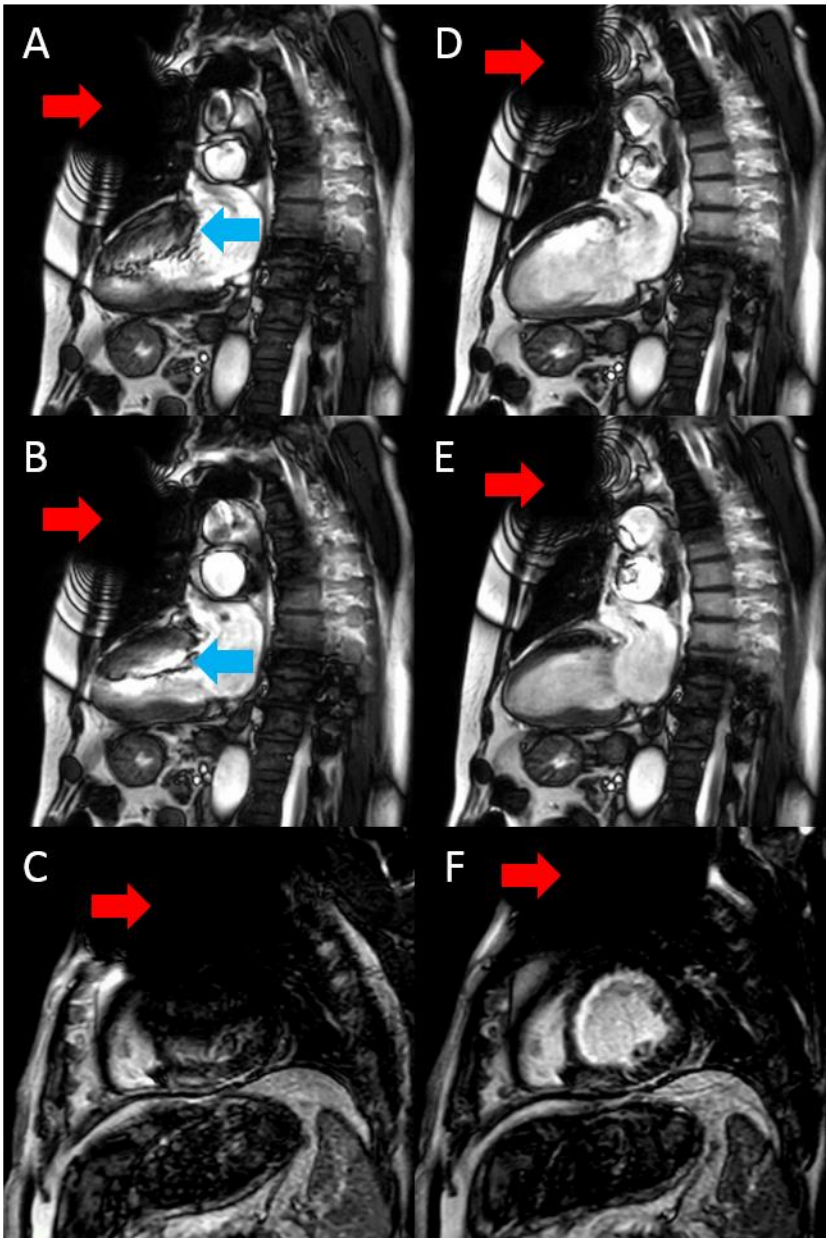


Figure 1-2: Effect of arm positioning on image quality at 1.5T.

Images demonstrate the effect of moving the patients left arm from next to the patient (Panel A-C) to above the head (Panel D-F) in minimising artefact over the heart. Balanced steady state free precession (SSFP images) (Panels A,B,D & E) in a patient with a pacemaker demonstrating how positioning the arm above the head moves the banding artefact (blue arrows) away from the heart at both end-diastole (Panels A & D) and end-systole (Panels B & E). Late gadolinium enhancement (LGE) images (Panels C & F) in a patient with an ICD and an anteroseptal subendocardial infarction demonstrating how positioning the arm above the head moves the signal void (red arrows) away from the heart.

1.4.2 Imaging sequences

1.4.2.1 Cine Imaging

Cine imaging is commonly used in CMR for accurate assessment of both left and right ventricular volumes. The most widely used technique for evaluation of ventricular function and volumes is balanced steady state free precession (SSFP). SSFP sequences have better signal to noise ratio allowing greater endocardial and epicardial definition and thus are more accurate and reproducible for assessment of LV volumes than spoiled gradient echo (SGE) sequences of LV volumes (55). However SSFP sequences are very susceptible to magnetic field inhomogeneity, leading to frequent image distortion and banding artefacts secondary to the IPG or ICD (Figure 1-2). Indeed, although signal void from the device is very similar in both SSFP and SGE sequences (5-6cm), the overall artefact distance from the IPG is greater in SSFP compared to SGE (10-12cm vs ~6cm respectively) due to banding artefacts (53). In patients with ICDs overall artefacts are even larger on both SSFP (up to 14.1cm) and SGE (up to 7.9cm) acquisitions (56).

In patients with pacemakers the presence of the IPG can impact on the image quality obtained with SSFP acquisitions with artefacts most commonly seen over the anterior and anteroseptal LV segments (53, 57, 58). Published data suggest that good or excellent image quality obtained with SSFP imaging varies from 48-84% for the LV and 87-93% for the RV (54, 57, 59). Image quality that is acceptable for diagnostic purposes may be as high as 95% and 98% for the LV and RV respectively (59). The use of SGE can further improve image quality particularly in those with non-diagnostic SSFP imaging (53, 54, 57, 58). Kaasalainen *et al.* have also shown in a small study of sixteen patients that use of a frequency scout to optimise the centre offset frequency led to improved image quality by moving banding artefacts away from the myocardium (53). MRI conditional devices, compared to non-conditional devices, are also less likely to be affected by artefact presumably due to the lower ferromagnetic content. The same applies to generators implanted on the right side, relating to the increased distance from the heart (49, 54, 57).

In patients with ICD or cardiac resynchronisation therapy (CRT) devices the larger ferromagnetic content has the potential for greater image distortion. Schwitter *et al.* showed that good to moderate image quality using SSFP, in patients with a single MRI conditional ICD system, was obtained in 53% for the LV and 69% for the RV (56). In

another study that included a mixture of conditional and non-conditional systems, good LV image quality was seen much less frequently with SSFP imaging, i.e. in only 6% of ICD patients and 14% of CRT-defibrillator patients (CRT-D) (54). The use of SGE improved the proportion of patients with good or moderate image quality to 68-74% which was significantly better than SSFP acquisitions (Figure 1-3). Furthermore, in the latter study, the use of post-contrast SGE led to further small incremental improvements in the proportion of patients with good image quality.

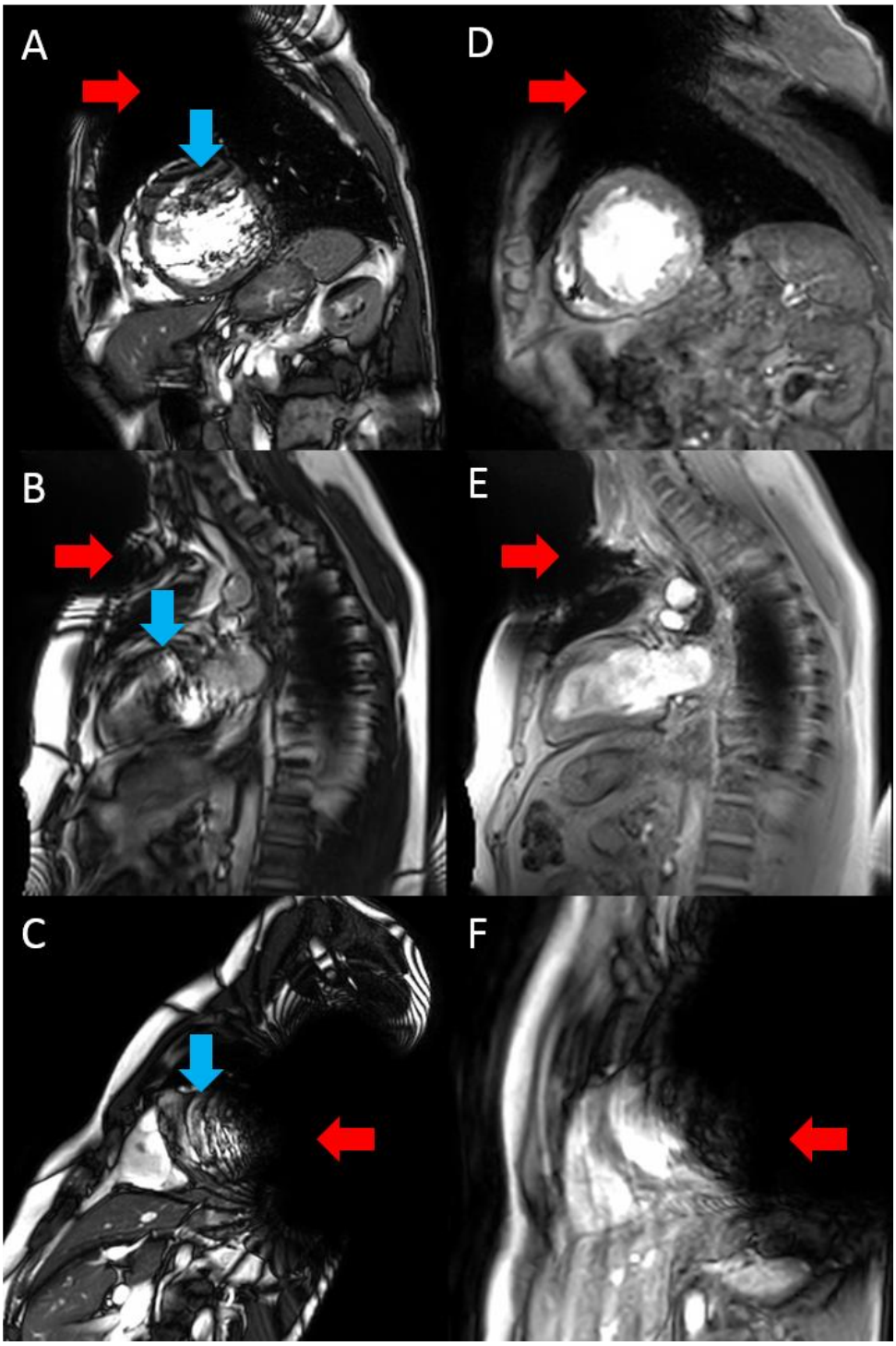


Figure 1-3: Effect of cine imaging sequence on image quality in patients with ICDs.

Images demonstrate the effect of changing from an SSFP acquisition (Panel A-C) to a SGE acquisition (Panel D-F) on artefact in patients with ICDs. There is minimal impact on signal void (red arrows) but loss of banding artefact (blue arrows) with SGE acquisitions. Image quality was substantially improved in patients with left sided ICDs at both 1.5T (Panel A & D) and 3T (Panel B & E) but little improvement was observed in a patient with a subcutaneous ICD (Panel C & F).

Therefore the data suggest that diagnostic cine image quality is possible in nearly all pacemaker patients and over three quarters of patients with ICD or CRT devices with a stepwise approach to image acquisition. However, despite these changes, diagnostic image quality may not be possible in some patients (Figure 1-3).

1.4.2.2 T2 weighted imaging

T2 weighted imaging, specifically T2 short tau inversion recovery (STIR) sequences, are often used for assessment of myocardial oedema to look for specific pathologies such as acute myocardial infarction or myocarditis. Due to the short echo time they are less sensitive to susceptibility artefacts from the device (Figure 1-4). Indeed little or no artefacts were seen using T2 STIR sequences in patients with both pacemakers and ICDs (49, 53, 54, 57, 58).

Figure 1-4: T2 STIR acquisition in a patient with a pacemaker.

No artefact from the IPG is seen over the heart. Image shows high signal in the basal septum in a patient with sarcoidosis.

1.4.2.3 First pass perfusion

Assessment for myocardial perfusion is a common indication for CMR (8). Patients with CIEDs often have co-existent coronary artery disease so diagnostic image quality is key in this group of patients (60). Hilbert *et al.* have recently shown that artefacts with test SSFP and SGE acquisitions were in agreement with the respective cine imaging (54). Furthermore they found that artefact free delineation of all myocardial segments was achieved in >99% of patients, with SGE acquisition, regardless of the type of device (Figure 1-5) (54). These findings are similar to previously published work using SGE perfusion acquisitions (49, 57, 61).

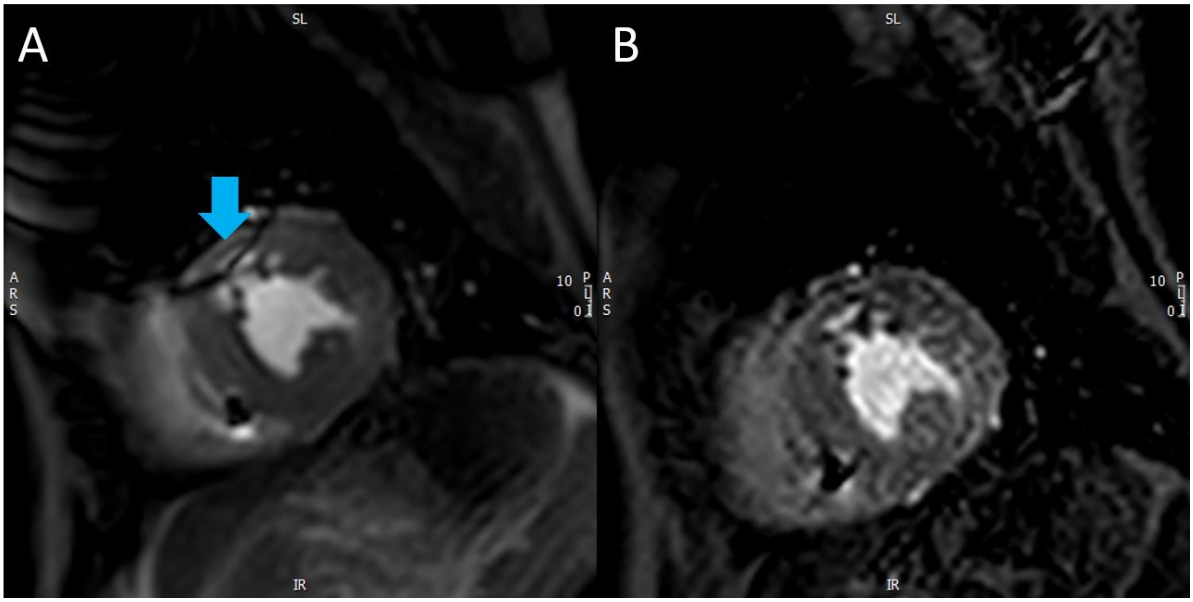


Figure 1-5: Mid ventricular short axis perfusion acquisitions in a patient with an ICD at 1.5T.

SSFP acquisition (Panel A) has better signal-to-noise ratio (SNR) but banding artefact (blue arrow) is present over the anterior wall which may affect image interpretation. No banding artefact is seen on the SGE acquisition (Panel B).

1.4.2.4 Parametric mapping

Parametric mapping techniques such as pre- and post-contrast T1 mapping are increasingly used in both clinical and research practice as tools to evaluate intracellular myocyte character and extracellular fibrosis (62). To date there are very few published data on the feasibility or reproducibility of T1 mapping techniques in patients with CIEDs.

However T1 and T2 weighted sequences show very little artefact in the presence of pacemakers and pre-clinical work has demonstrated the feasibility of utilising wideband sequences to overcome the off resonance effects caused by ICDs (63, 64).

1.4.2.5 Late gadolinium enhancement

Late gadolinium enhancement imaging is a well-established technique for assessment of replacement myocardial fibrosis for both diagnosis and prognosis in a broad range of cardiovascular conditions (65-69). In patients with pacemakers, LGE imaging is less prone to artefact than cine imaging and good to excellent quality images are obtained in 84-100% of clinical studies (49, 57, 58, 70, 71). The presence of an ICD or CRT can cause a frequency shift of 2-6 kHz within 5-10cm of the device. As this off resonance is outside the usual bandwidth, typically 1.9 kHz, of the inversion pulse used in conventional LGE sequences it can lead to hyper intensity artefacts over the LV which may make image interpretation challenging or can potentially lead to the artefact being misinterpreted as myocardial fibrosis (72, 73). Indeed conventional LGE sequences are often less interpretable in those with ICDs or CRTs with artefact free LV segments being present in only 69% and 50% of segments respectively (54, 71). Therefore diagnostic or nearly diagnostic exams are as low as 11% in these patients (70). The recent development of wideband sequences that increase the spectral bandwidth of the inversion pre-pulse can overcome the hyper-intensity off resonance effects (Figure 1-6). Hilbert *et al.* showed a significantly greater proportion of artefact free LV segments using a wideband acquisition compared to a conventional LGE sequence (96.4% vs. 73.1%; $p<0.01$). In another study, Bhuva *et al.* have shown that using wideband LGE can provide diagnostic imaging in the 32% of patients whose conventional LGE imaging was non-diagnostic (70). Furthermore in these patients the use of wideband LGE provided an unexpected diagnosis in 16% of patients and altered management in a further 83%.

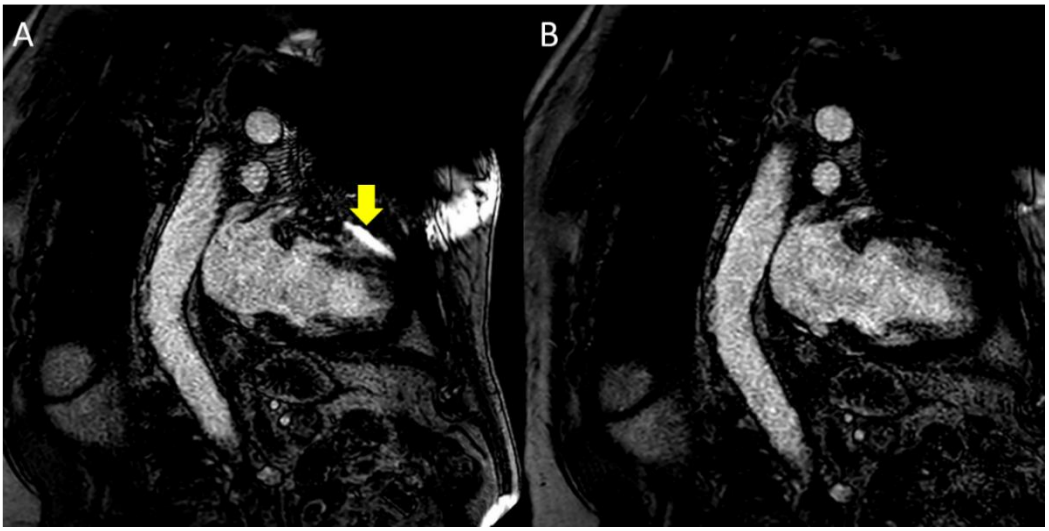


Figure 1-6: Late gadolinium enhancement images in a patient with an ICD.

Hyper-intensity artefacts (yellow arrow) are seen on the conventional phase sensitive inversion recovery (PSIR) LGE sequence (Panel A). Artefact disappears with the use of a wideband LGE sequence (Panel B) with a frequency offset 0Hz and inversion pulse bandwidth 4MHz.

1.5 Conclusion

Real world data suggest that, if imaged with the correct sequence, good image quality is attainable in the majority of patients with CIEDs. This is particularly important as recent work has shown that CMR alters either diagnosis or management strategy in at least two thirds of patients with pacemakers or ICDs (58) (70). However, there is not a single strategy for imaging patients with CIEDs and a flexible approach that trades off image quality and safety against overall scan time is required. A proposed pathway for imaging patients with CIEDs is shown in Figure 1-7.

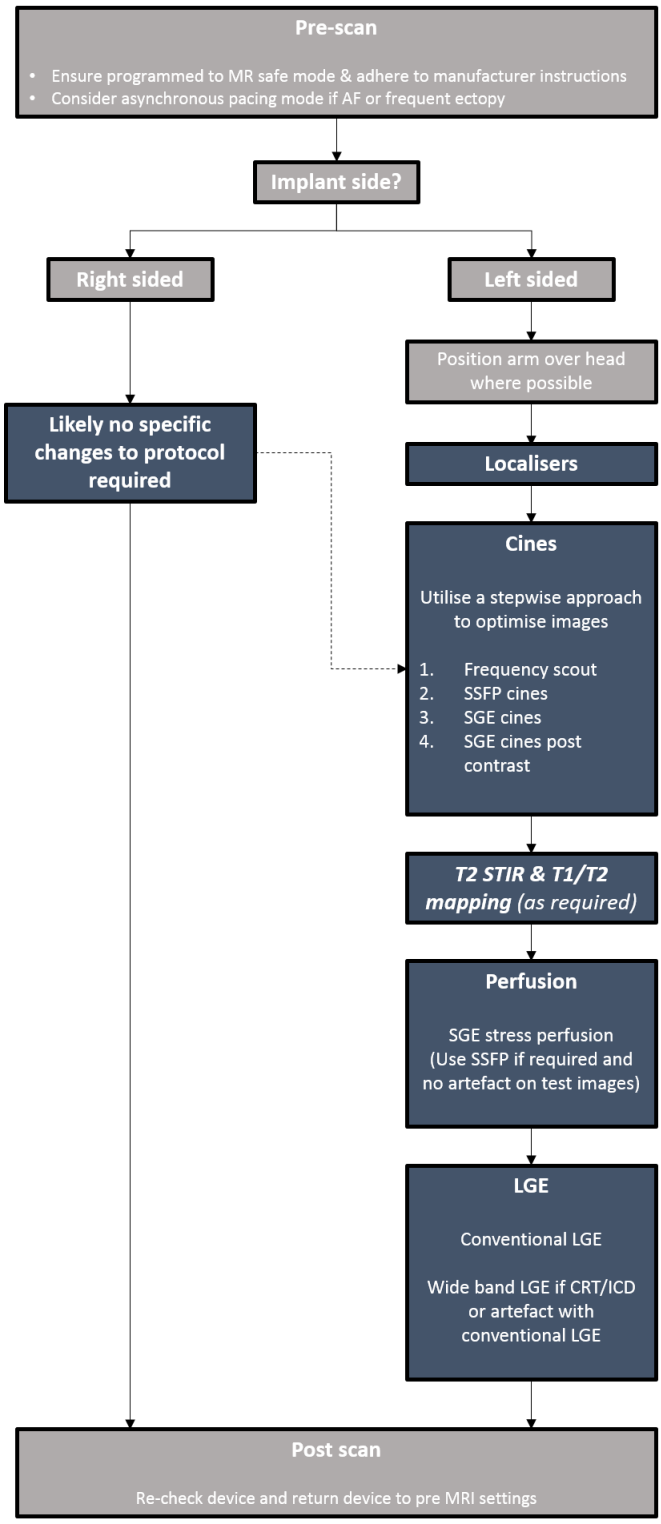


Figure 1-7: Suggested algorithm for CMR imaging in patients with CIEDs.

Abbreviations: AF: atrial fibrillation, CRT: cardiac resynchronisation therapy, ICD: implantable cardioverter defibrillator, LGE: late gadolinium enhancement MRI: Magnetic resonance imaging, SGE: spoiled gradient echo, SSFP: steady state free precession, STIR: short tau inversion recovery.

Chapter 2 Pacing Induced Cardiomyopathy: Pathophysiology, Treatment and the Role of Imaging

2.1 Introduction

Since the first implantation of a pacemaker in man on October 8th, 1958 (74) cardiac pacing has transformed the management of patients with symptomatic bradycardia by normalising life expectancy and improving quality of life (75). Currently cardiac pacing is a class I recommendation in European Society of Cardiology (ESC) guidelines for symptomatic sinus node disease (SND), Mobitz type II 2nd degree and 3rd degree atrioventricular (AV) block (30). At present 555 pacemakers per million population are implanted annually in England and given the ageing population this is on an upward trend (1).

Wiggers *et al*. identified as early as 1925 that artificial ventricular simulation results in reductions in left ventricular performance (76). Since the advent of transvenous cardiac pacing the RV apex has been the most commonly adopted site for ventricular stimulation due to ease of access and lead stability. Animal and human studies have demonstrated that RV apical pacing induces abnormal electrical and mechanical activation patterns (dyssynchrony) which can lead to worsening in haemodynamic parameters and adverse remodelling (50, 77). Indeed large clinical trials evaluating optimal pacing modes over the last two decades have highlighted the potential deleterious effects of long term RV pacing on clinical outcomes and heart failure (78-80).

The development of left ventricular (LV) dysfunction in the setting of chronic RV pacing, which in turn may lead to the development of heart failure symptoms, has been termed pacing-induced cardiomyopathy (PICM). However many patients tolerate RV pacing for years without clinically apparent adverse sequelae. There is therefore a need to improve identification of patients at particular risk of developing PICM in order to prevent the clinical and economic implications of chronic heart failure.

2.2 Pathophysiology of adverse effects of RV pacing

In the human heart electrical propagation occurs very rapidly (2-3m/s) through the His-Purkinje system enabling synchronous contraction starting at three separate endocardial sites throughout the LV, with RV activation occurring rapidly (5-10ms) afterwards (81). However this process is slower in RV apical pacing where the wavefront propagates from the LV apex to base as conduction occurs from myocyte to myocyte (0.3-0.4m/s) with little involvement of the Purkinje system (81, 82). This electrical dyssynchrony is most commonly measured using the QRS duration on a surface electrocardiogram (ECG). The resulting heterogeneous electrical activation can lead to both inter- and intraventricular dyssynchrony (83). Intraventricular dyssynchrony can occur as there is early activation in the septum with the later activation of the basal infero-posterior LV which is similar to that seen in left bundle branch block (LBBB) (84).

It is thought that the electrical and subsequent mechanical dyssynchrony induced by RV pacing is likely to be responsible for adverse effects on haemodynamics, remodelling and myocardial perfusion (Figure 2-1).

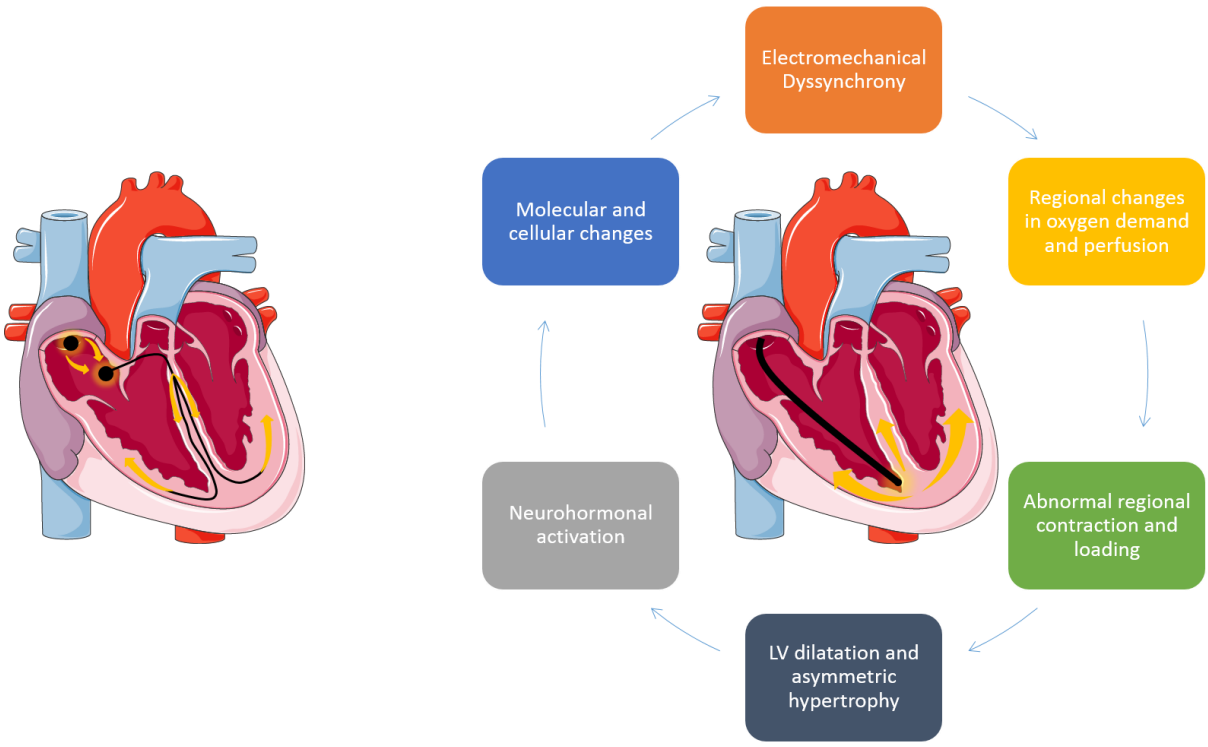


Figure 2-1: Proposed Mechanism of Pacing Induced Cardiomyopathy

Left panel: Normal atrioventricular conduction through the atrioventricular node and His-Purkinje system.

Right panel: Pacing lead activating the right ventricular apex with subsequent propagation of the electrical wavefront from myocyte to myocyte. Coloured boxes represent the proposed pathophysiology mechanisms leading to heart failure.

Adapted from Servier® Smart Medical Art (85)

2.2.1 Animal work evaluating RV pacing

Animal studies evaluating the effects of RV pacing have demonstrated that RV apical pacing is associated with changes in LV haemodynamics (86). Prizen *et al*. used magnetic resonance tagged images in canines during right atrial (RA), RV apical and LV basal pacing to evaluate changes in LV strain and work (77). Ventricular pacing, in particular RV pacing, led to a redistribution of myocardial strain and work throughout the LV. Systolic fibre shortening and work were reduced at the sites of early activation and increased to twice the normal values at most remote sites to activation, while the number of hypo-functioning regions near the pacing site was greatest during RV pacing. Therefore pacing causes differences in the timing of onset of contraction as well as local contraction patterns. Early contraction of segments, against low pressure, closest to the

pacing site causes pre-stretching at the opposing sites of latest activation. Pre-stretching of these late activated segments causes an increased local force of contraction due to the Frank-Starling mechanism and imposes loading on the earlier activated segments so they undergo paradoxical systolic stretch (Figure 2-2).

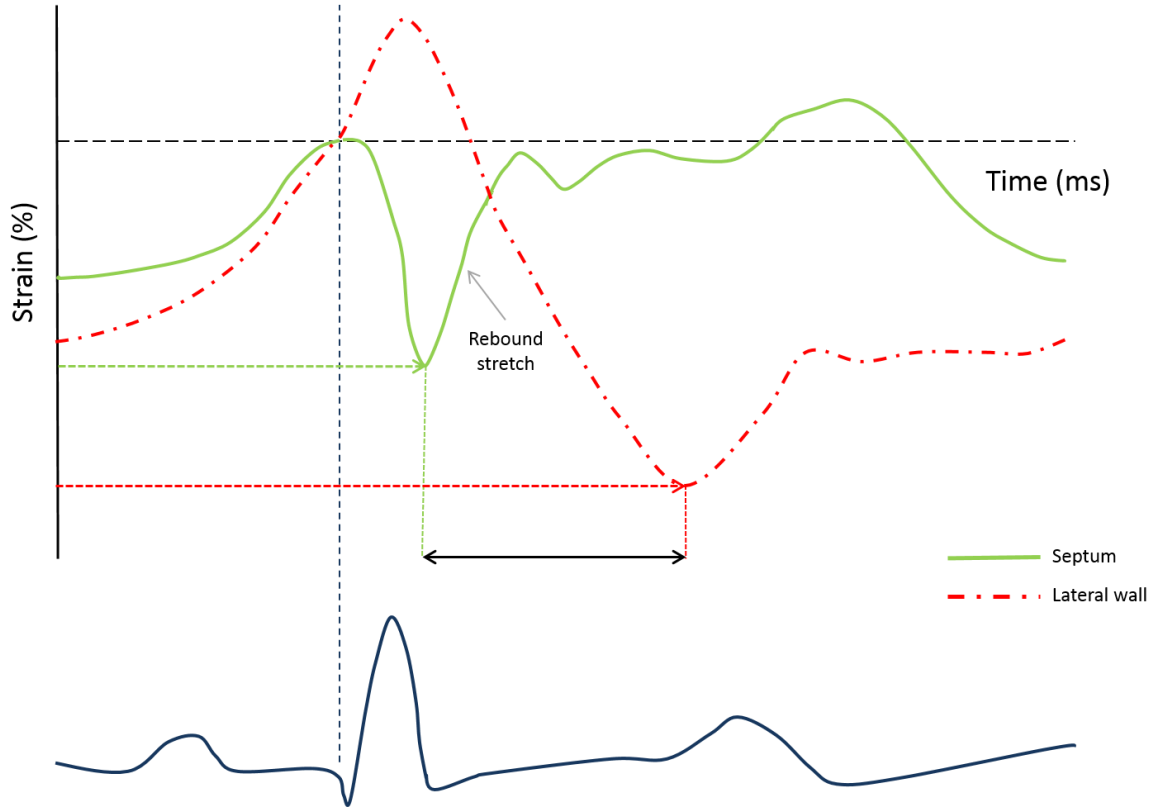


Figure 2-2: Strain traces of left ventricular walls during RV pacing.

Representative strain traces of the lateral (red) and septal (green) walls during right ventricular apical pacing. There is a reduction in the peak strain of the early activated septum (green arrow) with rebound stretch (grey arrow) as the lateral wall is activated and begins contraction. There is a delay in the time to peak strain delay between the septal (green arrow) and lateral (red arrow) walls due to delayed mechanical activation which results in intraventricular dyssynchrony (black arrow). The blue trace represents the electrocardiogram.

This reciprocal stretching and contraction of opposing LV walls results in inefficient contraction and energy waste (87). These regional changes in strain are associated with reduction in blood flow and myocardial oxygen consumption in the earliest activated segments compared to the latest activated (88, 89). This in turn may further worsen

electrical conduction and myocardial contraction (90). Disco-ordinate contraction and reduction in LV contractility lead to rightward shift of the LV end-systolic pressure volume relationship with subsequent slower ejection times as well as reduced LVEF and diastolic filling time (86, 91). Right ventricular apical pacing has also been shown to induce mitral regurgitation in dogs using contrast echocardiography which may further contribute to reductions in effective stroke volume (92).

Over the longer term these abnormal activation and contraction patterns lead to LV remodelling with LV dilatation and re-distribution of cardiac mass (93, 94). Hypertrophy of the late activated segments and thinning of the early activated segments suggest that local mechanical loading may be an important stimulus. Longer term ventricular pacing leads to increased sympathetic stimulation and locally elevated tissue catecholamine activity which may contribute to remodelling (95). Cellular and histological changes have also been described with myofibrillar cellular disarray and dystrophic calcifications as well as evidence of downregulation of proteins involved in calcium homeostasis and impulse generation in late activated segments (96, 97). On a molecular level, pacing induced dyssynchrony has been shown to be associated with activation of extrinsic and intrinsic apoptotic pathways and altered myocardial calcium handling (98).

2.2.2 Effects of RV pacing in humans

The acute effects of RV pacing have been studied extensively in humans predominantly using echocardiography based techniques to evaluate LV dyssynchrony and mechanics. Delgado *et al*. have demonstrated using speckle tracking strain imaging that RV apical pacing induces acute dyssynchrony through impairment of LV longitudinal shortening and twist, leading to a significant drop in LVEF compared to baseline (50). Similar findings have been shown using echocardiography in patients with SND and dual chamber pacemakers (DDD) pacemakers where dual chamber pacing is associated with acute dyssynchrony and impaired LV twist leading to reductions in LVEF compared to atrial pacing and intact AV conduction (99, 100). However not all patients develop significant dyssynchrony. In a study of 93 patients with SND who had been paced for at least 6 months only half developed mechanical dyssynchrony with acute ventricular pacing although the presence of dyssynchrony was associated with increases in LV volumes and deterioration in LVEF (101). Importantly as with the animal models, RV apical pacing is associated not only with changes in timing of contraction and global impairment of LV function but also regional changes in contraction and strain, particularly

in the apical segments (102-104). Temporary RV pacing is also associated with cardiac sympathetic activation (105).

Over the longer term RV apical pacing may also be associated with changes in LV function and remodelling. In patients with congenital complete heart block followed up over 10 years, RV apical pacing was associated with LV dyssynchrony, LV cavity dilatation, asymmetrical LV hypertrophy and worse exercise capacity than matched controls (106). Histological evidence of remodelling, from cardiac biopsy, has also been shown in patients with congenital complete heart block with interstitial fibrosis, fat deposition and variations in myofibre size (107).

Myocardial perfusion has also been shown to be affected in the longer term with RV apical pacing. The use of exercise perfusion scintigraphy in patients with chronic pacing has shown that localised perfusion defects, particularly in the inferior and apical segments, are present in two-thirds of patients even in the absence of flow limiting coronary artery disease (CAD) (108, 109). Over the longer term persistent RV apical pacing was associated with a higher incidence of perfusion defects and lower LVEF compared to right ventricular outflow tract (RVOT) pacing (110). Interestingly these perfusion defects may be reversible with cessation of pacing as global myocardial blood flow, assessed by positron emission tomography, improves significantly when patients are programmed from dual chamber pacing modes (such as DDD) to atrial demand pacing (AAI) at the same base rate despite long term ventricular pacing (111). Therefore it seems that functional ischaemia is a consequence of RV apical pacing and this may possibly contribute to longer term myocardial dysfunction. RV pacing can also increase or cause mitral regurgitation, worsen endothelial function as well as lead to long term changes in regional myocardial glucose metabolism (112-114).

2.3 Incidence of Pacemaker Induced Cardiomyopathy

The incidence of PICM reported in the literature depends on the definition applied as well as the study population and has never been examined in any large prospective study. The majority of registry studies have defined PICM as a greater than 10% fall in LVEF from baseline in the absence of an alternative cause for a cardiomyopathy (Table 2-1). Khurshid *et al.* showed in 257 patients with frequent RV pacing (>20%) that 19.5% patients developed PICM (≥10% decline in LVEF resulting in LVEF of <50% with

exclusion of alternate causes of cardiomyopathy) over a mean follow up of 3.33 years with mean baseline LVEF, in these patients, falling from 62.1% to 36.2% (115). Using the same diagnostic criteria Lim *et al.* showed a prevalence of 16.1% at a mean of 4.5 years in patients with baseline preserved LVEF and complete heart block (116). However Kiehl *et al.* found the prevalence of PICM fell to 12.3% when PICM was defined as post pacemaker LVEF of less than or equal to 40% or CRT upgrade in a similar cohort of patients (mean follow up 4.3 years) (117). Conversely a retrospective analysis by Ebert *el al.* of 991 patients with predominantly normal baseline LVEF found that only 6% of patients had a significant reduction in LVEF (drop in two predefined LVEF categories: at least an 11-15% fall in LVEF) at 44 months compared to baseline (11). These studies demonstrate the difficulty in interpreting retrospective analyses particularly as patient numbers were generally small, definitions of PICM differed and there was selection bias given a large number of patients failed to meet inclusion criteria. Kaye *et al.* have recently demonstrated that variability in incidence of PICM is largely dependent on the definition applied (118). Using three different definitions of PICM in their cohort of 118 patients the prevalence of PICM ranged from 5.9% to 39%. They concluded that a significant proportion of patients experience a decline in LVEF (39%) after pacemaker implantation but a clinically significant deterioration in LVEF was much less prevalent (5.9%-9.3%). Indeed a recent prospective study of 55 patients, with preserved LVEF and 2nd or 3rd degree AV block, has demonstrated that pacing induced left ventricular dysfunction (decline in LVEF of ≥5%) is much more prevalent than pacing induced cardiomyopathy (LVEF <45%) at 12 months (27% vs. 7% respectively) (119).

Study	n	Nature of study	Follow up (Mean)	Inclusion criteria	Definition of PICM	Incidence of PICM
Kachboura *et al.* (2008) (120)	43	Prospective	18 months	Preserved LVEF 2nd or 3rd degree AV block	Post-implant LVEF ≤40%*	25%*
Dreger *et al.* (2012) (121)	26	Retrospective	24.6 years	RVP >15 years due to 3rd degree AV block	LVEF ≤45%, dyskinesia during RVP and absence of other known causes of cardiomyopathy	15.4%
Khurshid *et al.* (2014) (115)	257	Retrospective	3.3 years	RVP >20% Pre-implant LVEF ≥50%	≥10% decrease in LVEF, resulting in LVEF <50% and absence of other known causes of cardiomyopathy	19.5%
Kiehl *et al.* (2016) (117)	823	Retrospective	4.3 years	3rd degree AV block Pre-implant LVEF >50%	CRT upgrade or post-PM LVEF ≤40%	12.3%
Ebert *et al.* (2016) (11)	991	Retrospective	44 months	Any indication for PM Pre-implant LVEF ≥41%	Deterioration of LV systolic function ≥2 pre-defined LVEF categories (≥11% fall in LVEF)	6%
Khurshid *et al.* (2016) (122)	184	Retrospective	3.4 years	RVP >20% Pre-implant LVEF ≥50%	≥10% decrease in LVEF, resulting in LVEF <50%	22.8%

				Absence of other known causes of cardiomyopathy		
Ahmed *et al.* (2017) (119)	55	Prospective	12 months	Pre-implant LVEF ≥55% 2nd or 3rd degree AV block	Reduction in LVEF to <45%	7.2%
Kim *et al.* (2018) (116)	130	Retrospective	4.5 years	3rd degree AV block Preserved LVEF	>10% decrease in LVEF, with a resultant LVEF <50%	16.1%
Kaye *et al.* (2018) (118)	118	Retrospective	3.5 years	Any indication for PM TTE <12 months prior to implant Absence of other known causes of cardiomyopathy	3 separate pre-defined groups 1. LVEF ≤40% if baseline LVEF ≥50%, or absolute reduction in LVEF ≥5% if baseline LVEF was <50% 2. LVEF ≤40% if baseline LVEF ≥50%, or absolute reduction in LVEF ≥10% if baseline LVEF ≤50% 3. Absolute reduction in LVEF ≥10% irrespective of baseline LVEF	9.3% 5.9% 39.0%

Cho *et al.* (2019) (123)	618	Retrospective	7.2 years∞	AV block or SND Pre-implant LVEF >50% No history of heart failure	LVEF <50% with either ≥10% decrease in LVEF or new regional wall motion abnormality unrelated to CAD Absence of other known causes of LV dysfunction	14.1%
Lee *et al.* (2019) (124)	604	Retrospective	5 years	AV block or SND Pre-implant LVEF >50% Absence of other known causes of cardiomyopathy.	≥10% decrease in the LVEF, with a resultant LVEF <50%	6.1%
Safak *et al.* (2019) (125)	170	Retrospective	2 years∞	Any indication for PM Pre-implant LVEF >45%	LVEF ≤45%, dyskinesia during RVP and absence of other known causes of cardiomyopathy	6.5%

Table 2-1: Incidence of pacing-induced cardiomyopathy in studies of right ventricular pacing

* Pacing induced cardiomyopathy with a post implant left ventricular ejection fraction of less than 40% was not a pre-defined outcome

∞Median follow up

Abbreviations: AV: atrioventricular, CAD: Coronary artery disease, CRT: Cardiac resynchronisation therapy, LV: Left ventricle, LVEF: Left ventricular ejection fraction, PICM: Pacing induced cardiomyopathy, PM: Permanent pacemaker, RVP: Right ventricular pacing, SND: Sinus node disease, TTE: Transthoracic echocardiogram

Furthermore the majority of studies did not report the clinical implications of these arbitrary changes in LVEF and therefore we do not know if they are in fact predictive of the development of heart failure. A recent study in 604 patients with SND and complete heart block has shown, over a 5 year follow up, that 51 patients (8.4%) developed either heart failure (HF) requiring hospitalisation and/or PICM (HF admission: 30 patients; PICM: 37 patients) suggesting significant overlap between these two entities (124). However these definitions largely ignore patients who may have heart failure with preserved ejection fraction and indeed Kaye *et al.* have demonstrated that a significant proportion of patients who experience a drop in LVEF still have a LVEF greater than 50% at follow up (118).

Development of heart failure symptoms or HF hospitalisation clearly need to be taken into consideration when defining PICM particularly as HF hospitalisation is prevalent among cardiac implantable device recipients. In the Mode Selection Trial in Sinus-Node Dysfunction (MOST) trial HF hospitalisation rates were between 10.3-12.3% dependent on pacing strategy at follow up (median 33 months) with a greater risk seen in those with a higher RV pacing burden (79, 126). Similarly in the The United Kingdom Pacing and Cardiovascular Events (UKPACE) trial of patients with high degree AV block, new or worsening heart failure developed in nearly 10% of patients at 3 years (60). Furthermore the risk seems to be higher for patients with a baseline reduction in LV function with heart failure hospitalisation occurring in over a quarter of patients assigned to RV pacing in the Biventricular Versus Right Ventricular Pacing in Patients with AV block (BLOCK HF) trial and 22.6% of those patients assigned to dual chamber pacing in the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial (80, 127). Data from a large registry of 21,202 patients demonstrated that new onset heart failure occurred in nearly 16.8% at a median follow up of 2.35 years and the risk was increased for patients with complete AV block (128). Furthermore Tayal *et al.* have recently shown in a large registry of 27,704 that the cumulative incidence of heart failure in patients with pacemakers and a right ventricular pacing lead without pre-existing heart failure was 10.6% up to 2 years (10). Importantly risk of heart failure was significantly greater than age and sex matched controls with the risk being highest in the first 6 months after implantation.

Although variable approximately 10-15% of patients with normal baseline LV function will experience a significant decline in LV function after pacemaker implantation. The extent to which a decline in LVEF leads to the clinical syndrome of heart failure is unclear and variability in both changes in LV function and HF hospitalisation between studies suggests that several patient and pacemaker related factors influence the development of PICM. Furthermore, one could argue that LVEF may not be the most useful defining

factor for PICM. Ejection fraction is calculated by the following formula where LV stroke volume (SV) is calculated by the difference between the left ventricular end-diastolic volume (LVEDV) and the left ventricular end-systolic volume (LVESV)

$$LVEF\ (\%) = LVSV/LVEDV \times 100$$

Equation 1: Calculation of Left Ventricular Ejection Fraction

This in turn means that LVEF is very dependent on LVEDV. End-diastolic volume (EDV) is largely dependent on preload which may vary greatly in patients awaiting pacemaker implantation. Indeed during bradycardia the LV filling time is increased leading to a larger preload and subsequently bigger EDV. In addition this may be confounded in patients with AV block where loss of AV synchrony further augments preload. Left ventricular end-systolic volume, which is relatively insensitive to preload, is a better measure for the longitudinal assessment of response to pacing and subsequent cardiac remodelling. White *et al.* have previously shown in patients with myocardial infarction with impaired LV function that LVESV has greater predictive value in survival than LVEDV or LVEF (129). Furthermore in patients undergoing CRT, reductions in LVESV are associated with clinical response to therapy and lower risk of long term heart failure events (130, 131). Therefore changes in LVESV can potentially be used to evaluate remodelling and heart failure risk over the longer term.

2.4 Risk factors for pacing-induced cardiomyopathy and development of heart failure

Given a significant proportion of pacemaker recipients have a measurable decline in LV function following implantation, several studies have attempted to identify risk factors, both before and after implantation, that may lead to development of heart failure or PICM. As with the data on prevalence of PICM, the data often focus on small retrospective cohorts with differing definitions of PICM and variable lengths of follow up.

2.4.1 Pre-implantation factors

Pre-implantation risk factors identified for development of PICM range from patient factors such as older age at implantation and male sex to simple ECG criteria (115, 132).

Baseline ECG parameters that have been associated with PICM include wider intrinsic QRS duration and pre-implantation LBBB (115, 123). Interestingly pre-implantation LBBB in pacemaker recipients has been shown to be an independent predictor of heart failure hospitalisation and death (133). Lower preimplantation LVEF and a baseline LVEF <50% are associated with development of PICM and the risk of heart failure hospitalisation (115, 117, 133).

Using the ECG to derive a myocardial scar score has also been shown to be associated with the development of pacing induced heart failure (132). Perhaps the myocardial substrate plays an important role in development of heart failure after pacing. Sub-analysis of the MOST trial highlighted the presence of AV block, pre-existing heart failure, lower LVEF and history of myocardial infarction as pre-implantation factors that were associated with an increased risk of subsequent heart failure (134). Tayal *et al.* have more recently shown in a large registry that the risk of heart failure after RV pacing was increased with male sex, chronic kidney disease and history of myocardial infarction (10). They speculated that perhaps underlying myocardial fibrosis in the presence of RV pacing is the mechanism for the development of heart failure. Indeed the presence of dyssynchrony, assessed by echocardiography, in patients after acute myocardial infarction has been shown to be a strong predictor of long term hospitalisation for heart failure (135). They thought a similar mechanism may exist in those with chronic kidney disease as myocardial fibrosis is prevalent in these patients (136).

2.4.2 Post implantation factors

Data from the MOST and DAVID trials identified a threshold of total RV pacing burden over 40% for the 'tipping point' at which the risk of heart failure hospitalisation is greatly increased (126, 137). However retrospective studies examining the burden of RV pacing on development of PICM are conflicting. It has been found to act as a continuous variable or a categorical variable with the latter ranging from a cut off of >20% to ≥86% (117, 123, 132).

Longer paced QRS durations have been shown to be associated with development of PICM in those with preserved LVEF although cut off for the duration differed between studies (116, 122). Khurshid *et al.* found that a paced QRS duration of >150 milliseconds (ms) was 95% sensitive for PICM. Similarly Kim *et al.* showed a paced QRS >140ms had a sensitivity of 95% and a QRS duration >167ms had a specificity of 90% for detecting

PICM. A paced QRS duration >163ms was also associated with a significantly increased risk of HF hospitalisation over a 5 year follow up (HR 3.37; 95% CI 1.53-7.43; p=0.003) (124). Furthermore a paced QRS duration of >163ms with an axis of ≥-65° has been shown to be associated with a nearly six times greater risk of heart failure than <163ms with an axis of <-65° (138).

More recent work has focussed on the use of advanced imaging techniques to improve identification of those at risk of decline in LV function. Two separate studies in patients with AV block and preserved LVEF have evaluated the role of strain analysis and global longitudinal strain (GLS) for subsequent detection of decline in LV function. Xu *et al.* performed 3-dimensional (3D) speckle tracking in 68 patients to assess whether GLS at one month could predict subsequent pacing-induced LV dysfunction (PIVD; reduction of LVEF by ≥5% at 12 months) (139). On multivariate analysis only GLS at one month was an independent predictor of PIVD at 12 months (Odds ratio 1.62; 95% CI 0.986-2.210; p=0.009). Similarly in a study of 55 patients, 27% of whom developed PIVD, GLS was significantly lower at one month in those who developed PIVD at 12 months compared to those who did not (119). Global longitudinal strain also had high predictive accuracy for not only PIVD at 12 months but also for PICM (reduction in LVEF to <45%) although the absolute number who developed PICM was low (n=4)

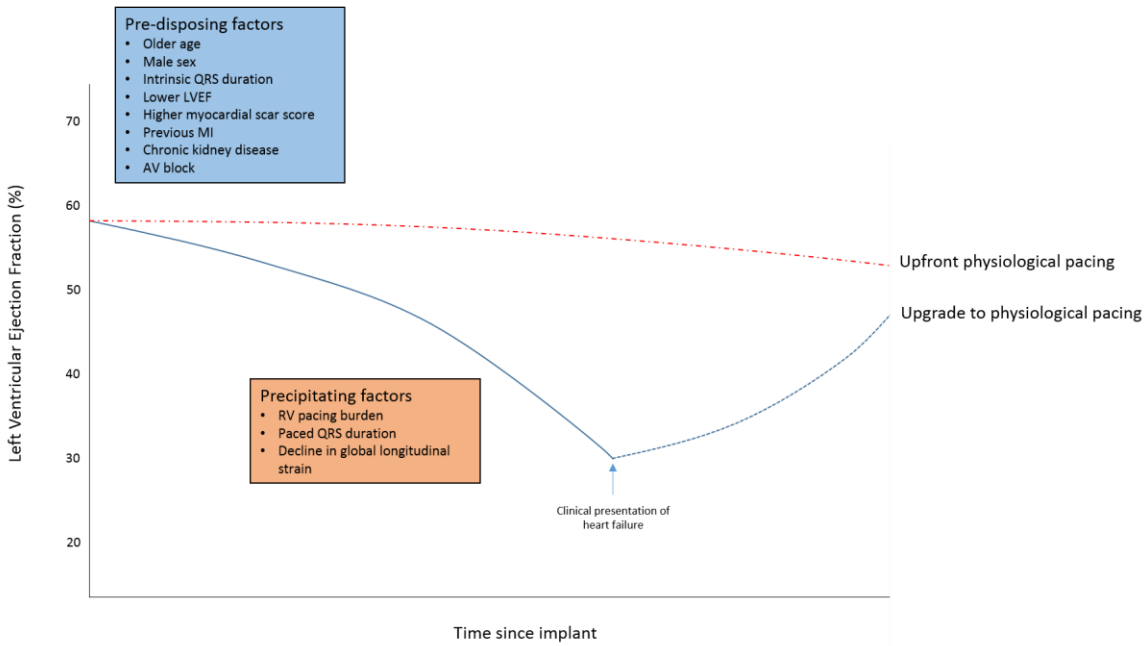


Figure 2-3: Factors implicated in development of pacing induced cardiomyopathy and potential effect of upfront physiological pacing

Figure shows the pre-disposing (blue box) and precipitating (orange box) factors that have been implicated in PICM and how upfront physiological pacing (red dotted line) in susceptible individuals could prevent the development of heart failure (blue line) and need for re-intervention (blue dashed line).

Abbreviations: AV: atrioventricular, LVEF: left ventricular ejection fraction, MI: myocardial infarction, RV: right ventricle

Despite numerous studies evaluating risk factors for PICM it seems that no single factor is absolutely predictive of the development of PICM (Figure 2-3). Indeed, the risk of PICM increases with the number of risk factors present in an individual (123). The data suggest that those with LV dysfunction upfront are at higher risk and perhaps this is because pacing induced dyssynchrony and electromechanical decoupling are exaggerated in the presence of intrinsic myocardial tissue damage. In those with a normal LVEF at baseline the presence of subclinical disease may potentially be 'unmasked' by the induction of RV pacing leading to an increased risk of heart failure or decline in LV function. Risk factors such as longer intrinsic and paced QRS durations and lower GLS are not mechanisms of development of PICM and perhaps just reflect an underlying problem with the myocardial substrate that leads to slower myocardial conduction times and altered deformation. Fent *el al*. have previously shown that GLS is lower in patients with prior myocardial infarction even when LVEF is preserved (140). Therefore, it may be the interaction between the underlying substrate and pacing factors such as paced QRS duration or burden of RV pacing that ultimately determine an individual's risk of heart failure. However, assessing for subclinical disease in patients is challenging and even more so in patients with advanced AV block and haemodynamic instability.

2.5 Prognosis of PICM

Unfortunately, despite a growing body of evidence of the adverse effects of RV pacing, there are very little data on the prognosis of patients who develop PICM. Cho *et al.* have recently shown that at median follow up of 7.2 years the risk of all-cause death or heart failure admission was significantly higher in patients with PICM compared to those without PICM [38.3% vs. 54.0%, adjusted hazard ratio (HR) 2.93; 95% confidence interval (CI) 1.82–4.72; p<0.001] (123). Baseline impairments of LV function or a greater burden of RV pacing seem to pose the greatest risk of heart failure hospitalisation (79, 80, 126). Indeed in an unselected population of bradycardia pacemaker recipients, there was an 8% increased risk of death from heart failure per 10% increase in RV pacing (141). A greater degree of LV dyssynchrony induced after long term RV pacing was also associated with the risk of heart failure hospitalisation and mortality (142). Furthermore the development of heart failure after pacing in patients with acquired AV block (>90% RV pacing) was an adverse prognostic marker with greater downstream cardiovascular mortality compared to individuals who do not develop heart failure (36.7% vs. 2.7%, p< 0.001) (143).

2.6 Therapeutic options for prevention or treatment of pacing-induced cardiomyopathy

Pacing mediated factors such as RV pacing burden and paced QRS duration have been implicated in the development of PICM and heart failure after initiation of RV pacing. These associations have stimulated research into attempting to mitigate for these factors through the avoidance of unnecessary RV pacing, alternate RV pacing lead positions and upfront physiological pacing.

2.6.1 Biventricular Pacing

One potential therapeutic option for the prevention and treatment of pacing induced heart failure is the advent of biventricular pacing or CRT. Biventricular pacing has been shown to improve ventricular dyssynchrony as well as leading to improvements in LVEF, hospitalisation for HF and mortality in symptomatic patients with prolonged QRS duration and severely reduced LV systolic function (144-146).

2.6.1.1 Upgrading to biventricular devices in RV paced patients

Several studies have demonstrated that CRT upgrade in patients with chronic RV pacing, symptomatic heart failure and impaired LV function is associated with improvements in ejection fraction, functional class, dyssynchrony, reverse remodelling and risk of hospitalisation (147-149). Current guidelines give a Class 1B recommendation to upgrade to CRT in HF patients with an LVEF <35% and high burden of RV pacing and New York Heart Association (NYHA) functional Class III-IV despite optimal medical therapy (30). Furthermore upgrading to CRT in patients with chronic RV pacing is associated with a similar reduction in all-cause mortality and comparable improvements in functional capacity and reverse remodelling to patients receiving *de novo* CRT implantation (150). Interestingly even in patients with relatively mild LV dysfunction, LVEF <40% or left ventricular end-diastolic diameter (LVEDD) >55 mm, upgrading to a CRT device led to reversal of LV remodelling and improvements in NYHA Class compared to RV pacing (151). In patients listed for routine generator replacement with mild or no heart failure symptoms, >80% RV pacing and left ventricular dysfunction, upgrading to CRT compared to standard generator replacement was associated with improvements in left ventricular function, exercise capacity and quality of life (152). Therefore perhaps there is a role for CRT upgrade in those with LV dysfunction even in the absence of significant heart failure symptoms.

2.6.1.2 Upfront RV Pacing versus Biventricular Pacing

The promising results of the data on upgrading RV pacing patients with LV dysfunction to CRT led to suggestions that perhaps patients with reduced LV function and a standard pacemaker indication or high expected burden of RV pacing may benefit from *de novo* CRT. The evidence from RCTs of *de novo* CRT compared to RV pacing in patients with conventional pacemaker indications is discussed below (Table 2-2).

2.6.1.2.1 Reduced LVEF at baseline

Early work in the Homburg Biventricular Pacing Evaluation (HOBIPACE) and the Conventional Versus CRT Pacing in Heart Failure and Bradyarrhythmia Therapy (COMBAT) trials both found CRT to be superior to conventional RV pacing (153, 154). HOBIPACE was a prospective randomised study of 30 patients with LV dysfunction (LVEDD ≥60 mm and LVEF ≤40%) and AV block who received 3 months of either RV pacing or biventricular pacing after which they crossed over to receive the other pacing modality. Biventricular pacing in both trials was associated with improvements in LVESV, LVEF and quality of life. In the COMBAT trial there was also significantly greater mortality during RV pacing in comparison to CRT.

More recently the BLOCK HF study evaluated the effects of CRT compared to RV pacing in patients with LV dysfunction (LVEF ≤ 50%) and AV block without a conventional indication for CRT (127). 691 patients underwent CRT implantation (with or without ICD) and were randomised to either RV apical pacing or biventricular pacing and the majority of patients were in NYHA class II-III. At a mean follow up of 37 months the study reported a significant reduction in the primary outcome of time to death from any cause, urgent care visit for heart failure or ≥15% increase in LV end-systolic volume index (LVESVi) with biventricular pacing compared to RV pacing [45.8% vs. 55.6%; HR, 0.74; 95% CI: 0.6 to 0.9]. The outcome was primarily driven by an increase in LVESVi. However, when this was removed from the analysis, there was still a 27% risk reduction in death from any cause or urgent care visit for heart failure with biventricular pacing (HR 0.73; 95% CI, 0.57 to 0.92). Sub analysis of the trial has shown that biventricular pacing was associated with improved quality of life, heart failure status and LV reverse remodelling (155, 156). There are a number of limitations of the trial particularly due to a high crossover rate from RV to biventricular pacing and a significant proportion of patients with missing echocardiographic data. The results may have also been influenced by the

proportion of patients with significant LV dysfunction (nearly one third with LVEF<35%) and the fact that 20% of patients with first degree AV block had forced RV pacing. Translating these findings to all patients with LVEF ≤ 50% and AV block is challenging particularly as LV lead implantation carried a complication rate of 6.4%.

2.6.1.2.2 Normal LVEF at baseline

Albertsen *et al.* randomised 50 patients with normal LVEF and high grade AV block to either DDD with rate response pacing or biventricular pacing and found that the latter preserves LV function, reduces dyssynchrony (number of segments with reduced longitudinal shortening) and N-terminal-pro Brain Natriuretic Peptide (BNP) compared to DDD pacing at 12 months and the findings were maintained at 3 year follow up (157, 158). Similarly the Biventricular pacing in patients with bradycardia and normal ejection fraction (PACE) trial implanted 177 patients with a CRT system for SND or AV block and randomised to either RV or biventricular pacing (159). The primary endpoints of LVEF and LVESV measured by echocardiography remained unchanged in the biventricular group but LVEF decreased progressively at follow up (mean duration 4.8 years) in the RV group with a corresponding increase in LVESV. Longer term follow-up showed a higher prevalence of HF hospitalisation in the RV pacing group compared to the biventricular group (23.9% vs. 14.6%, p=0.006) (160). In contrast to these findings the Preventing Ventricular Dysfunction in Pacemaker Patients without Advanced Heart Failure (PREVENT-HF) trial failed to demonstrate any improvements in LVEF or LV volumes with biventricular pacing (161). The reasons for the differences in outcomes between these trials are not clear but may be due differences in not only the baseline LVEF, which was higher in the PACE population, but also the timing of baseline echocardiography. In the PACE study echocardiography was performed prior to device implantation but in the PREVENT-HF study it was done prior to hospital discharge so some changes in LVEF may be attributable to the immediate effect of pacing induced dyssynchrony.

Unfortunately, the largest study in this field has never been formally published. The Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronisation (BioPace) trial released preliminary results in 2014 (162, 163). The study recruited patients with AV block (average LVEF 55%) and 902 were assigned to CRT and 908 to RV pacing. The study did not show any difference in first hospitalisation secondary to heart failure or time to death between RV and biventricular pacing (follow up 5.6 years)

although there was a trend in favour of biventricular pacing. Importantly results were similar for patients with an LVEF below 50% and those over 50%.

Trial	N	Design	Inclusion criteria	Treatment	Follow up	Primary Endpoint	Outcomes
HOBIPACE (2006)(153)	30	Prospective, randomised crossover	AV block LVEDD ≥60mm & LVEF ≤40%	Run in period then 3 months RVP or BiVP and crossover	3 months then crossover	LVESV LVEF Peak oxygen consumption.	BiVP significantly reduced LVESV by 17%, increased LVEF by 22% and peak oxygen consumption by 12% compared to RVP.
Albertson *et al.* (2008)(157)	50	Randomised, cross over	High grade AV block	DDD (n=25) BiVP (n=25)	12 months	LVEF	No significant difference in LVEF
PACE (2009)(159)	177	Prospective, randomised, double blind, multi-centre	LVEF>45% Any indication for pacing	RVP (n=88) BiVP (n=89)	12 months	LVEF LVESV	Significantly lower LVEF (55% vs. 62%) and higher LVESV (36ml vs. 28ml) in RVP arm.
COMBAT (2010)(154)	60	Prospective, randomised, double blind, crossover	NYHA II-IV LVEF<40% AV block	Group A:RVP then BiVP then RVP Group B: BiVP then RVP then BiVP	At least 3 months for each mode	QoL NYHA class	Significant improvements in QoL and NYHA Class with BiVP

PREVENT-HF (2011)(161)	108	Prospective, randomised, multi-centre	Expected RVP burden of >80%	DDD (n=58) BiVP (n=50)	12 months	Primary: LVEDV Secondary: LVESV, LVEF, mitral regurgitation and combined HF hospitalisation & mortality	No significant differences in any outcome
Block-HF (2013)(127)	691	Prospective, randomised, multi-centre	AV block NYHA I-III LVEF≤50%	RVP (n=342) BiVP (n=349)	Mean 37 months	Time to death from any cause, urgent care visit for HF or ≥15% increase in LVESVi	Significantly lower incidence of primary outcome in BiVP group 46% vs. 56% (HR: 0.74; 95% CI: 0.6 to 0.9)
BioPace (2014)(162)	1810	Prospective, randomised, multi-centre	AV block or chronic AF (rate ≤60) Any LVEF	RVP (n=908) BiVP (n=902)	Mean 5.6 years	Composite of time to death or first HF hospitalisation	Non-statistically significant trend towards BiVP pacing

Table 2-2: Randomised clinical trials comparing right ventricular pacing and biventricular pacing.

Abbreviations: AF: atrial fibrillation, AV: atrioventricular, BiVP: biventricular pacing, CI: confidence interval, DDD: dual chamber pacemaker, HF: heart failure, HR: hazard ratio, LVEDD: left ventricular end-diastolic diameter, LVEF: left ventricular ejection fraction, LVESV: left ventricular end-systolic diameter, LVESVi: left ventricular end-systolic diameter, NYHA: New York Heart Association, QoL: quality of life, RVP: right ventricular pacing

Therefore we are left with inconclusive data on those individuals who may benefit from CRT particularly given the conflicting results of BLOCK-HF and BioPace. Patients in BLOCK-HF did appear to have more severe baseline heart failure with a lower mean LVEF (40% vs. 55%) and more prevalent LBBB (32.5% vs. 17.2%). The role of CRT in patients with a predicted high burden of RV pacing and normal or modest depression in LV function is certainly less clear. However, a recent meta-analysis in patients with LVEF >35% which collated data from the PACE, PREVENT-HF and Albertson *et al.* trials found, at a mean follow up of 1.91 years that patients with biventricular pacing had smaller end-systolic (mean difference -7.2ml; $p<0.01$), end-diastolic volumes (mean difference -2.7ml; $p<0.01$) and higher LVEF (mean difference 6.3%; $p<0.01$) (164). Indeed a meta-analysis of eleven RCTs of biventricular pacing versus right ventricular pacing in AV block, including patients undergoing AV node ablation, found biventricular pacing to be associated with reductions in LVESV and LVEDV at 3,6 and 12 months and a higher LVEF at all follow up time points even after 2 years (165). The study also reported that results were not changed in sensitivity analysis after removing patients with induced AV block and excluding those with LVEF less than 50%. Furthermore a pooled analysis of twelve RCTs has shown that biventricular pacing may be associated with better clinical endpoints as both all-cause mortality and heart failure hospitalisation were significantly lower than with RV pacing (166). It should be noted that none of the meta-analyses contained data from the BioPace trial.

2.6.2 Alternate pacing sites

The RV apex is easily accessible and therefore often used as a standard pacing site for lead implantation. Alternative pacing sites have been sought within the right ventricle to try and facilitate more physiological conduction and subsequent contraction. The most commonly studied sites are the RVOT, RV septum and proximal conducting system (Bundle of His).

2.6.2.1 RV Septal leads

The RV outflow tract and septal regions have been evaluated in several small studies with differing results. A recent meta-analysis has reported that RV non-apical pacing is associated with higher ejection fraction at follow up compared to RV apical pacing (167). However two large trials, the Effect of right ventricular pacing lead site on left ventricular function in patients with high-grade atrioventricular block (Protect-Pace) and Chronic Apical and Non-apical Right Ventricular Pacing in Patients with High-Grade

Atrioventricular Block (Right Pace), failed to demonstrate any benefits with non-apical pacing sites (168, 169). The Protect-Pace study randomised 240 patients with high grade AV block (>90% pacing) and LVEF >50% to receive RV apical or RV high septal pacing and at 2 years' follow-up found no significant differences in LVEF, heart failure hospitalisation, mortality or burden of atrial fibrillation between the groups. Given the disappointing results from trials, RV non-apical pacing has not been routinely adopted in clinical practice particularly as it associated with longer lead positioning and fluoroscopy times (168).

2.6.2.2 His bundle pacing

His bundle pacing (HBP) provides an alternative method of performing bradycardia pacing and is theoretically more physiological as it allows impulses from the sinoatrial node to be rapidly propagated through the His-Purkinje network to both ventricles, thereby preserving both electrical and mechanical synchrony. Indeed HBP has been shown to normalise QRS duration in bundle branch block (170). Several smaller studies have suggested that HBP may improve quality of life, NYHA class, lower risk of atrial fibrillation, and preserve LV function (171-174). Recently two observational studies, in patients with a bradycardia indication for pacing, comparing HBP at one institution with RV pacing at another institution have shown promise as both studies met the primary endpoint (175, 176). In the first study of 198 patients the primary outcome of either death or HF hospitalisation at 5 years was significantly lower in the group assigned to HBP pacing compared to RV pacing where the pacing burden was >40% (32% vs 53% respectively; HR 1.9;p=0.04) (175). However HBP was only successful in 80% of patients and there was a higher need for lead revisions (6.7% vs 3%) and generator change (9% vs 1%) compared to those assigned to RV pacing. The second study in 765 patients found the primary endpoint of death, HF hospitalisation, or upgrade to CRT was significantly reduced in the HBP group compared to the RV pacing group (25% vs. 32% respectively HR 0.71; p=0.02) at a mean follow up of 2 years and was primarily observed in patient with RV pacing burden over 20% (176). Interestingly the success rate of HBP was better than the aforementioned study (92%) although lead revisions were still higher in the HBP group (4.2% vs. 0.5%).

There are no long term RCTs directly evaluating clinical outcomes between HBP and alternate RV pacing sites although studies such as His Optimized Pacing Evaluated for Heart Failure (HOPE-HF) trial should shed further light on this (177). A lack of RCT data and concerns regarding the technical challenges of permanent HBP as well as a higher

complications rate have limited its use in clinical practice to date. Interestingly upgrading to HBP in 16 patients with pacing dependent heart failure and LVEF <50% was associated with shorter paced QRS duration (156.9+/-21.7 ms to 107.1+/-16.5ms; p<0.01), increases in LVEF from baseline (35.7%+/-7.9% to 52.8%+/-9.6% (p<0.01) and lower NYHA Class at 1 year and therefore may provide an alternative to CRT in this population (178).

2.6.3 Ventricular pacing avoidance algorithms

The development of specific pacing algorithms is another approach that has been taken in order to try to minimise the amount of RV pacing and thereby avoid the induction of dyssynchrony. These algorithms try to preserve AV conduction and allow normal ventricular activation (179). Several studies have shown that ventricular pacing algorithms do successfully reduce the burden of ventricular pacing, particularly in patients with SND, and prolong estimated battery longevity (179-182). Furthermore Gierula et al. have demonstrated that by implementing a simple protocol prior to pacemaker generator replacement it is possible to see significant reductions in the RV pacing burden with a resultant improvement of 6% in mean LVEF at 6 months (p<0.0001 from baseline) (183). However a recent meta-analysis of seven RCTs comparing standard DDD programming to ventricular pacing reduction algorithms found no difference in the incidence of persistent AF, all cause hospitalisation or mortality (182). One possible explanation for this is that pacing avoidance algorithms can lead to prolonged ‘non-physiological’ AV delays which can lead to reductions in LV preload, raised left atrial pressure and may induce diastolic mitral regurgitation (184). This AV dyssynchrony may lead to a higher incidence of atrial fibrillation and heart failure events (185). In addition, these algorithms are of limited use in patients with advanced AV block where ventricular pacing is unavoidable.

2.6.4 Medications

Medications such as beta blockers and angiotensin converting enzyme inhibitors are established therapies in symptomatic HF with reduced LVEF with strong recommendations in current guidance (186). However, there is a paucity of data on their use in pacing induced dysfunction and patients with pacemakers were often excluded from large clinical trials. Schwerg *et al.* evaluated use of optimal medical therapy and CRT on patients screened for PICM at outpatient clinics (187). In the 20 patients that

underwent CRT upgrade mean LVEF before upgrade was 33.3% and improved to 47.6% ($p<0.001$) within 6 months whereas in the 17 patients on optimal medical therapy alone, LVEF did not change from baseline (mean 40.5%) over 1 year. Given the lack of LVEF improvement, one might surmise that medical therapy can prevent deterioration in LVEF although it remains unclear whether neurohormonal blockade can overcome the electrical and mechanical dyssynchrony induced by RV pacing to the point of improving LVEF.

2.7 Current recommendations for physiological pacing

Current international guideline recommendations on the use of physiological pacing (CRT or His bundle pacing) are summarised in Table 2-3. Recent ESC guidelines in patients with systolic heart failure give a Class IA recommendation to the use of CRT over RV pacing in patients with an indication for pacing and high-grade AV block (186). This strong recommendation is based not only on data from BLOCK-HF but also on patients with symptomatic AF undergoing AV node ablation which is a different population, who may be more prone to development of heart failure, compared to those presenting solely with symptomatic bradycardia (127, 188, 189). Interestingly this is at odds with previous ESC and Canadian Cardiovascular Society (CCS) guidelines where upfront CRT only carries a IIa and IIb recommendation respectively (30, 190). Interestingly the development of newer pacing techniques, namely His bundle pacing, have seen the most recent American guidelines defining a further cohort of patients with a mild to moderate LV impairment (LVEF 35-50%) due to uncertainties about whether physiologically pacing (CRT or His bundle pacing) is superior to RV pacing in this population (191). Based on a systematic review conducted for the guidelines it was concluded that it was reasonable to choose physiological pacing over RV pacing if the RV pacing burden was expected to be over 40% (Class IIa) (164, 191). Furthermore this guideline is the first to suggest a role for His bundle pacing in those with AV block with any pre-implant LVEF (Class IIb).

Recommendation	Society	Year of publication	Class	Level
Reasonable to choose physiological pacing (CRT or His bundle pacing) over RVP in patients with AV block with an indication for pacing and a LVEF between 36% and 50% with an expected RVP burden of >40%.	ACC/AHA/HRS(191)	2018	IIa	B
Reasonable to choose RVP over physiological pacing in patients with AV block with an indication for pacing and a LVEF between 36% and 50% with an expected RVP burden of <40%.	ACC/AHA/HRS(191)	2018	IIa	B
Consider His bundle pacing in patients with AV block at the level of the AV node who have an indication for permanent pacing.	ACC/AHA/HRS(191)	2018	IIb	B
Reasonable to consider CRT in patients with LVEF ≤35% undergoing new or replacement device implantation with an expected RVP burden of >40%.	ACCF/AHA(192)	2013	IIa	C
Recommended to upgrade from PM or ICD to a CRT device in patients with a high burden of RVP, LVEF<35% and NYHA III-IV despite medical therapy.	ESC(30)	2013	I	B
Consider upfront CRT in patients with heart failure, reduced LVEF and an expected high burden of RVP to reduce the risk of worsening HF.	ESC(30)	2013	IIa	B
Recommended to use CRT rather than RVP in patients with HFrEF* who have an indication for ventricular pacing and high grade AV block including patients with AF	ESC(186)	2016	I	A

Consider CRT upgrade in patients with HFrEF* with a conventional pacemaker or ICD who have a high burden of RVP and develop worsening HF despite guideline directed therapy.	ESC(186)	2016	IIb	B
Consider CRT in patients with HF symptoms and reduced LVEF that require chronic RVP.	CCS(190)	2017	IIb	B

Table 2-3: Guideline recommendations for physiological pacing in patients requiring bradycardia support

*HFrEF: Heart failure reduced ejection fraction – defined as symptoms and/or signs of heart failure and LVEF<40%

Abbreviations: ACC: American College of Cardiology, ACCF: American College of Cardiology Foundation, AF: atrial fibrillation, AHA: American Heart Association, AV: atrioventricular, CRT: cardiac resynchronisation therapy, ESC: European Society of Cardiology, HF: heart failure, HRS: Heart Rhythm Society, ICD: implantable cardioverter defibrillator, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, PM: pacemaker, RV: right ventricle, RVP: right ventricular pacing

Unfortunately these guidelines use differing terminology with different patient populations while ultimately trying to address the same question: Should we consider more physiological pacing techniques for patients presenting with bradycardia? Therefore the correct interpretation and implementation of guidelines in this group of patients remains a challenge. The fact that the most recent American guidelines have attempted to define treatment based on LVEF and pacing burden highlights the need for a more individualised device selection in these patients. Several important questions remain unanswered in trying to identify those who will benefit most from physiological pacing. Firstly, although patients with lower baseline LVEF appear most susceptible to development of heart failure after RV pacing there are conflicting data from the two largest RCTs, namely BLOCK-HF and BioPACE, about whether these patients benefit from CRT (127, 162). Even the recent systematic review incorporated into the latest American guidelines conceded that the meta-analysis was limited by the small number of predominantly single centre studies (164). Furthermore guidelines do not address those with a normal baseline LVEF as currently there are no RCT data to support physiological pacing although clearly a significant subset of these patients develop heart failure or have a measurable reduction in LV function with RV pacing (Table 2-1). Secondly, guidelines use differing wording for the potential burden of RV pacing from 'expected high burden of RV pacing', to those with high grade AV block and finally those with a pacing frequency of over 40%. The actual threshold for RV pacing after which patients develop heart failure is contentious and may be as low as 20%; some studies suggest that RV pacing burden does not influence the development of heart failure at all (117, 124). Predicting the burden of RV pacing over the longer term prior to implantation may also be challenging particularly with the development of RV pacing avoidance algorithms. Thirdly, the attainment of more 'physiological' pacing needs to take into account any potential complications such as battery longevity, longer procedure times and device or lead malfunction. Indeed, in the BLOCK-HF trial LV lead complications occurred in 6.4% of patients and the need for lead revision and generator change is higher with His bundle pacing compared to RV pacing (127, 175, 176).

Clearly there are limitations to the guideline suggested strategies which only carry a level B or C recommendation. However, prevention of heart failure should remain of paramount importance especially as it carries such a poor prognosis (193). Therefore even watchful watching may not be the correct approach, as although subsequent upgrades to CRT or HBP seem effective at reversing LV remodelling in this cohort, the risk of complications for a revision procedure are often greater, especially for CRT where they can be as high as 19% (150, 194). There is a need for randomised controlled

studies using newer objective measures to identify patients upfront to prevent the development of heart failure and balance the competing risks.

2.8 Role of imaging in identification and risk stratification of PICM

It appears that CRT, whether implanted *de novo* or as an upgrade to CRT can partially reverse remodelling associated with RV pacing particularly in those with symptoms and severe reductions in LVEF. Outside of this population, it remains unclear which patients are most susceptible to developing PICM. As such there may be a role for imaging techniques to help identify these patients to allow closer monitoring or guide therapy.

2.8.1 Echocardiography

Data from BLOCK-HF and smaller studies have suggested that impaired baseline LVEF (<50%) is associated with further reductions in LVEF at follow up, and development of PICM, as well as heart failure (117, 127, 195). These findings were not replicated in the BioPace study and there is no cut off of LVEF that is absolutely predictive of PICM. In addition there remains limited understanding of the factors that influence development of PICM in patients with preserved systolic function (162). Importantly LVEF has large variability and once LVEF is decreased not all patients will respond to interventions such as CRT (117, 196).

Therefore efforts have focussed on more advanced echocardiographic techniques in order to identify those at risk of PICM. Both tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) divide the myocardium into pre-defined segments and then track their motion throughout the cardiac cycle (197). However the use of the Doppler Effect with TDI imaging means that motion can only be measured in one direction and may be influenced by factors such as regional tethering of the myocardium. Speckle tracking allows angle-independent assessment of myocardial motion in two dimensions thus overcoming the limitations of TDI imaging. These techniques allow the assessment of LV dyssynchrony, global and regional strain as well as LV torsion.

The use of these echocardiographic techniques has helped provide insight into the LV changes induced by RV pacing. Acute right ventricular pacing has been shown to induce dyssynchronous contraction, regional changes in strain as well as impairing LV

longitudinal shortening and LV twist (50, 100, 198). Ooka *et al.* showed in patients with mildly reduced LVEF that acute RV pacing was associated with significant increases in dyssynchrony compared to those with preserved baseline LVEF (195). Similar findings were described by Pastore *et al.* across a range of LV ejection fractions with the prevalence and degree of pacing induced dyssynchrony significantly higher in those with lower LVEF (199). In patients with SND randomised to AAI or DDD pacing, patients receiving DDD pacing had greater LV dyssynchrony at 12 months with an increase in dyssynchrony from baseline to follow up and this was associated with a decline in LVEF (200).

The use of TDI and STE techniques on LV remodelling and clinical outcomes have also been evaluated. Tissue Doppler imaging analysis of participants in the PACE trial found that 32% of patients had pacing induced dyssynchrony at 1 month after implantation and this was more common in those with RV apical pacing compared to BiVP (50.7 vs. 12.3%; $p<0.001$) (201). At median follow up (4.8 years) patients with early pacing-induced dyssynchrony had lower LVEF and greater LVESV and the presence of early pacing-induced dyssynchrony independently predicted subsequent decline in LV function. Importantly the induction of LV dyssynchrony has been shown to be independently associated with mortality and increased rates of heart failure hospitalisation at 5 years (142). Two recent studies have demonstrated that reduced GLS at 1 month has a high predictive accuracy for a reduction in LVEF ≥5% at 12 months (119, 123). The number of patients who developed PICM was very small and it was not possible to conclude whether this small drop in LVEF correlates with symptoms and development of heart failure. These techniques further our understanding of PICM and highlight the importance of induction of dyssynchrony and changes in strain. These tools may therefore be of use in monitoring patients for development of PICM but further work is needed to determine their utility in changing the upfront management of these patients.

2.8.2 Cardiovascular Magnetic Resonance

Cardiovascular magnetic resonance is a vital tool for the clinical assessment of a variety of cardiovascular diseases leading to its inclusion in many international guidelines and multi-parametric CMR has a vast array of research applications (9). Until recently magnetic resonance imaging (MRI) was contraindicated in patients with implanted cardiac devices due to the susceptibility of pacemaker leads to heating or movement in the magnetic field, and inappropriate inhibition of pacing or therapies by radio frequency gradients (202). In 2011 the first MRI conditional cardiac devices were licensed for use

and now most implanted cardiac devices are MRI conditional. MRI conditional devices are programmed with specific software which is activated before entering the magnetic field. This safe mode is typically asynchronous pacing with high voltage bipolar outputs (to avoid inadvertent inhibition) and temporarily disabled anti-tachycardia therapies. Furthermore many chronically implanted pacing systems have now been retrospectively shown to be safe for MRI under certain conditions (22). A suggested scan protocol for patients with implantable devices to provide mechanistic insight and surveillance of patients at risk of PICM is shown in Figure 2-4 and the individual aspects of this protocol are discussed in more detail below.

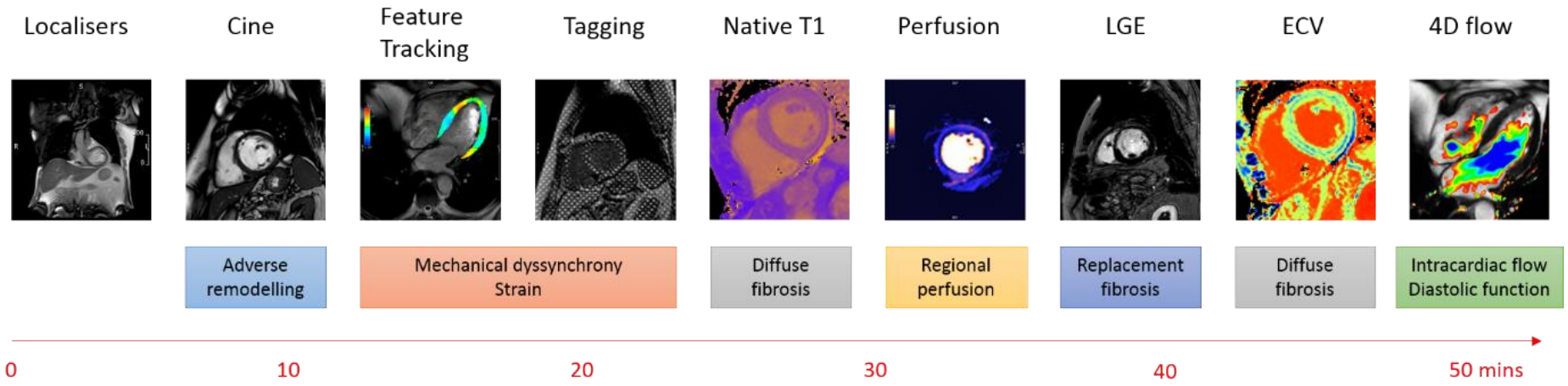


Figure 2-4: Proposed CMR scan protocol in patients with pacemakers and/or ICDs to evaluate mechanisms underlying PICM

Abbreviations: ECV: extracellular volume, LGE: Late gadolinium enhancement

2.8.2.1 Volumetric and functional assessment

Prior to the advent of MRI conditional devices most longitudinal studies of LVEF were conducted using echocardiography. However, echocardiography is limited by low reproducibility and poor inter-observer variability in the serial assessment of any interventions on cardiac volumes and function. Cardiovascular magnetic resonance is recognised to be highly reproducible in both left and right ventricular volumetric and functional assessment (203, 204). Indeed CMR had a superior interstudy reproducibility with better coefficient of variability for LVESV (4.4% to 9.2% vs 13.7% to 20.3%, $p < 0.001$), LVEF (2.4% to 7.3% vs 8.6% to 19.4%, $p < 0.001$), and LV mass (2.8% to 4.8% vs 11.6% to 15.7% $p < 0.001$) compared with 2D echocardiography including patients with heart failure and LV hypertrophy (204). The improved inter-study reproducibility of CMR compared with echocardiography has the potential to reduce significantly the sample size when evaluating for small volumetric and functional changes. In patients with heart failure sample size can be reduced by 85% for a 10ml change in LVESV and 88% for an absolute change of 3% in LVEF (204). The advent of MRI conditional pacing systems allows the accurate and reproducible longitudinal assessment of cardiac volumes and function in patients with pacemakers. In particular CMR allows serial assessment of the adverse remodelling that has been associated with long term RV pacing including chamber dilatation, reductions in LVEF and changes in regional hypertrophy. Importantly in patients with pacemakers image quality is often good with standard cine SSFP sequences despite the presence of the IPG and pacing leads. In patients with ICDs utilising SGE sequence can reduce artefacts from the device and improve image quality (Figure 2-5) (54, 58, 59).

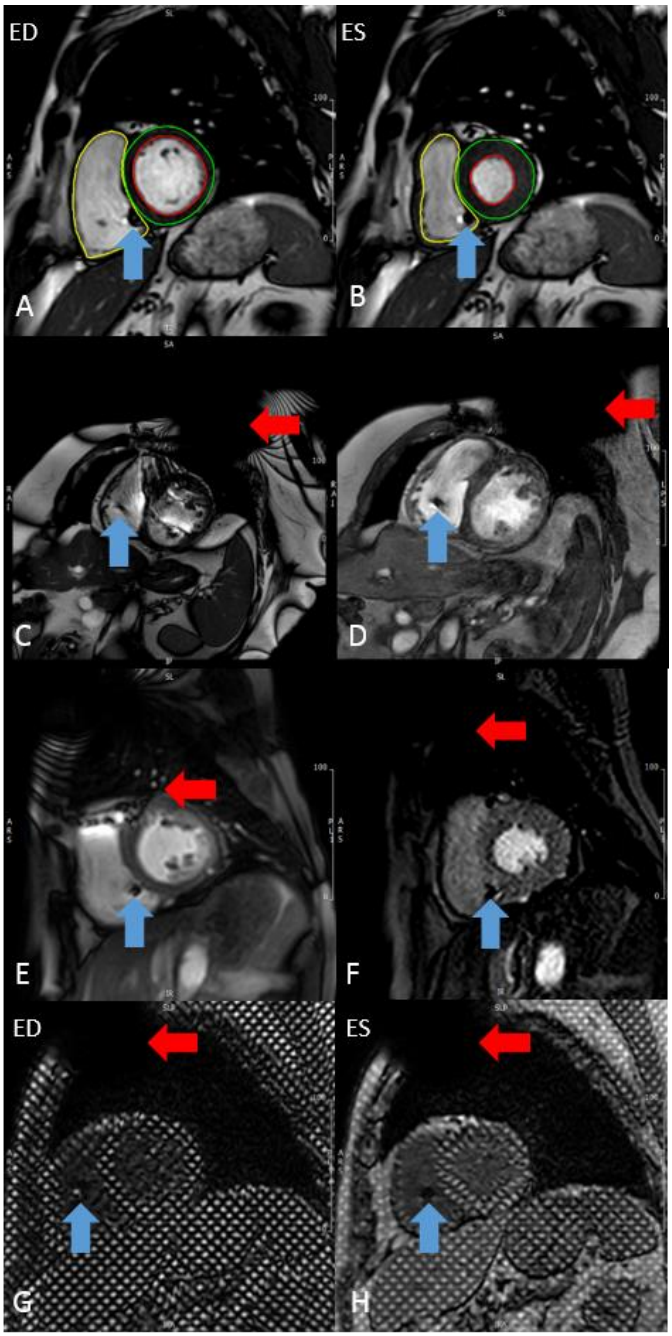


Figure 2-5: CMR images in patients with cardiac implantable electronic devices.

Images demonstrate artefact caused by the IPG or ICD (red arrows) and pacing leads (blue arrows). SSFP acquisition in a patient with a pacemaker showing no artefact over the heart so LV endocardial (red line), LV epicardial (green line) and RV endocardial (yellow lines) can be accurately contoured at end-diastole (Panel A) and end-systole (Panel B). In a patient with an ICD changing from SSFP (Panel C) to SGE (Panel D) removes banding artefact and good endocardial definition can be seen. First pass perfusion is also improved in a patient with an ICD by changing from SSFP (Panel E) to SGE (Panel F) acquisition. MR tagging in a patient with a pacemaker at end-diastole (Panel G) and end-systole (Panel H).

2.8.2.2 Strain imaging

The abnormal pattern of mechanical activation caused by RV apical pacing is thought to be a contributory factor to future LV dysfunction. Advanced CMR techniques allow for assessment of regional myocardial function, strain and can quantify LV dyssynchrony through MR tagging or feature tracking (205). In MR tagging the magnetisation of tissue is modified locally by alternating the direction of magnetisation and a grid pattern is projected over the myocardium (Figure 2-5). Grid points can then be tracked through the cardiac cycle by analysing the signal amplitude or harmonic phase (HARP) and can therefore be used to measure LV dyssynchrony (206). MR tagging has been shown to be feasible, with good image quality in pacemaker patients (n=16) when using a complementary spatial modulation of magnetisation (CSPAMM) acquisition, which has a high reproducibility for dyssynchrony assessment (59, 205). Feature tracking software, which enables retrospective strain analysis on standard cine imaging, overcomes the need for a dedicated pulse sequence and the significant post processing required by tagged imaging (207). Feature tracking has shown good correlation with global strain obtained from tagged HARP imaging (208). Therefore feature tracking allows faster evaluation of strain and dyssynchrony and has been shown to be feasible and reproducible in patients with pacemakers (209). Indeed the investigators found that peak radial and circumferential strain were reduced in patients with forced RV pacing compared with controls. The effect of RV pacing on dyssynchrony and strain can also be assessed within the MR environment in individuals by comparing asynchronous intrinsic AV conduction (AOO) and asynchronous dual chamber pacing (DOO) (Figure 2-6)

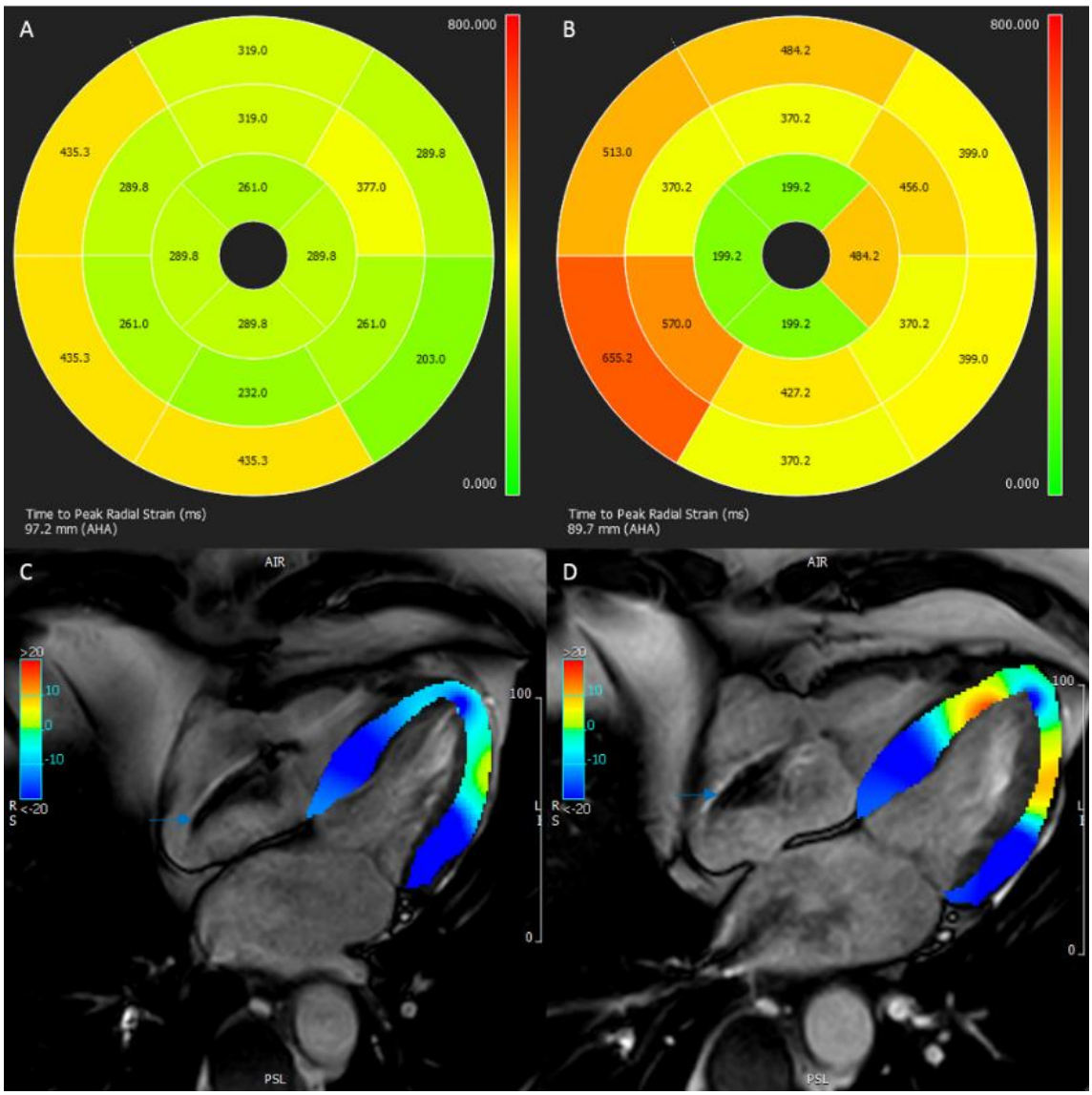


Figure 2-6: CMR Feature tracking images in a patient with a pacemaker.

Images demonstrate differences in LV segmental time to peak strain (Panels A & B) and global longitudinal strain (Panels C & D) between AOO (Panels A & C) and DOO (Panels B & D) pacing modes.

2.8.2.3 Myocardial fibrosis

Cardiovascular magnetic resonance offers unparalleled soft tissue characterisation and allows an accurate and reliable assessment of diffuse and focal myocardial fibrosis without the need for ionising radiation. The techniques for assessment of myocardial fibrosis are discussed below.

2.8.2.3.1 Late gadolinium enhancement

Gadolinium is an extracellular contrast agent that filters into areas of extracellular expansion within the myocardium. As myocardial fibrosis leads to expansion of the extracellular matrix there is excessive retention of gadolinium within these areas following intravenous administration. An inversion recovery sequence is then used to 'null' normal myocardium, which appears black, and areas of gadolinium retention appear bright. Therefore LGE enables visualisation and detection of focal fibrosis with unparalleled sensitivity and spatial resolution (Figure 2-7) (210). Late gadolinium imaging is now a well-established technique for assessment of myocardial fibrosis in a range of cardiovascular conditions including ischaemic and non-ischaemic cardiomyopathy, cardiac amyloidosis and cardiac sarcoidosis (65-69). Furthermore the presence of focal fibrosis detected by LGE is an independent predictor of mortality and adverse cardiovascular outcomes in these conditions.

In patients with pacemakers LGE imaging is less prone to artefact than standard cine imaging with diagnostic quality imaging varying between 84 and 94% (Figure 2-7) (54, 58, 70). Diagnostic LGE imaging for patient with ICDs and CRT-Ds is substantially lower but development of wideband techniques which aim to overcome hyper intensity off resonance artefacts by increasing the spectral bandwidth of the inversion pre-pulse have been shown to enable diagnostic images to be obtained in those with suboptimal conventional LGE (Figure 2-7) (70).

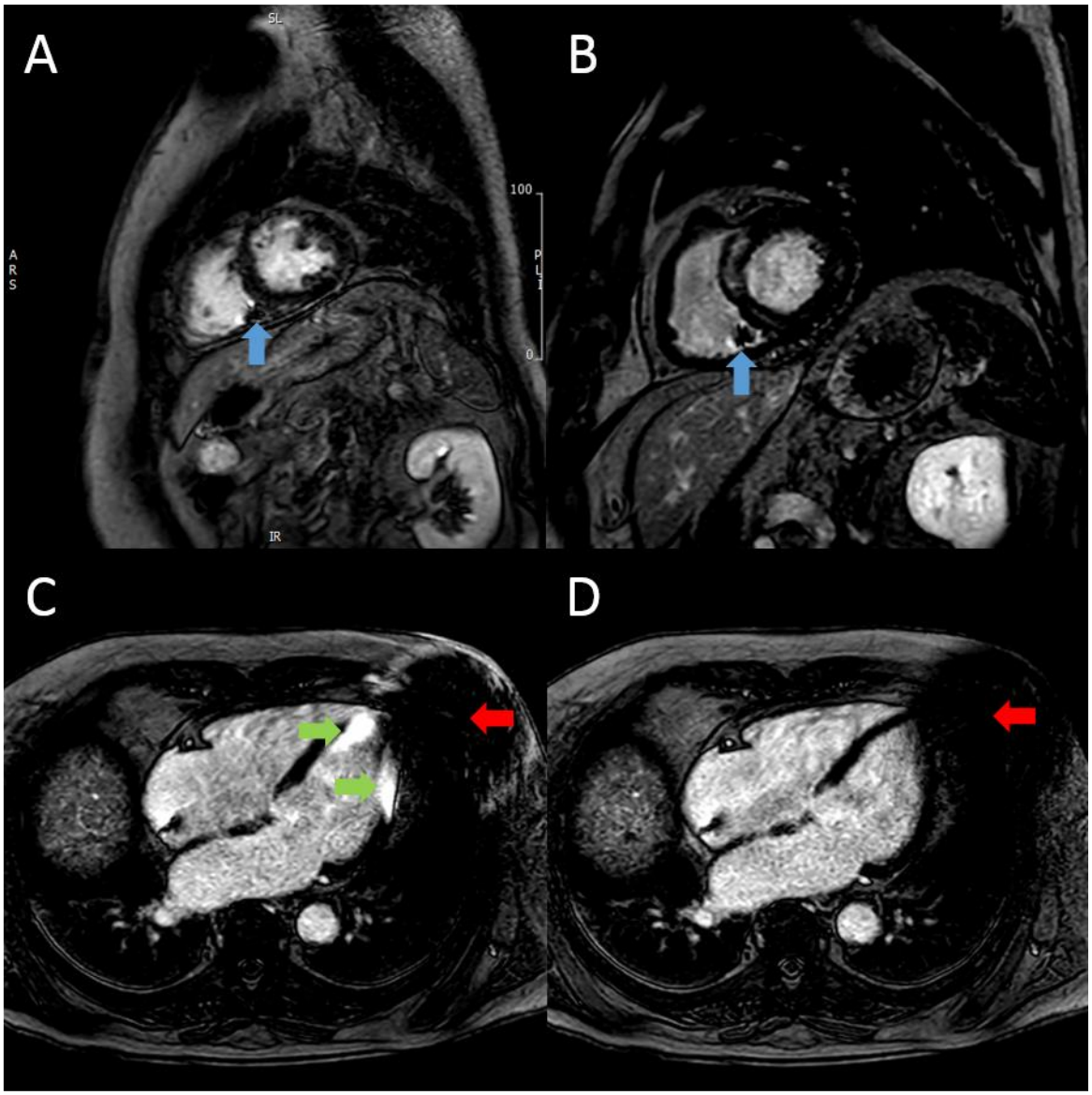


Figure 2-7: Late Gadolinium Enhanced Images in patients with CIEDs.

Standard LGE images in two different patients with pacemakers demonstrate subendocardial hyperenhancement in the mid anterior wall (Panel A) and mid wall hyperenhancement in the basal septum (Panel B) with minimal artefact from the pacing leads (blue arrows). Signal void (red arrows) and off resonance hyper-intensity artefacts (green arrows) are seen using a standard LGE sequences in a patient with an ICD (Panel C) with the latter artefact no longer visible after using a wideband LGE sequences (Panel D).

The prevalence or prognostic impact of replacement fibrosis have never been studied in a bradycardia pacemaker population. Little is known about the interaction of underlying myocardial fibrosis, detected by late gadolinium enhanced imaging, and pacing-induced

dyssynchrony. Interestingly it has been shown in patients with LBBB and myocardial scar, detected by LGE, that LVEF is disproportionately reduced compared to controls despite a smaller scar volume (211). Perhaps this indicates that dyssynchrony together with scar impairs the potential for the heart to compensate for a loss of myocardial contractility. Furthermore the risk of heart failure in patients with RV pacing is greater in those with a history of myocardial infarction (10, 134). In patients with acute myocardial infarction the presence of dyssynchrony is strongly associated with the future risk of heart failure hospitalisation (135).

CMR has previously been used in patients with CRT devices and the presence of replacement fibrosis was associated with poor response rate in both ischaemic and non-ischaemic cardiomyopathy, especially in those with posterolateral scar or greater transmural extent of scar (212-215). Using CMR to guide LV lead deployment away from scarred myocardium results in a better clinical outcome than a conventional approach to CRT implantation particularly as pacing scarred myocardium is associated with an adverse prognosis (216). Combining LGE with other CMR techniques such as feature tracking has the potential to individualise therapy further as the deployment of LV leads over non-scarred areas of late mechanical activation was associated with reverse LV remodelling and improved clinical outcomes after CRT (217).

Detection of myocardial fibrosis in patients undergoing CRT implantation seems to help predict clinical response and this can be further enhanced by combining advanced CMR techniques. The effects of inducing LV dyssynchrony, via right ventricular pacing, in patients with and without myocardial fibrosis has never been assessed but multi-parametric CMR may be able to provide novel mechanistic insights into the pathophysiology of PICM and future risk of heart failure. The use of upfront LGE in these patients to guide decision making around device selection is also of potential interest although the feasibility of imaging patients with very low heart rates and at risk of asystole or further arrhythmias has yet to be assessed.

2.8.2.3.2 T_1 mapping

Using T_1 mapping it is possible to detect diffuse fibrosis even in patients without focal fibrosis on late gadolinium enhancement. T_1 mapping encodes the absolute T_1 relaxation time of tissue on a voxel by voxel basis. Native T_1 values often overlap between patients and healthy individuals and are sensitive to the imaging sequence used as well as the

magnetic field strength which limits its widespread utility. Extracellular volume (ECV) fraction can also be calculated by measuring both pre and post contrast T_1 values and in theory this technique corrects for T_1 differences between sequences and scanners so may be more widely clinically applicable (Figure 2-8) (218). These techniques have been validated histologically in dilated cardiomyopathy and are associated with risk of heart failure hospitalisation and death across the spectrum of ejection fraction and heart failure stage (219-223). Lin *et al.* have recently shown that regional increases in ECV are associated with longer times to regional wall thickening and intra ventricular dyssynchrony irrespective of global LV function (224). Whether regional changes in ECV are the cause or effect of dyssynchrony remains unclear.

In patients with ICDs, T_1 mapping may be more prone to artefact but recent work using wideband sequences to overcome off resonance effects of ICDs has demonstrated the feasibility of T_1 mapping in patients with devices although this has yet to be validated clinically (63, 64).

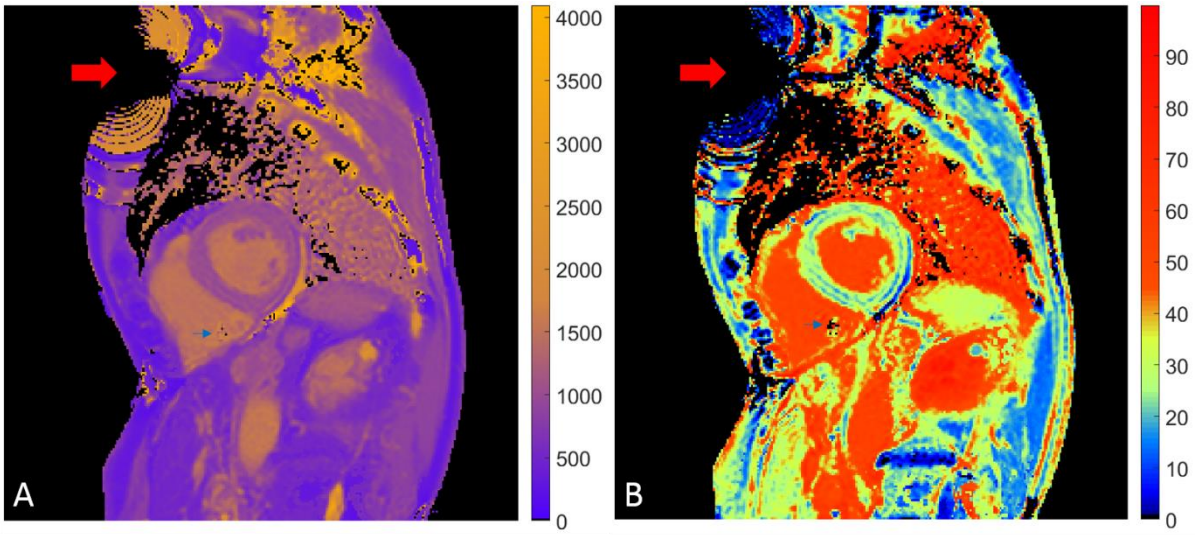


Figure 2-8: Parametric mapping in a patient with a pacemaker.

Native T1 (Panel A) and ECV (Panel B) maps are shown with very little artefact from the device (red arrows).

Whether the presence of diffuse and focal fibrosis are related to a subsequent decline in LV function and development of heart failure after pacemaker implantation remains to be seen. Given their prognostic value in other disease processes the relationship between

myocardial fibrosis and alterations in myocardial activation by right ventricular stimulation warrant further investigation particularly if they can be used to identify those at greatest risk of heart failure.

2.8.2.4 Perfusion

Animal and human studies on pacing have demonstrated regional changes in myocardial perfusion after RV apical pacing even in the absence of flow limiting coronary artery disease (108, 110). Furthermore these changes have been observed to be reversible on cessation of pacing suggesting that functional ischaemia may contribute to myocardial dysfunction (108, 111). First pass perfusion, particularly using spoiled gradient echo acquisition over SSFP has been shown to be feasible with very little artefact in humans with pacemakers and ICDs (49, 54, 57) (Figure 2-5). The recent development of inline pixel wise myocardial perfusion maps may help quantify regional perfusion more accurately and further our understanding of how pacing-induced perfusion changes may lead to adverse remodelling in this population (225, 226).

2.8.2.5 Four-dimensional (4D) Intra-cardiac Flow

In addition to direct effects of RV pacing on LV contractility PICM is also likely to be caused by the haemodynamic consequences of RV pacing. Non-invasive assessment of cardiac haemodynamics has conventionally been performed by Doppler echocardiography or phase contrast MRI. Both of these are only able to assess flow in one plane (and in the case of echocardiography also limited by acoustic windows and beam alignment). Four-dimensional (4D) flow cardiovascular magnetic resonance involves phase contrast MRI with flow-encoding in three spatial dimensions and the dimension of time in the cardiac cycle (227). Using this technique, it is possible to assess complex intracardiac flow in all directions and regions comprehensively in a way that would not be possible by Doppler echocardiography or phase contrast MRI (228). Recent advances in 4D flow acquisition and post-processing techniques are optimising the time for analysis and have reduced the time to acquire a whole-heart flow data to under 10 minutes (229-231). Using 4D flow MRI data, it is possible to quantify flow accurately and precisely through the aortic, mitral, pulmonary and tricuspid valves using retrospective valve tracking (231, 232). In addition, cardiac efficiency (using particle tracing), LV blood flow kinetic energy (KE) and analysis of vortex formation can also be performed (227, 233, 234). Changes in diastolic flow in the LV, from particle tracing, and reductions in inflow kinetic energy have been demonstrated in patients with dilated cardiomyopathy

compared to controls despite equivalent LV stroke volumes (234). Furthermore, in patients with heart failure early diastolic LV filling forces, derived from 4D flow CMR, were more orthogonal to predominant LV flow direction in patients with dyssynchrony (LBBB) compared to those without, highlighting the potential role of flow-derived measures in the assessment of mechanical dyssynchrony (235). Diastolic vortex formation may have a role in optimising cardiac performance by helping flow redirection and preserving kinetic energy which may be applicable to pacemaker recipients as flow patterns have been shown to be altered in animal models during ventricular pacing (236-238). Therefore these biomarkers may provide novel mechanistic insight into changes in intra-cardiac flow patterns in pacing-induced dyssynchrony and be able to detect early subclinical changes in LV function associated with RV pacing.

2.8.2.6 Research value of CMR in PICM

The development of MRI conditional devices may enable us to use multi-parametric CMR to gain a greater understanding of the pathophysiology underlying the development of heart failure after right ventricular pacing. Furthermore, by identifying novel pre-disposing and precipitating factors, it may be possible to risk stratify these patients and individualise management. The use of paired CMR studies permits accurate longitudinal assessment of changes in LVESV or LVEF with greater accuracy and smaller sample sizes than can be achieved with echocardiography.

2.9 Conclusions

The deleterious effects of RV pacing on LV function have been described in numerous clinical studies although the exact pathophysiological mechanisms underlying this process remain incompletely understood. Although the majority of patients undergoing pacing do not develop heart failure the data suggest the prevalence of PICM appears to be around 10-20%. Furthermore the development of PICM or heart failure after pacing is associated with a worse prognosis. It seems likely that development of heart failure after right ventricular pacing is a balance between underlying substrate, for example previous myocardial infarction or pre-existing conduction disease, and pacing factors including the burden of RV pacing and the paced QRS duration. CRT has been shown to be effective in treating patients with PICM and may prevent adverse LV remodelling in patients with impaired LVEF and AV block which makes sense as they already have overt abnormalities of the myocardium. There are conflicting data on the use of physiological pacing and other therapeutic modalities in preventing LV remodelling in

patients with preserved or modest impairment of LV function and often these upfront interventions come with a greater risk of complications. With the aging population and increasing number of pacemaker implants there is an urgent need to improve risk stratification of patients in order to implant the correct device based on individual risk. The use of multi-parametric CMR, in particular scar imaging, may help detect subclinical myocardial disease which could aid in understanding the underlying pathophysiology as well as providing prognostic information which could be used to determine upfront device selection.

Chapter 3 Feasibility and validation of four-dimensional flow cardiovascular magnetic resonance imaging in pacemaker recipients

3.1 Abstract

Background: 4D flow CMR is a potentially valuable tool for studying cardiovascular haemodynamics for disease monitoring and/or treatment planning. It is unknown if this technology can be feasibly and reliably used in patients with pacemakers. The aim of this study was to investigate the feasibility of 4D flow in pacemaker patients and test the validity of transvalvular flow quantification using inter-valvular flow consistency methods.

Methods: Thirteen patients with MRI conditional pacemakers were prospectively recruited from a single centre. All patients underwent 4D flow scans in in two asynchronous pacing modes (AOO & DOO). Visual grading of the image quality was undertaken using a 4 point scale. For flow assessment, consistency between aortic, mitral and tricuspid stroke volumes (SV) was investigated for both pacing modes.

Results: All MRI examinations were completed safely with no changes in the pre-/post device variables. Image quality for left sided heart valves was good with little or no artefact. Moderate to severe susceptibility artefacts were observed in the region of pacing lead across the tricuspid valve. These artefacts lead to overestimation of transvalvular SV compared to when susceptibility artefact was excluded by manual contouring (AOO: 77 ± 18 vs 69 ± 18 ml; $p<0.001$ and DOO: 74 ± 17 vs 68 ± 17 ml; $p<0.001$) and therefore the latter values were used for comparison to left sided heart values. No significant bias for SV in AOO or DOO pacing modes was observed between the aortic, mitral and tricuspid valves ($p>0.05$ for all).

Conclusion: 4D flow CMR in patients with MRI conditional pacemakers is feasible and allows accurate and consistent assessment of valvular flow.

3.2 Introduction

Approximately 524 cardiac pacemakers per million people are implanted in Europe per year with an increasing year-on-year trend (239). It is estimated that up to 75% of pacemaker recipients will need an MRI in their lifetime (30). The burden of cardiovascular disease in pacemaker recipients, coupled with the increasingly prominent role of CMR in European guidelines for the diagnosis, management and monitoring of patients with cardiovascular disease has meant providing CMR to this population has become a necessity (9, 11). The advent of MRI conditional pacemakers has facilitated safe scanning of these patients although individual manufacturer's restrictions remain in place.

Previous studies have established the feasibility and safety of performing CMR in pacemaker patients for acquisition of cines, late gadolinium imaging and perfusion (59, 61, 70, 240). Furthermore there is increasing evidence that CMR in patients with CIEDs can often aid diagnosis or change clinical management (58, 70). 4D flow CMR is one of the emerging MRI techniques which has demonstrated high accuracy and precision for intracardiac flow and haemodynamic assessment (232, 241). Due to its advantage over two-dimensional phase contrast acquisition and other Doppler based imaging methods, it is being increasingly advocated for challenging cases of congenital heart disease, valvular heart disease and haemodynamic assessment (242-244). Retrospective valve tracking using 4D flow CMR has immediate clinical applicability in the assessment of valvular flow and regurgitation quantification (232, 245).

Right ventricular pacing is not physiological and leads to dyssynchronous ventricular contraction. 4D flow CMR has potential to be a powerful tool to investigate the mechanisms and consequences of ventricular pacing. However the feasibility, safety and reliability of this technique remains to be confirmed in pacemaker patients.

We hypothesised that 4D flow CMR is feasible in patients with pacemakers and can accurately quantify valvular flow. Therefore, the main aim of the study was to (1) assess the feasibility of performing 4D flow in patients with MRI conditional pacemakers and (2) investigate the consistency and reliability of retrospective valve tracking in quantification of valvular flow in patients with pacemakers in both atrial (AOO) and dual chamber (DOO) asynchronous pacing modes.

3.3 Methods

3.3.1 Study Population

The study was approved by the local Ethics Committee and the study complied with the Declaration of Helsinki. All patients gave written informed consent before MRI examinations. The study protocol was approved by the National Research Ethics Service (Ref 12/YH/0551 and Ref 18/YH/0168) (Appendix).

Thirteen patients with MRI conditional dual chamber pacemakers were prospectively recruited from a single centre. Inclusion criteria: Adults (aged over 18), MRI conditional dual chamber pacemaker system, ventricular pacing burden of less than 5% on most recent device interrogation. Exclusion criteria: Contraindication to MRI (including non-MRI conditional pacemakers, intra-orbital debris, severe claustrophobia), pregnant or breastfeeding, history of prior myocardial infarction, known cardiomyopathy or congenital heart disease and moderate to severe valvular heart disease.

3.3.2 Device Programming

Prior to entering the MRI room, the patients underwent full pacemaker interrogation which included determination of battery voltage, lead impedance, pacing thresholds and P- and R-wave sensing amplitude. Devices were then programmed into manufacturer specific MRI safe mode. Patients were programmed to either AOO or DOO asynchronous pacing, in a random order, at 10 beats per minute above intrinsic heart rate to avoid competition. All patients were scanned in both AOO and DOO pacing modes during a single visit in order to check internal consistency of valvular flow quantification. Throughout the MRI examination patients were monitored using VCG signal and non-invasive blood pressure monitoring. Following MRI a safety check was performed assessing the device battery voltage, lead impedance, pacing thresholds and sensing amplitudes and compared to values obtained prior to the MRI. Patients were then reprogrammed to pre MRI device settings.

3.3.3 Cardiovascular Magnetic Resonance

All patients had CMR imaging at 1.5T (Ingenia, Philips, Best, The Netherlands) with a phased array receiver coil (24-channel equipped with Philips dStream digital broadband

MR architecture technology) between November 2017 and October 2018. The mean time between device implantation and MRI examination was 281 days (range: 88-853 days). All patients were scanned in normal operating mode (Upper limit of SAR level up to 2 W/kg body weight) with maximised gradient slew rate up to 200T/m/s and according to the manufacturer's specific device instructions.

3.3.4 Image Acquisition

The MRI protocol was as follows:

1. Survey images
2. Cine imaging: Acquired using balanced steady state free precession (bSSFP) in a single slice breath-hold sequence. Images obtained included a LV volume contiguous short axis stack as well as two, three and four chamber views. Typical image parameters were as follows: Slice thickness 10mm, echo time (TE) 1.5 milliseconds (ms), repetition time (TR) 3 ms, flip angle 60°, sensitivity encoding (SENSE) factor 2 with 30 phases per cardiac cycle.
3. Whole heart 4D flow: Field of view (FoV) was planned in the transaxial plane with changes to FoV and number of slices performed as necessary to ensure whole heart coverage. Acquisition was performed using a fast field echo (FFE) pulse sequence [Echo planar imaging (EPI) based with sensitivity encoding acceleration, 3D] as previously described with retrospective ECG triggering (231). Acquisition voxel size approximately 3x3x3mm. Typical scan parameters were as follows: TE 3.5 ms, TR 13 ms, flip angle 10°, velocity encoding (VENC) 150cm/sec, FoV 400mm, number of signal averages 1, EPI acceleration factor of 5 and SENSE factor of 2. Images were acquired during free breathing with no respiratory motion correction. Number of slices was 39 with temporal resolution of 40 ms. Number of reconstructed phases was set at 30.
4. Patients were taken out of the MRI room and the device was re-programmed to alternate pacing mode at the same base rate and steps 1 to 3 were repeated.

3.3.5 Image Analysis

Image analysis was performed offline using MASS software (Version 2018EXP, Leiden University Medical Centre, Leiden, The Netherlands). All images were analysed by CS (2 years' experience in advanced CMR). Endocardial contours were traced on the LV

short-axis (SA) cine stack at end-diastole and end-systole, with exclusion of papillary muscles and trabeculation, to determine end-diastolic volume, end-systolic volume, stroke volume and ejection fraction for both left and right ventricles (summation of disks methodology). Epicardial contours were contoured for the left ventricle at end-diastole to calculate left ventricular mass (Equation 2).

LV mass = (Epicardial volume − Endocardial volume) * myocardial density [1.05 g/cm^3].

Equation 2: Calculation of Left Ventricular Mass

For each 4D flow data set, visual quality checks on the phase contrast and magnitude images were performed by CS who was supervised by PG (>5 years' experience in 4D flow CMR). Images were visually evaluated for the following artefacts; phase wrap and distortion, signal void and distortions and graded according to a 4-point scale (231). 0: excellent quality with no artefacts, 1; good quality with minimal blurring artefacts in magnitude images, 2; moderate quality with moderate blurring artefacts on magnitude and phase images, 3; poor quality with severe artefacts on velocity images in the area of interest leading to potentially non-evaluable data. Phase unwrapping was performed on source images if aliasing occurred in the region of interest according to previous guidelines on phase contrast methods (246). Spatial misalignment of 4D flow to cine imaging was corrected prior to flow analysis. This was achieved by visualising streamlines in 4-chamber view in peak systole and repositioning them over descending aorta and in 3-chamber view in peak systole and repositioning them over ascending aorta. Similar checks were performed in diastole for peak mitral inflow streamlines in 2-, 3- and 4-chamber views.

All 4D flow assessments were performed using validated retrospective valve tracking techniques with the measurement planes positioned perpendicular to inflow or outflow direction on two-, three- and four chamber cines (245). Background velocity correction (for correction of through plane motion and phase offset) was used from velocity sampled in the myocardium as per guidelines on phase contrast methods (246). Contour segmentation was performed manually. Artefacts due to the pacemaker leads were expected to be present across the tricuspid valve. Therefore tricuspid valve planes were manually contoured twice; initially to include the entire tricuspid orifice area and then subsequently with exclusion of miscalculated pixels caused by susceptibility artefact from the pacing lead (Figure 3-1).

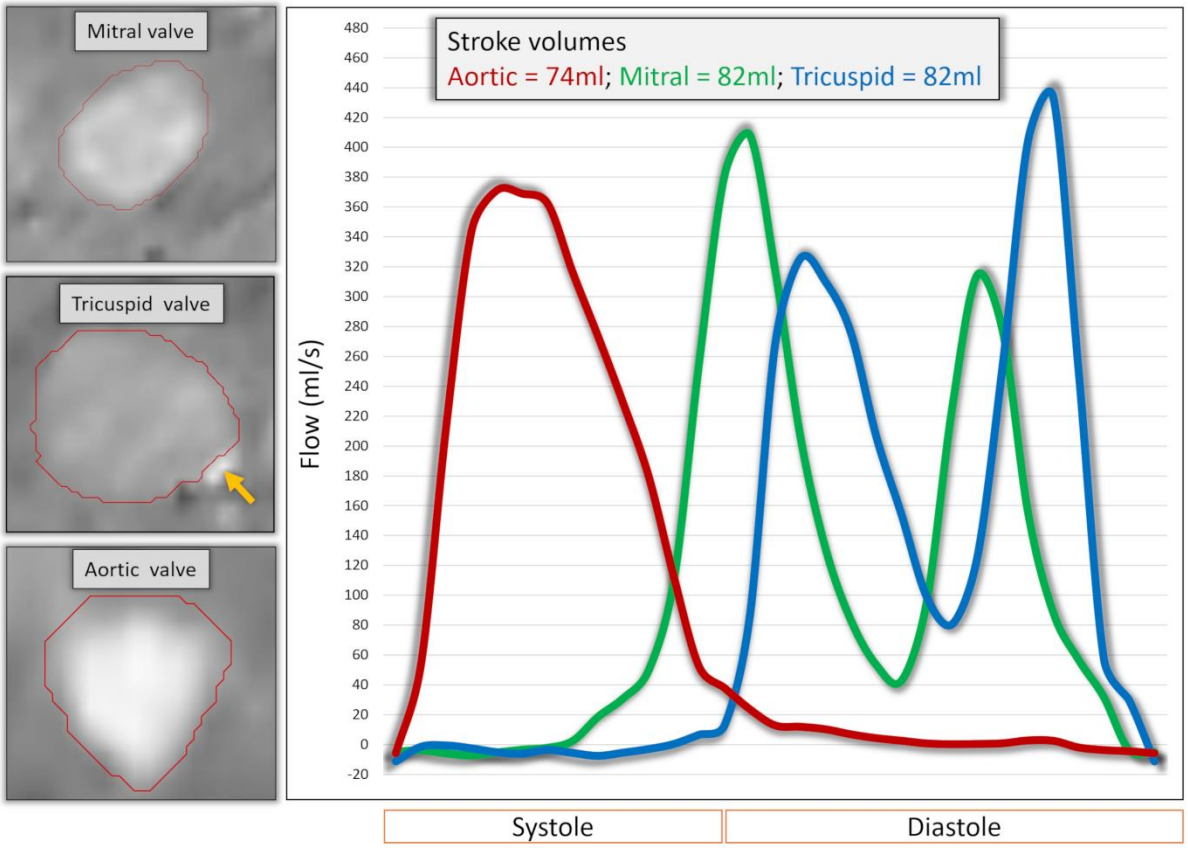


Figure 3-1: Example of how valvular flow contours were segmented on the phase contrast multiplanar reconstruction.

For the tricuspid valvular flow, we just excluded the area with artefact from through plane valvular flow quantification (orange arrow). The right hand panel demonstrates flow curves for the same patient in AOO mode with comparable stroke volumes through the 3 valvular planes.

3.3.6 Statistical analysis

Statistical analysis was performed using SPSS 21 (International Business Machines, Armonk, New York, USA). Normality for quantitative data was established using Shapiro-Wilk test. Continuous data measurements are presented as mean ± standard deviation. For image quality analysis the Wilcoxon signed rank test was performed to establish significant differences. For investigating agreement between left ventricular stroke volumes from cine imaging and aortic, mitral and tricuspid stroke volumes derived from 4D flow we used repeated measures analysis of variance with Bonferroni correction. Agreement between the two methods was expressed as bias (in percentage) according to Bland-Altman analysis. Association between aortic and mitral and tricuspid stroke

volumes was performed using Pearson correlation coefficient test. For pre and post MRI device parameters a paired samples t-test was performed for normally distributed variables and the Wilcoxon signed rank test for not normally distributed variables. A p value <0.05 was considered significant.

3.4 Results

3.4.1 Patient Characteristics

All thirteen patients, mean age 69 ± 11 years, seven males, completed the full study protocol. Five patients were assigned to an initial AOO pacing mode and the remainder to DOO first. A summary of the baseline demographic characteristics of the study participants is provided in Table 3-1. The pacemaker and lead details for patients can be seen in Table 3-2.

Characteristic	n=13
Male gender	7 (54%)
Age (yr)	69 ± 11
Heart rate (bpm)	80 ± 9.9
Height (cm)	171.7 ± 9.8
Weight (kg)	87.9 ± 21.4
AOO pacing first	5 (38%)

Table 3-1: Clinical characteristics of patients recruited to study.

Continuous variables are expressed as mean± standard deviation and categorical variables are expressed as counts (percent).

Manufacturer	Model	Number
Implantable Pulse Generator		
Boston Scientific®	Proponent MRI (EL231)	5
Medtronic®	Ensura DR MRI (EN1DR01)	2
St Jude Medical®	Assurity MRI (PM2272)	2
	Endurity MRI (PM2172)	4
Lead		
Boston Scientific®	Ingevity MRI (7731, 7732, 7735, 7736, 7741, 7742)	10
Medtronic®	Capsure Fix (5076)	4
St Jude Medical®	Tendril STS (2088TC)	8
	Tendril MRI (LPA1200M)	2
	Isoflex (1944)	2

Table 3-2: Pacemaker and lead models in the study population.
Abbreviations: MRI: magnetic resonance imaging

3.4.2 Safety and device parameters

All examinations were completed safely with no adverse clinical events and no unusual symptoms reported during the scan. All devices were interrogated before and immediately after MRI (Table 3-3). No significant differences were noted between battery voltage, lead impedance, capture threshold or P- and R-wave amplitude. No individual changes in lead parameters were considered clinically significant.

Parameter	Pre MRI value	Post MRI value	p-value
Pacing lead impedance (Ω)			
- **Atrial lead**	527.5 ± 94.1	514.5 ± 66.9	0.64
- **Ventricular lead**	665.6 ± 146.6	634.8 ± 154.2	0.11
Pacing lead capture threshold (V)			
- **Atrial lead**	0.6 ± 0.2	0.6 ± 0.2	0.76
- **Ventricular lead**	0.9 ± 0.4	0.8 ± 0.2	0.92
Battery Voltage (V) (n=9)*	3.02 ± 0.1	3.02 ± 0.1	NA
P-wave amplitude (mV)	4.0 ± 1.4	4.1 ± 1.4	0.48
R-wave amplitude (mV)	12.3 ± 5.6	12.1 ± 5.3	0.95

Table 3-3: Comparison of device parameters before and immediately after the MRI examination.

The data are presented as mean ± standard deviation.

*Boston Scientific® devices were excluded as the programmer does not given a numerical value for battery voltage.

3.4.3 Baseline CMR data

Baseline characteristics derived from cine imaging can be seen in Table 3-4. Parameters are taken from measurements during AOO pacing as normal atrioventricular conduction was maintained in this pacing mode.

Variable	n=13
LV End-Diastolic Volume (ml)	119.7 ± 30.5
LV End-Systolic Volume (ml)	48.8 ± 13.6
LV Stroke Volume (ml)	70.9 ± 18.4
LV Ejection Fraction (%)	59.3 ± 3.8
LV Mass (gram)	74.2 ± 19.5
RV End-Diastolic Volume (ml)	113.9 ± 28.1
RV End-Systolic Volume (ml)	44.8 ± 12.0
RV Stroke Volume (ml)	69.1 ± 17.4
RV Ejection Fraction (%)	59.6 ± 3.6

Table 3-4: Baseline CMR parameters of patients in AOO pacing mode.

Data are presented as mean ± standard deviation.

Abbreviations: LV: left ventricle, RV: right ventricle

3.4.4 Image quality assessments

Artefact scoring for images across the aortic and mitral valves was similar with generally no or minimal artefacts observed in both AOO and DOO pacing modes (Figure 3-2). Overall there was no significant difference in the presence of artefacts, across each heart valve, on images between pacing modes (aortic; p=0.35, mitral; p=0.30 or tricuspid; p=0.07). Due to the presence of the pacing leads, moderate or severe susceptibility artefacts were seen on all tricuspid valvular planes.

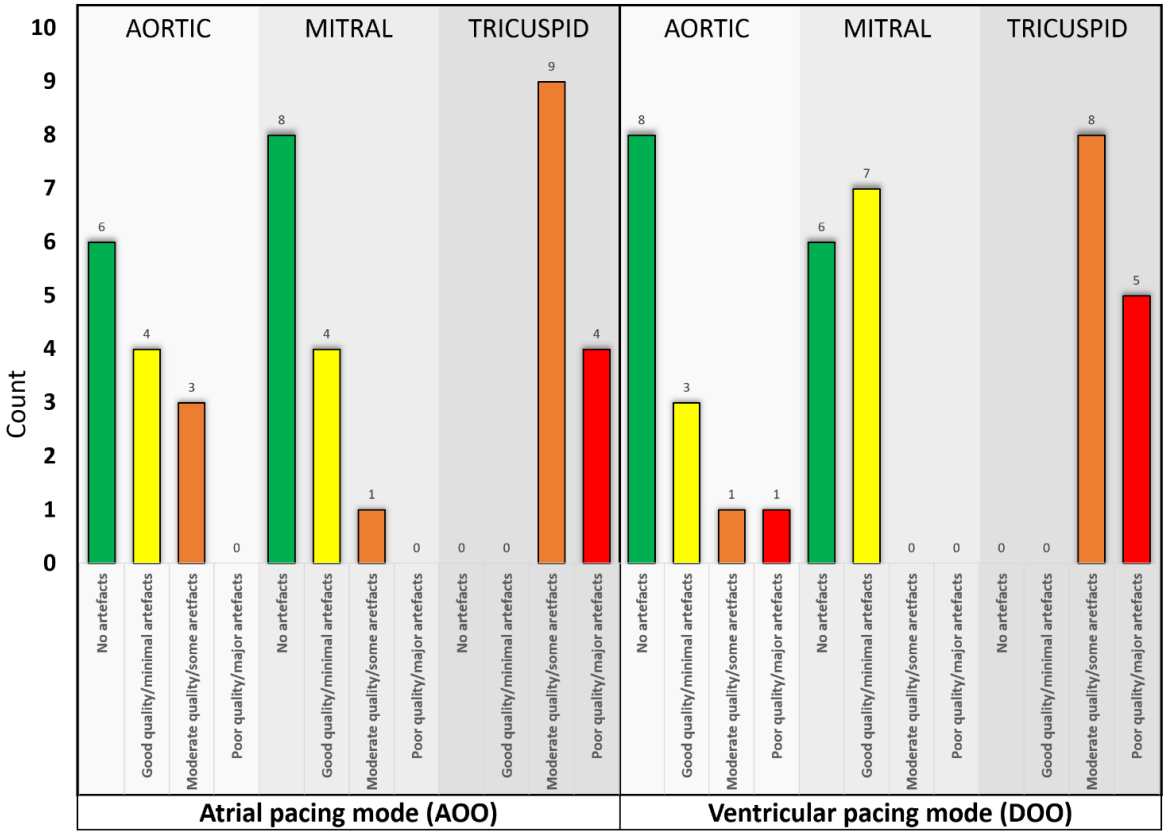


Figure 3-2: Qualitative assessment of flow in the raw data prior to valvular plane reconstruction.

Even though poor quality for tricuspid flow was more often noted, by removing the pixels caused by lead susceptibility artefact, we were able to quantify tricuspid stroke volume.

3.4.5 Tricuspid flow quantification - with/without inclusion of pacemaker lead artefact

On direct comparison of tricuspid flow with the inclusion of the RV lead artefact versus exclusion of the lead artefact, we noted that when we included the RV lead artefact there was significant overestimation of transvalvular stroke volume in both AOO (77 ± 18 vs 69 ± 18 ml; P<0.001) and DOO modes (74 ± 17 vs 68 ± 17 ml; P<0.001). Therefore the values that excluded the RV lead artefact were used for subsequent comparison with stroke volumes on left sided heart valves (Figure 3-1).

3.4.6 Consistency of 4D Flow Derived Flow Volume Assessment

In AOO pacing mode SV for the aortic valve significantly correlated with both mitral (r=0.95; p<0.001) and tricuspid (r=0.96; p<0.001) valvular SVs (Figure 3-3). Bias for SV in AOO pacing mode was highest between the aortic and tricuspid valves (-3.5%, LOA -17 to 10%; p=0.09) although was not significant (Figure 3-4). In DOO pacing mode, SV for the aortic valve again significantly correlated with both mitral (r=0.95; p<0.001) and tricuspid (r=0.97; p<0.001) valvular SVs (Figure 3-3). No significant bias for the SV in this pacing mode was observed between aortic valve and mitral and tricuspid valves (-4.8%, LOA -26 to 16%; p=0.13 and -5.6%, LOA -32 to 20%; p=0.15 respectively) (Figure 3-4).

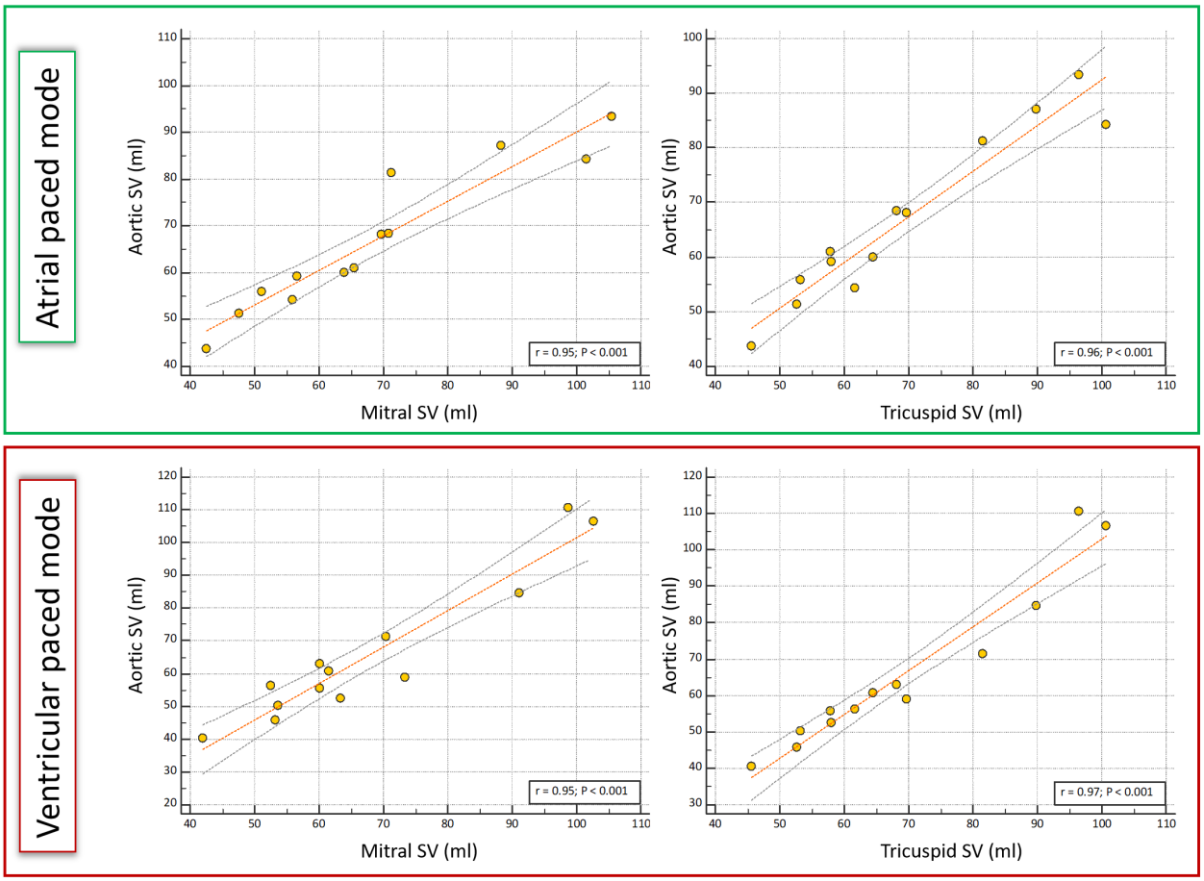


Figure 3-3: Scatter plots of aortic stroke volume (SV) against mitral and tricuspid SV for AOO and DOO pacing modes to investigate consistency between methods.

Excellent correlation was noted for all (r>0.95).

Abbreviations: SV: stroke volume

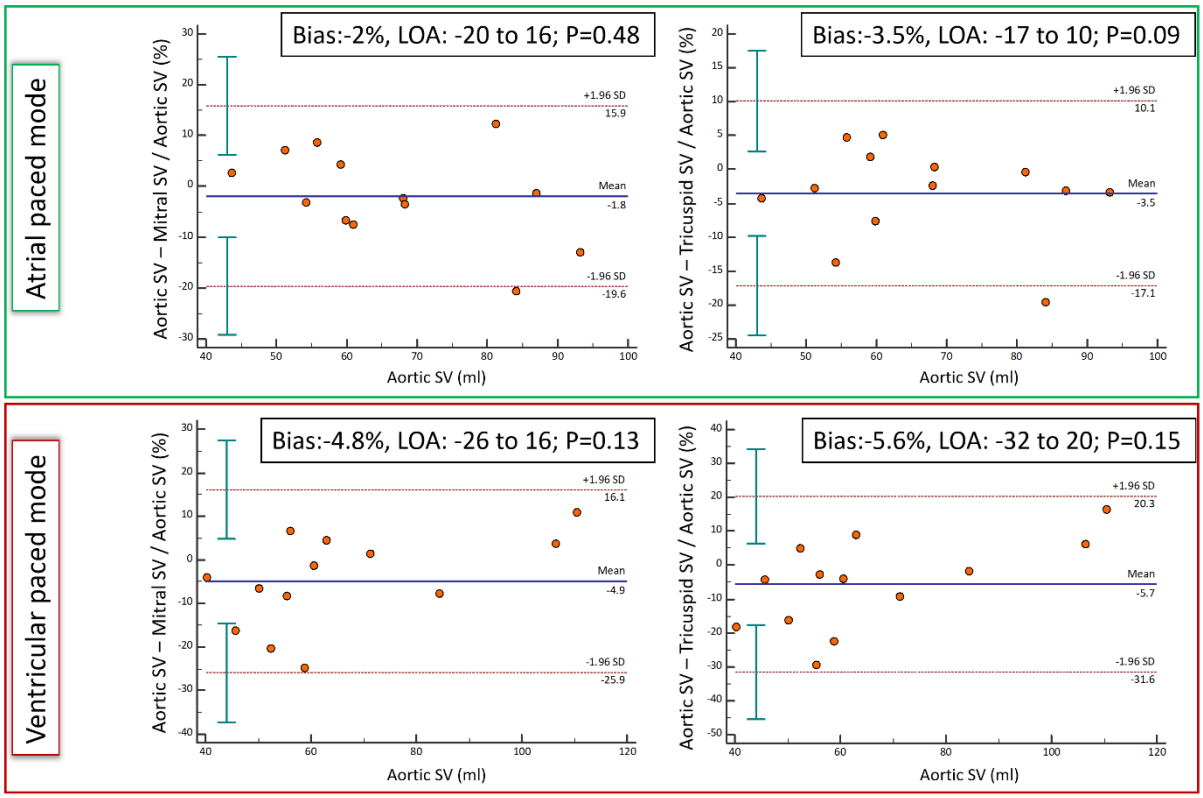


Figure 3-4: Bland Altman analysis for the assessment of aortic stroke volume (SV) against mitral and tricuspid SV for AOO and DOO pacing modes.

No significant differences were noted.

Abbreviations: LOA, limits of agreement, SV: stroke volume

3.4.7 Comparison of Cine and 4D flow derived valvular stroke volumes

In both AOO and DOO pacing modes there was no significant difference between the mean SV from LV short-axis cine and 4D flow derived aortic, mitral or tricuspid SV (Figure 3-5). Furthermore there were no significant differences in a pairwise comparison between cine SV and aortic, mitral or tricuspid SV by 4D flow for either pacing mode (P>0.05) (Table 3-5 and Table 3-6). Bland-Altman analysis did not demonstrate any significant bias between cine SV and 4D flow methods for valvular SV in either pacing mode (P>0.05) (Figure 3-5).

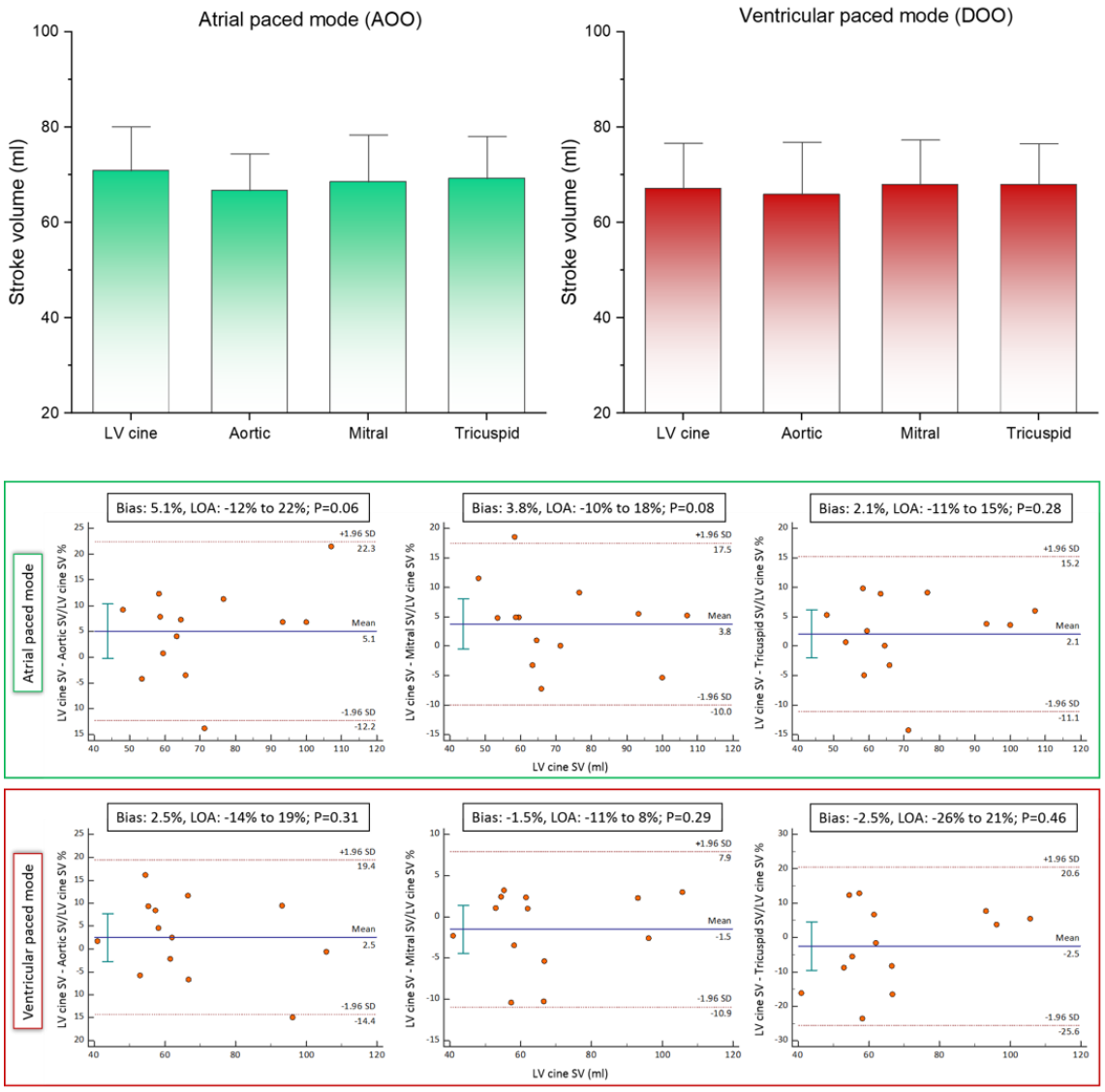


Figure 3-5: Comparison of valvular flow to left ventricular short-axis cine stroke volume.

The first two panels demonstrate that there was no significant differences between the mean stroke volume by cine and the 4D flow derived aortic, mitral and tricuspid stroke volumes in both AOO and DOO modes. In addition, the Bland-Altman analysis did not demonstrate any significant bias between cine SV and the 4D flow methods derived SV ($p>0.05$).

Abbreviations: LOA, limits of agreement, LV: left ventricle, SV: stroke volume

Factors			Mean difference	Std. Error	p-value
LV cine SV	-	Aortic SV	4.148	2.105	0.43
	-	Mitral SV	2.352	1.292	0.56
	-	Tricuspid SV	1.618	1.321	NS
Aortic SV	-	LV cine SV	-4.148	2.105	0.43
	-	Mitral SV	-1.797	1.967	NS
	-	Tricuspid SV	-2.53	1.412	0.59
Mitral SV	-	LV cine SV	-2.352	1.292	0.56
	-	Aortic SV	1.797	1.967	NS
	-	Tricuspid SV	-0.733	1.441	NS
Tricuspid SV	-	LV cine SV	-1.618	1.321	NS
	-	Aortic SV	2.53	1.412	0.59
	-	Mitral SV	0.733	1.441	NS

Table 3-5: Atrial pacing mode pairwise comparison of stroke volume by cine, aortic/mitral/tricuspid valves.

*Bonferroni corrected. NS= All P-values >0.9 were classified as NS.

Abbreviations: LV: Left ventricle, SV: Stroke volume

Factors			Mean difference	Std. Error	p-value
LV cine SV	-	Aortic SV	1.231	1.776	NS
	-	Mitral SV	-0.839	0.876	NS
	-	Tricuspid SV	-0.866	2	NS
Aortic SV	-	LV cine SV	-1.231	1.776	NS
	-	Mitral SV	-2.07	1.939	NS
	-	Tricuspid SV	-2.097	2.492	NS
Mitral SV	-	LV cine SV	0.839	0.876	NS
	-	Aortic SV	2.07	1.939	NS
	-	Tricuspid SV	-0.0269	1.902	NS
Tricuspid SV	-	LV cine SV	0.866	2	NS
	-	Aortic SV	2.097	2.492	NS
	-	Mitral SV	0.0269	1.902	NS

Table 3-6: Ventricular pacing mode pairwise comparison of stroke volume by cine, aortic/mitral/tricuspid valves.

*Bonferroni corrected. NS= All p-values >0.9 were classified as NS.

Abbreviations: LV: Left ventricle, SV: Stroke volume

3.5 Discussion

The present study investigated the feasibility, accuracy and consistency of 4D flow derived valvular flow assessment in patients with MRI conditional pacemakers. The study demonstrates that:

1. 4D flow CMR is feasible in patients with MRI conditional pacemakers in two different pacing modes.
2. 4D flow derived valvular stroke volume quantification is comparable with the cine derived stroke volume.
3. Flow across aortic, mitral and tricuspid valves is consistent and reproducible in both AOO and DOO pacing modes.
4. Artefacts are commonly present on the tricuspid valve plane due to the RV pacing lead but this can be circumvented by excluding areas of pixel miscalculation from susceptibility artefact.

3.5.1 Safety

All the patients in the study underwent the full protocol with no significant changes in device parameters noted between the pre and post MRI device interrogation. Therefore the current study suggests that 4D flow CMR seems not to pose any additional risk in patients with MRI conditional pacemakers if scanned in normal operating mode (SAR level up to 2 W/kg body weight) with a maximised gradient slew rate up to 200T/m/s. These findings are in keeping with the previous literature demonstrating the safety of performing CMR on patients with MRI conditional pacemakers (54, 57, 58).

3.5.2 Image Quality and Qualitative Assessment of Flow

The presence of an MRI conditional pacemaker has previously been shown not to affect the image quality or generation of flow curves in 2D aortic phase contrast imaging (57). The current study demonstrated the image quality of the phase contrast and magnitude images for 4D flow acquisition in patients with pacemakers was generally good, particularly for the left heart. The reconstructed aortic and mitral valve planes generally had little or no artefact which allowed robust quantification of valvular flow. Furthermore, no significant artefacts were noted in two dimensional velocity vectors on cine images for either the left or right heart (Figure 3-6).

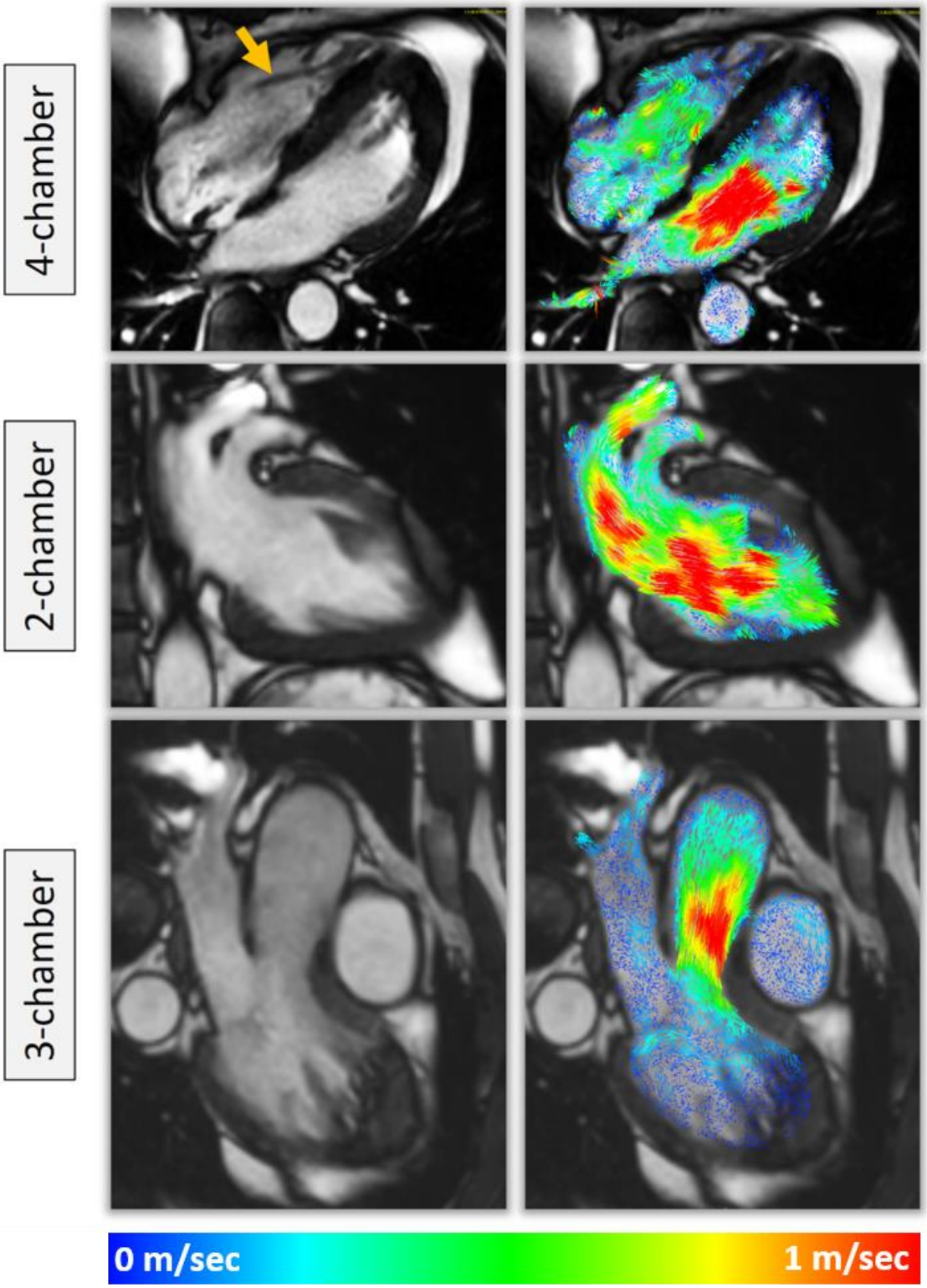


Figure 3-6: 4D flow velocity vectors.

A case example demonstrating two dimensional velocity vectors superimposed over cine images in a patient with a pacemaker and right ventricular pacing lead (orange arrow). No significant artefacts were noted.

Susceptibility artefacts, causing miscalculated pixels, secondary to the presence of the RV pacing lead were consistently seen on the phase and magnitude 4D flow data of the tricuspid valve plane. These were generally limited to few pixels associated with the RV lead. Contouring the entire orifice area, including the miscalculated pixels, led to overestimation of SV relative to the left sided heart valves. In all of our cases the RV pacing lead was at the edge of the valve orifice area and therefore repeat manual contouring with exclusion of the miscalculated pixels meant stroke volumes comparable to the aortic and mitral valves could be determined. This technique clearly requires additional post processing time and the effect of flow measurements when pacing lead is positioned in the middle of the valve orifice is unknown. In the latter circumstance we would suggest a second contour be drawn around the artefact and this value deducted from the total stroke volume for the entire orifice area; this assertion would benefit from validation in future research.

3.5.3 Quantitative assessment of transvalvular flow

Current methods of quantifying valvular flow and intra-cardiac shunts are based on Doppler echocardiography. These techniques are often limited by acoustic windows, difficulties with velocity assessment due to beam alignment and are dependent on operator experience meaning measurements often have limited reproducibility (247-249). Over recent years 4D flow derived measurements using valvular stroke volumes obtained by the retrospective valve tracking techniques have been shown to be accurate, consistent and reproducible across all four heart valves (230, 232, 245, 250). The present study has shown that SV quantification by retrospective valve tracking has a high degree of accuracy and consistency in patients with pacemakers and is reproducible in two separate pacing modes. These findings are consistent with a previous study by Garg *et al.*, using the same 4D flow sequence, which demonstrated robust correlation between values obtained for aortic and mitral net forward flow in healthy volunteers (231).

4D flow derived valvular stroke volumes were also consistent with SV determined by cine imaging. This is important as it demonstrates the robust and reproducible nature of the 4D flow derived values seen in this study.

3.5.4 Clinical Applications

The demonstration of feasibility as well as the consistency and accuracy of 4D flow derived flow measurements is important as the number of pacemaker implantations in Europe is on an upward trend due to the ageing population (239). Given the burden of cardiovascular disease in pacemaker recipients it seems probable that a significant proportion of them will require CMR during their lifespan given CMR is often recommended in International guidelines (9, 11). CMR has already been shown to provide important diagnostic and management changing information in patients with pacemakers (58, 70). 4D flow CMR can play a vital additive role as it provides accurate and consistent intra-scan assessment of blood flow with strong rescan reproducibility. Indeed 4D flow allows sampling and quantification of blood flow in any direction within the 3D volume so may forgo the need for a series of 2D cine breath held phase contrast sequences and retrospective valve tracking techniques may improve assessment of transvalvular flow (228, 232). This may be particularly pertinent in the repeated imaging of pacemaker patients with congenital or valvular heart disease where serial assessment of regurgitant volumes or shunts is required (241, 251-253).

3.5.5 Possible Future Applications

Right ventricular apical pacing induces electrical and mechanical dyssynchrony leading to alterations in cardiac haemodynamics and can lead to adverse cardiac remodelling and even the development of heart failure in the longer term (79, 80, 254). The mechanisms underpinning the development of this so called ‘pacing induced cardiomyopathy’ however are incompletely understood. 4D flow CMR affords the evaluation of a series of advanced cardiac haemodynamic parameters such as kinetic energy (KE), turbulent KE, particle tracing and vortex visualisation (228). These parameters are predominantly research tools but have been suggested as subclinical markers of LV dysfunction with reductions in average LV KE and end-diastolic KE observed in patients with ischaemic heart disease and little or no LV dysfunction (255, 256). More recently it has been shown in heart failure patients with dyssynchrony from LBBB that LV filling forces are more orthogonal to main LV flow direction during early diastole and the direct flow entering the LV has lower KE when compared to those without LBBB (235, 257). Suwa *et al.* have also demonstrated changes in vortex size and core locations during diastole in patients with heart failure suggesting vortex formation plays a role in LV ejection and filling (238). These metrics may allow us to evaluate how flow haemodynamics change in pacing induced dyssynchrony and may contribute to the pathophysiology of pacing induced left ventricular dysfunction and

development of heart failure. Indeed recent work using echocardiographic particle image velocimetry has demonstrated that blood flow momentum and KE dissipation are altered with RV apical pacing, highlighting the potential role that altered flow dynamics may play in adverse cardiac remodelling over the long term (258).

3.5.6 Limitations

There were several limitations to our study. The number of patients recruited to this study remains small and the implanted pacemakers were from a limited number of manufacturers with MRI conditional models. This study did not evaluate pulmonary valvular flow as the relevant right ventricular outflow tract cines for retrospective valve tracking planning were not acquired. Unfortunately no two dimensional phase contrast images, which are arguably the gold standard for flow volume quantification, were obtained for comparison with the 4D flow derived values (228). However previous studies have demonstrated comparable flow quantification between 2D phase contrast and 4D flow CMR (259, 260). The artefact created by the RV pacing lead meant tricuspid SV was overestimated. Although excluding this susceptibility artefact meant that stroke volumes were consistent with aortic and mitral valves, this could have important implications for calculating regurgitant volumes across the tricuspid valve, particularly if this occurs in close proximity to the pacing lead. The 4D flow sequence used in this study was not respiratory navigated. However respiratory navigated sequences have a longer acquisition time and this may preclude their application in clinical workflows. Furthermore in healthy volunteers the use of respiratory motion compensation has been shown to have no significant effect on intra-cardiac flow quantification (261). This study did not recruit patients with significant valvular heart disease, especially patients with tricuspid regurgitation. Future studies will need to establish the reliability of 4D flow in quantifying right ventricular and tricuspid flow in pacemaker patients with tricuspid incompetence or stenosis. This is not as relevant for the left heart as the artefacts are minimal. Larger studies are required to evaluate fully the safety of 4D flow CMR across a wider range of devices including cardiac resynchronisation pacemakers and implanted cardioverter-defibrillators.

3.6 Conclusion

4D flow CMR in patients with MRI conditional pacemakers is feasible. Retrospective valve tracking techniques generate accurate and consistent stroke volumes, particularly across left sided heart valves, irrespective of pacing mode and are comparable to stroke volumes obtained using cine imaging. 4D flow CMR can potentially be used in patients with pacemakers who need serial and reproducible assessment of congenital and valvular heart disease. Further research is needed in patients with defibrillators and cardiac resynchronisation devices to evaluate whether better device optimisation is possible by 4D flow guided cardiac haemodynamics.

Chapter 4 Impact of myocardial fibrosis on ventricular performance during intrinsic atrioventricular conduction and forced right ventricular pacing

4.1 Abstract

Background: Right ventricular apical pacing induces non-physiological ventricular activation which can lead to electromechanical dyssynchrony, which in certain patients can lead to a deterioration in cardiac function. Multi-parametric CMR enables accurate assessment of volumes, function, intracardiac blood flow and myocardial fibrosis. The aim of the study was to determine the effect of the presence of myocardial fibrosis on acute cardiac haemodynamics after initiation of RV pacing.

Methods: Forty three patients with MRI conditional pacemakers were recruited from a single centre. Patients underwent a multi-parametric CMR scan, including cine imaging, 4D flow and late gadolinium enhancement, in two asynchronous pacing modes (AOO & DOO) to compare intrinsic AV conduction with forced RV pacing.

Results: Thirty four patients were included in the final analysis with LGE present in 53%. During ventricular pacing there was a significant increase in LVESVi and fall in LVEF when compared to intrinsic AV conduction (all $p<0.01$). Patients with LGE had significantly greater changes in both LVESVi (5.3 ± 3.5 vs 2.1 ± 2.4 ml/m^2; $p<0.01$) and LVEF (-5.7 ± 3.4 vs. -3.2 ± 2.6%; $p=0.02$) compared to those without LGE. There was no significant differences in intrinsic or paced QRS duration between the groups ($p>0.05$) but patients with fibrosis developed significant mechanical dyssynchrony between AOO and DOO pacing modes (mechanical dyssynchrony index: 81.3 ± 17.6 vs. 88.8 ± 21.2 ms; $p=0.04$). There was a significant increase in peak A-wave KE and decrease in-plane KE between AOO and DOO pacing only in those with LGE. There were no adverse clinical events or significant changes in device parameters during the study.

Conclusions: In patients with myocardial fibrosis, compared to those without, there is more pronounced deterioration of cardiac function, greater mechanical dyssynchrony and less efficient intracardiac flow.

4.2 Introduction

Right ventricular pacing is an effective guideline recommended treatment for patients with symptomatic bradycardia and can normalise life expectancy and restore quality of life in appropriate patients (30, 191, 262, 263). The RV pacing lead is typically positioned at the RV apex because of ease of access and lead stability. However pacing from this position induces non-physiological ventricular activation leading to electrical and mechanical dyssynchrony (254, 264). Right ventricular apical pacing has been shown to induce acute LV dyssynchrony as well as reduce global longitudinal strain and twist leading to a subsequent fall in LVEF (100, 258, 265). Long term the dyssynchronous LV contraction patterns from chronic RV apical pacing can lead to adverse LV remodelling, increased sympathetic activation, mitral regurgitation and a reduction in systolic function (95, 104, 160). Large clinical trials have demonstrated that chronic RV apical pacing may be associated with an adverse prognosis and the development of heart failure in patients with normal and reduced LV function (80, 126). Despite this there is an incomplete understating of the exact pathophysiological mechanisms of 'pacing induced cardiomyopathy' and, which individuals are susceptible to the development of heart failure particularly when LV function is preserved or mildly reduced.

Multi-parametric CMR imaging is an established technique that has an important role in the clinical assessment of a variety of cardiovascular diseases as well as having a wide range of research applications (9, 266). CMR is validated as highly reproducible in the assessment of both LV and RV volumes and function and the use of feature tracking and tissue tagging techniques allow assessment of LV dyssynchrony and strain (203-205, 267). Furthermore, LGE imaging enables the detection of myocardial fibrosis which is a strong independent predictor of adverse outcomes in a variety of cardiovascular diseases (210) (68). These imaging techniques have been shown to be feasible in patients with cardiac implantable electronic devices (CIED), particularly in patients with pacemakers, with minimal impact on image quality (57, 59, 70, 209). Therefore multi-parametric CMR is a potentially valuable tool for the assessment of the haemodynamic consequences of right ventricular pacing and specifically the impact of focal myocardial fibrosis. 4D flow CMR allows assessment of intraventricular blood flow kinetic energy (KE) and can quantify the work performed by the heart to move the blood (234). Changes in LV KE have been demonstrated in patients with heart failure and myocardial infarction (233, 234, 255). The effect of right ventricular pacing on LV blood flow KE is unknown but may provide novel insight into the pathophysiology of LV dysfunction after initiation of RV pacing.

We hypothesise that forced RV pacing in presence of focal myocardial fibrosis leads to a greater immediate detrimental change in cardiac haemodynamics compared to those without myocardial fibrosis.

Therefore, the aims of this study are:

1. To assess the haemodynamic response of intrinsic AV conduction and forced RV pacing in those with and without focal myocardial fibrosis detected by LGE imaging.
2. To assess the impact of forced RV pacing on electrical synchrony and LV mechanics in those with and without focal myocardial fibrosis.
3. To quantify LV KE and characterise changes between intrinsic AV conduction and forced RV pacing in those with and without focal myocardial fibrosis.

4.3 Methods

4.3.1 Study Population

Forty three patients with MRI conditional dual chamber pacemakers were retrospectively recruited from a single centre.

Inclusion criteria: Adults (aged over 18), MRI conditional dual chamber pacemaker or dual chamber ICD systems, a ventricular pacing burden of <5% and presence of sinus rhythm at most recent device interrogation.

Exclusion criteria: Contraindication to MRI (including non-MRI conditional pacemakers, intra-orbital debris, severe claustrophobia), pregnant or breastfeeding, estimated glomerular filtration rate <30ml/min and severe valvular heart disease.

Twelve lead ECGs were performed (MAC3500, General Electric Medical Systems, Milwaukee, WI, USA or CT8000i, Seca, Hamburg, Germany) prior to CMR in atrial (AOO) and dual chamber (DOO) asynchronous pacing modes. Ventricular pacing rate, PR interval and QRS duration were recorded.

Three patients were excluded from analysis due to arrhythmia: patient one was in AF at the time of the scan so could not be programmed to the AOO pacing mode, patient two developed Type 2 AV block (Mobitz 1) when programmed into the AOO pacing mode and patient three developed very frequent ventricular ectopy in DOO pacing mode

Following completion of the full study protocol two patients with ICDs were subsequently excluded due to significantly degraded image quality secondary to device artefact and/or poor breath holding. Image quality was deemed of insufficient quality when endocardial and epicardial delineation was not possible on standard cine imaging and/or the absence or presence of hyperenhancement could not be reliably confirmed on LGE imaging (Figure 4-1).

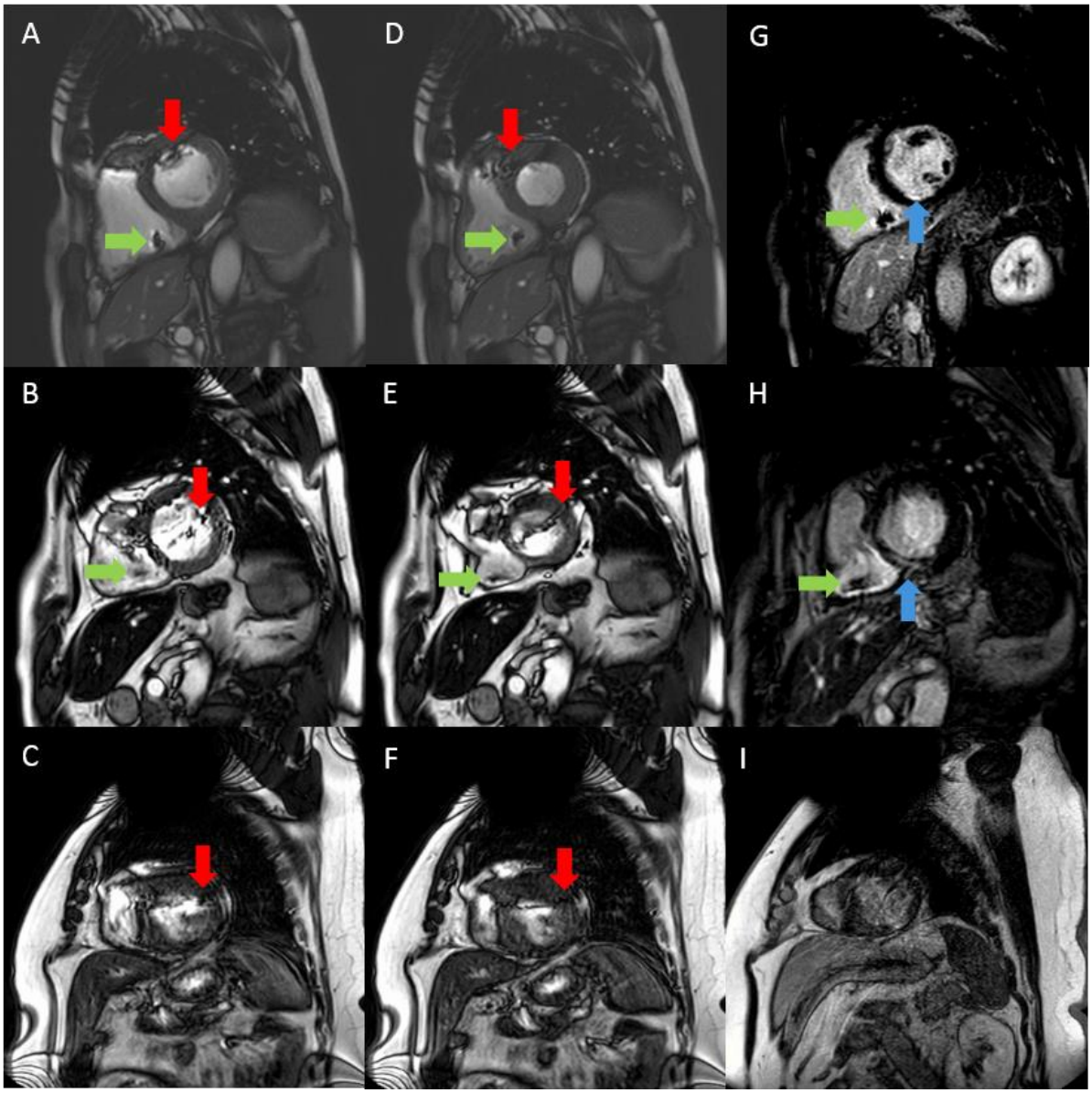


Figure 4-1: Short axis cine images in patients with implantable cardioverter defibrillators.

Images shown are SSFP at end-diastole (Panels A-C), end-systole (Panels D-F) and LGE (Panels G-I) acquisitions. Images for patient one (Panels A,D,G) and patient two (Panels B,E,H) were of deemed acceptable quality with clear endocardial and epicardial delineation at end-diastole and end-systole with good myocardial nulling and demonstration of hyperenhancement (blue arrows) on LGE imaging. Images for patient three (Panels C,F,I) were deemed of unacceptable quality due to poor endocardial and epicardial definition and inadequate myocardial nulling on LGE imaging. Patient three was excluded from further analysis. Susceptibility artefact from the ICD (red arrows) and the pacing leads (green arrows) are demonstrated.

Full image analysis was completed for all remaining participants. Patients were separated into two groups based on the presence or absence of LGE. In order to balance the total numbers and the LVEF between the groups any patients with a LVEF<40% were excluded from the final analysis. Data for those patients excluded is detailed in the Appendix (Page number 286). A cut off of LVEF<40% was chosen based on the definition of heart failure with reduced ejection fraction in current ESC guidelines (186). Therefore a further four patients were excluded leaving a total of thirty four patients. The patient recruitment pathway can be seen in Figure 4-2.

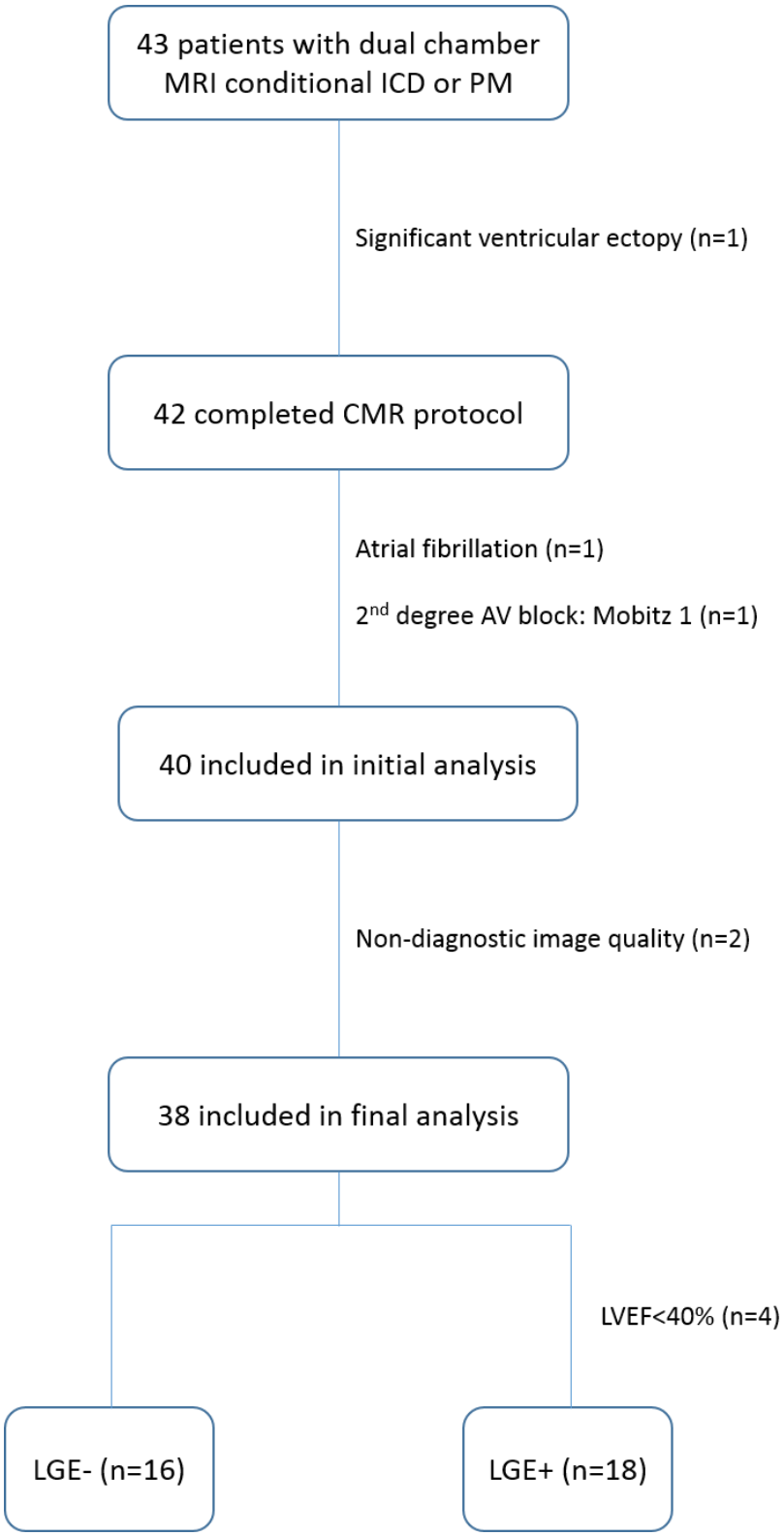


Figure 4-2: Patient recruitment pathway

Abbreviations: AV: atrioventricular, CMR: cardiovascular magnetic resonance, ICD: implantable cardioverter defibrillator, LGE: late gadolinium enhancement, LVEF: left ventricular ejection fraction, MRI: magnetic resonance imaging PM: pacemaker

4.3.2 Ethics Approval

The study complied with the Declaration of Helsinki (October 2000) and the study protocol was approved by the National Research Ethics Service (Ref 12/YH/0551 and Ref 18/YH/0168) (Appendix). All patients recruited in the study gave written informed consent. The relevant patient information sheet and consent form can be seen in the Appendix.

4.3.3 Device Programming

Before entering the MRI room, patients underwent full device interrogation which included determination of lead impedance, pacing thresholds and P- and R-wave sensing amplitude and battery voltage. Devices were then programmed into manufacturer specific MRI safe mode and tachyarrhythmia therapies were disabled in patients with ICDs. Patients were programmed to either atrial (AOO) or dual chamber (DOO) asynchronous pacing, in a random order, at least 10 beats per minute above intrinsic heart rate to avoid competition. After completing items 1 to 4 of the CMR protocol described below patients were taken out of the MRI room to reprogram the device to the alternate pacing mode at the same base rate (Figure 4-3). All patients were scanned in both AOO and DOO pacing modes during a single visit. During the MRI examination patients were monitored using non-invasive blood pressure and VCG signal. A device check was performed assessing the lead impedance, pacing thresholds, P- and R-wave sensing amplitudes and battery voltage after the MRI and compared to values obtained prior to the MRI. Patients were then reprogrammed to pre MRI device settings prior to discharge. The study protocol can be seen in Figure 4-3.

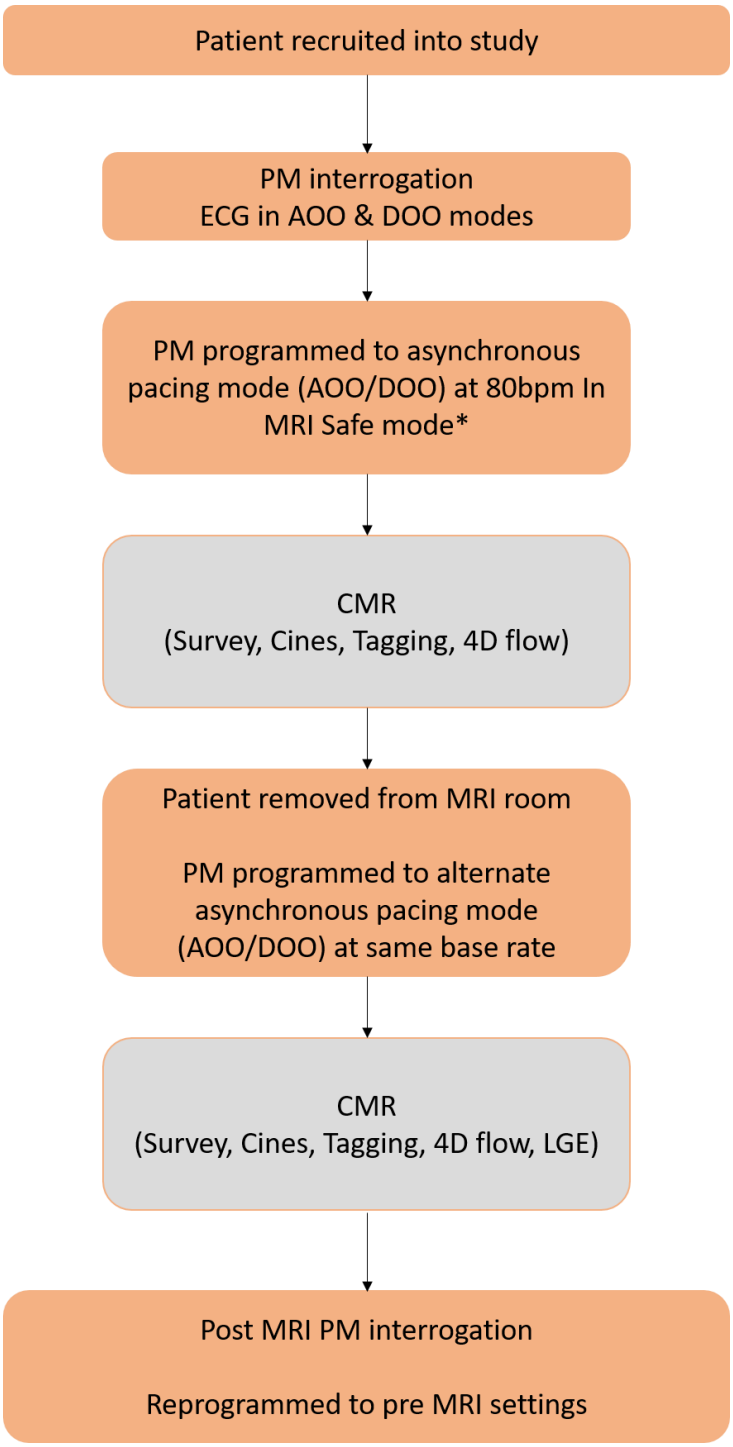


Figure 4-3: Study protocol

* Patients were programmed at a minimum base rate 80bpm or 10bpm above intrinsic rate

Abbreviations: AOO: atrial pacing, AV: atrioventricular, CMR: cardiovascular magnetic resonance, DOO: dual chamber pacing, ECG: electrocardiogram, LGE: late gadolinium enhancement, MRI: magnetic resonance imaging, PM: pacemaker

4.3.4 Cardiovascular Magnetic Resonance

All participants underwent CMR imaging at 1.5T (Ingenia, Philips, Best, The Netherlands) with a phased array receiver coil (24-channel equipped with Philips dStream digital broadband MR architecture technology) between November 2017 and April 2019. Patients were scanned in normal operating mode (Upper limit of SAR level up to 2 W/kg body weight) with maximised gradient slew rate up to 200T/m/s and according to the specific manufacturer's device instructions. All scans were supervised by a Cardiology Registrar (CS) with valid Advanced Life Support certification and a Cardiac Physiologist with expertise in cardiac devices.

When significant susceptibility artefact that limited delineation of endocardial and epicardial borders on SSFP imaging occurred, the patients arm (ipsilateral to location of the IPG/ICD) where possible (dependent on manufacturer specific device instructions and patient comfort) was positioned above the head. Repositioning of the arm moved the susceptibility artefact from the device further away from the heart and improved overall image quality (Figure 4-4).

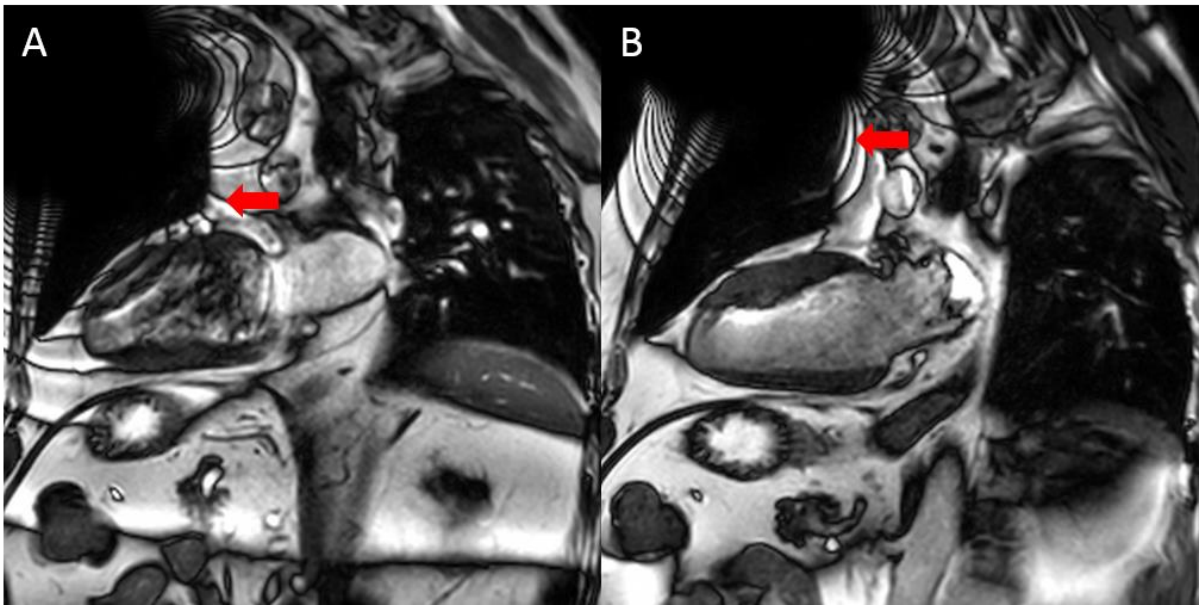


Figure 4-4: Vertical long axis SSFP acquisition in a patient with an implant cardioverter defibrillator.

Images demonstrate the effect of alteration in patient’s arm position from by their side (Panel A) to above their head (Panel B) on susceptibility artefact (red arrows) over the left ventricle.

4.3.5 Image Acquisition

The CMR protocol was as follows (Figure 4-3):

1. Survey images
2. Cine imaging: Acquired using SSFP in a single slice breath-hold sequence. Images obtained included a LV volume contiguous short axis stack as well as two, three and four chamber views. Typical image parameters were as follows: Slice thickness 10mm, TE 1.5 ms, TR 3 ms, flip angle 60°, SENSE acceleration factor 2 with 30 phases per cardiac cycle.
3. Tissue tagging: Spatial modulation of magnetization (SPAMM) acquired in three short axis slices using the 3 out of 5 technique (268). Typical image parameters: spatial resolution 1.99 × 2.33 × 8 mm^3, tag separation 7 mm, ≥12 phases, TR 4.1ms, TE 1.8ms, flip angle 10°.
4. Whole heart 4D flow: FoV was planned in the transaxial plane with changes to FoV and number of slices performed as necessary to ensure whole heart coverage. Acquisition was performed using a FFE pulse sequence (EPI based with SENSE acceleration, 3D) as previously described with retrospective ECG triggering (231). Acquisition voxel size approximately 3x3x3mm. Typical scan parameters were as follows: TE 3.5 ms, TR 13 ms, flip angle 10°, VENC 150cm/sec, FoV 400mm, number of signal averages 1 and EPI acceleration factor of 5. Images were acquired during free breathing with no respiratory motion correction. Number of slices was 39 with temporal resolution of 40 ms. Number of reconstructed phases was set at 30.
5. Patients were taken out of the MRI room and the device was re-programmed to alternate pacing mode (as detailed above) and steps 1 to 4 were repeated.
6. TI scout (Look-locker sequence, single mid-ventricular slice, 10mm thickness, FoV 300x300mm) to determine the optimal Inversion time (TI) to null the myocardium
7. Late gadolinium imaging was performed using a T1-weighted PSIR gradient echo pulse sequence 10-15 minutes after administration of an intravenous bolus of 0.15mmol/kg gadobutrol (Gadovist, Bayer, Berlin, Germany). Contiguous breath held short axis slices were planned to cover the entire left ventricle (Typically 10-12 slices: same geometry as LV cine imaging). Typical imaging parameters were as follows: 10mm thickness, no interslice gap, matrix 188 x 139, FOV 300 × 300 mm, TE 3.0 ms, TR 6.0 ms, , flip angle 25°, acquired in-plane resolution 1.60 × 2.15 mm^2 reconstructed to 0.89 × 0.89 mm^2, effective SENSE factor 1.8. Two,

three and four chamber views were also typically acquired and cross cuts and phase swaps were performed as necessary to confirm the presence or absence of LGE. In patients with ICDs a wideband LGE sequence was used to invert off resonant tissue resulting from presence of metal device. A PSIR pulse sequence utilising an increased bandwidth of the inversion pulse (adiabatic pulse of 4 kHz) which is similar to the bandwidth of 3.8MHz used in previously published work (70). No frequency shift was required as no significant artefact remained after utilising the aforementioned parameters (Figure 4-5).

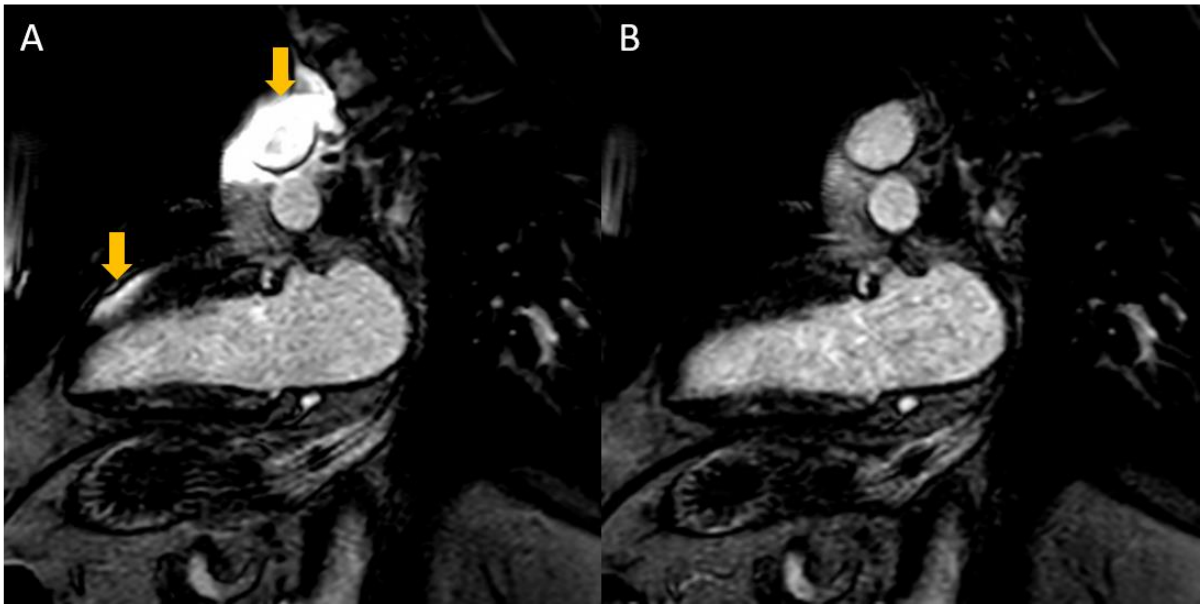


Figure 4-5: Late gadolinium enhancement phase sensitive inversion recovery sequences in a patient with an ICD.

Hyper-intensity artefacts (yellow arrows) that can be seen due to off resonance effects created by the ICD (Panel A), which could be interpreted as subepicardial LGE. Disappearance of hyper-intensity artefacts utilising a wideband LGE sequence (Frequency offset 0Hz; Inversion pulse bandwidth 4MHz) (Panel B).

4.3.6 Image Analysis

Cardiac magnetic resonance analysis was performed quantitatively offline by a single operator CS, blinded to clinical data and assigned pacing mode. Volumetric analysis was performed first using MASS software (Version 2018EXP, Leiden University Medical Centre, Leiden, The Netherlands) in order to maintain, where possible, blinding to LGE status. Endocardial contours were traced on the LV short-axis (SA) cine stack for all

temporal cardiac phases, with exclusion of papillary muscles and trabeculation, to determine end-diastolic volume, end-systolic volume, stroke volume and ejection fraction for both left and right ventricles (summation of disks methodology). Epicardial contours were contoured for the left ventricle at end-diastole to calculate left ventricular mass. Volumetric analysis was performed

All values were indexed to body surface area which was calculated using the Mosteller equation (269). Values obtained during AOO pacing with intrinsic AV conduction were used for comparison of baseline characteristics.

For analysis of the late gadolinium images each slice was inspected for the presence or absence of LGE and this was categorised as being either an infarct (subendocardial) or non-infarct (midwall/subepicardial) pattern (Figure 4-6). In those patients with LGE automated quantification was performed using commercially available software (Cvi42, Circle Cardiovascular Imaging, Calgary, Canada). Quantification was performed using the semiautomated full-width half maximum method (threshold of 50% of the maximum intensity within areas of LGE) (270). Endocardial and epicardial contours were manually contoured on the LV short axis stack and two user defined regions of interest (ROI) were defined when LGE was present. The first ROI was drawn in remote myocardium (no LGE present) and a second ROI was drawn around the hyperenhanced myocardium (LGE present). Finally manual correction was undertaken to exclude blood pool or artefact (270). Automated calculations of the total LGE mass (grams) and the percentage of LGE relative to the entire LV mass were then performed.

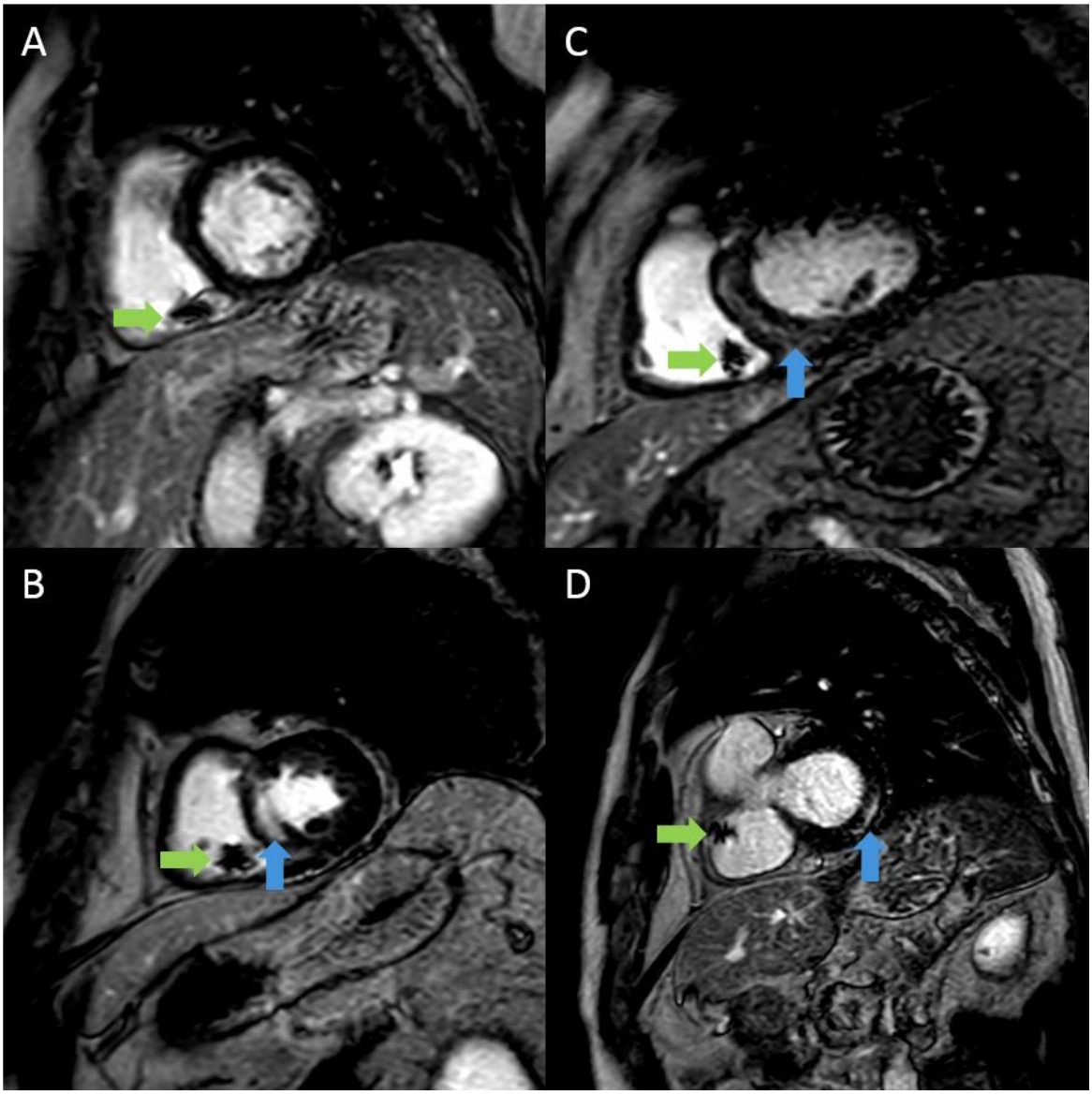


Figure 4-6: Short axis late gadolinium enhancement images in study patients.

Patients were initially grouped according to the absence (Panel A) or presence (Panels B-D) of hyperenhancement (blue arrows). In those with LGE the distribution of enhancement was either classified as an infarct (subendocardial pattern [Panel B]) or non-infarct (midwall [Panel C] or subepicardial [Panel D]) pattern. Artefact from the pacemaker leads is shown (green arrows).

Strain parameters were calculated using feature tracking software (Cvi42, Circle Cardiovascular Imaging, Calgary, Canada) from the short axis LV and 2-, 3- and 4-chamber SSFP cine acquisitions. Prior to analysis brightness and contrast settings were adjusted in order to optimise endocardial and blood pool differentiation. Epi- and endocardial borders were traced manually at end-diastole and the software then tracked

the voxel features of the myocardium to quantify myocardial motion and calculate strain values (Figure 4-7) (271). For the short axis strain analysis the anterior RV insertion point was used as the reference point for differentiating anterior wall and septum. Basal slices with through plane distortion of the LV outflow tract during the cardiac cycle and apical slices with no clear blood pool in systole were not analysed (272, 273). The global circumferential, longitudinal and radial (for both short and long axis orientations) as well as the time to peak radial strain was derived for 16 segments of the 17 segment model (apex was excluded) proposed by the AHA (Figure 4-7) (274). A mechanical dyssynchrony index (MDI) was then calculated from the standard deviation of the segmental time (ms) to maximum radial strain for the 16 AHA segments similar to a technique previously described (275).

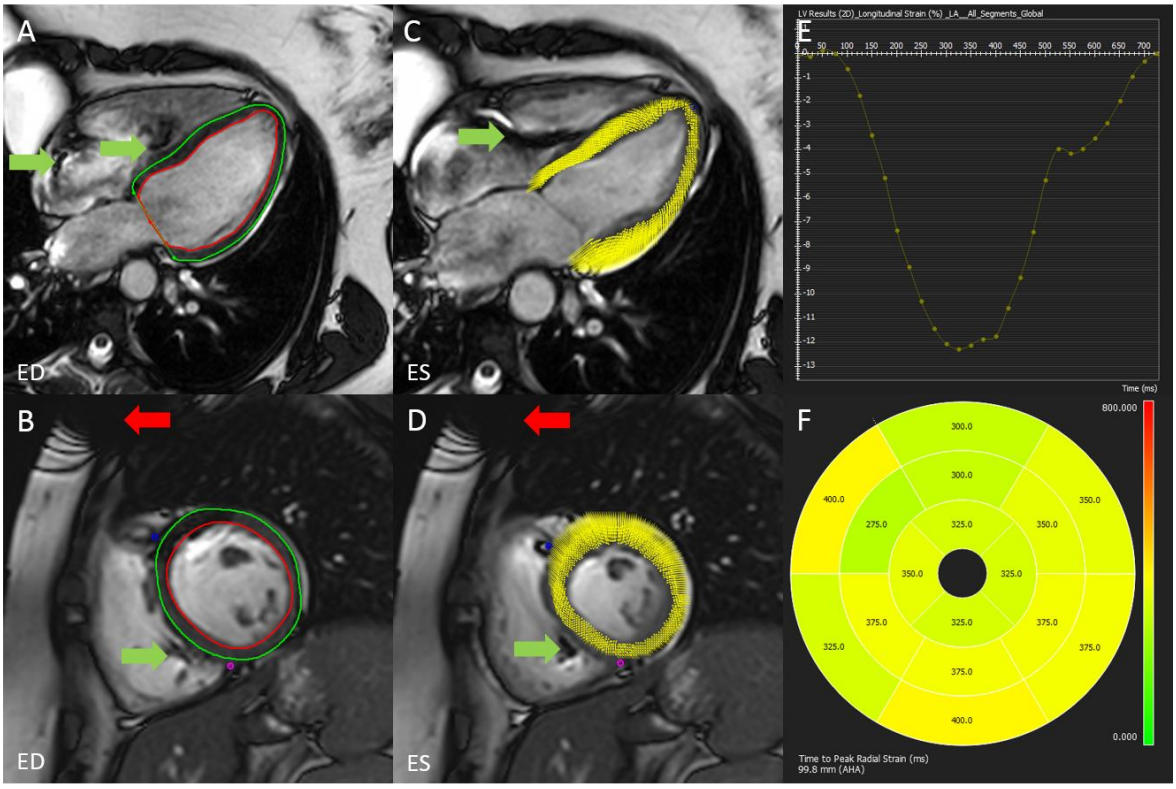


Figure 4-7: Calculation of global longitudinal strain and time to peak strain using CMR feature tracking in a patient with a pacemaker.

Panel A 4Ch SSFP cine acquisition with manually contoured endocardial and epicardial contours. Panel B Short axis SSFP cine acquisition with manually contoured endocardial and epicardial contours and anterior (blue circle) and inferior (pink circle) RV insertion points. Panel C and D Feature tracking acquisition of the 4Ch and SA cines respectively. Panel E Graph showing the GLS [x-axis: time (ms) and y-axis: longitudinal deformation (%)]. Panel F Bullseye plot for the time to peak strain (ms) in all 16 AHA segments after contouring all short axis slices – these values are then used to calculate the mechanical dyssynchrony index. Susceptibility artefacts from the pacemaker (red arrows) and the pacing leads (green arrows) are demonstrated.

A surrogate of left ventricular contractility was calculated using the formula below (Equation 3) which has been previously validated against invasive methods (276, 277).

LV Contractility = Systolic Blood Pressure (SBP)/LV end-systolic volume index (LVESVi)

Equation 3: Calculation of LV Contractility

4.3.6.1 4D flow analysis

Each three directional phase contrast data set was evaluated for phase aliasing artefacts. If required phase unwrapping was performed on source images if aliasing occurred in the region of interest according to previous guidelines on phase contrast methods (246). Spatial misalignment of 4D flow to cine imaging was corrected prior to flow analysis. This was achieved by visualising streamlines in 4-chamber view in peak systole and repositioning them over descending aorta and in 3-chamber view in peak systole and repositioning them over ascending aorta. Similar checks were performed in diastole for peak mitral inflow streamlines in 2-, 3- and 4-chamber views. 4D flow analysis was supervised by a colleague with over five years' experience in 4D flow CMR (PG).

Kinetic Energy mapping

LV endocardial contours were manually contoured for all temporal phases using dedicated software (MASS Version 2018EXP) (Figure 4-8). Translational and rotational misalignment between the 4D flow acquisition and the SA cine stack were corrected using previously published automated image registration methods (278).

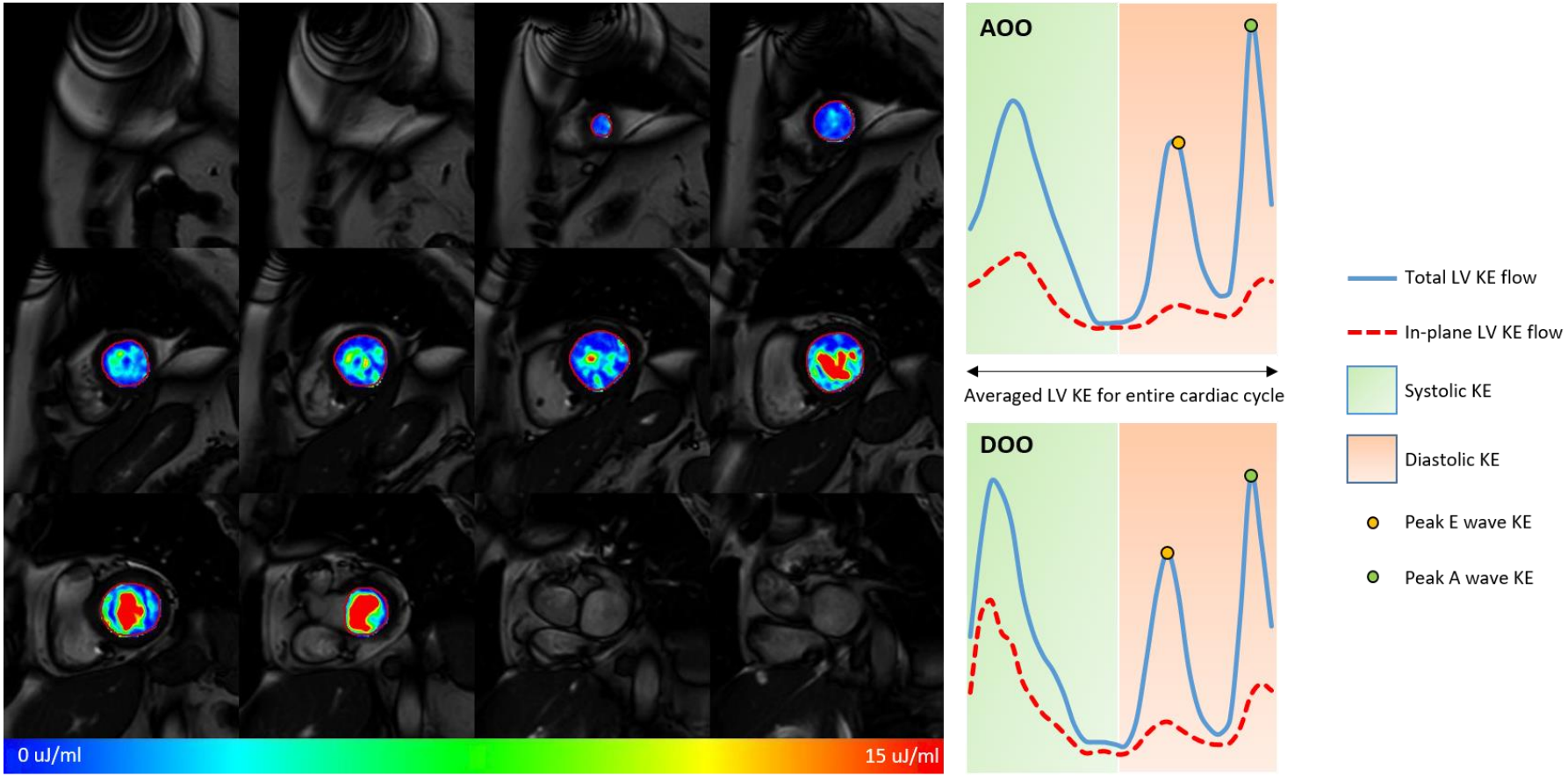


Figure 4-8: Endocardial segmentation on left ventricular short axis stack in a patient with a pacemaker.

The intra-cavity kinetic energy (KE) during late diastolic filling is demonstrated (left panel). KE curves generated for both AOO and DOO pacing modes (right panel).

Calculation of LV blood flow KE parameters was performed as per previously published methods (279). The LV volumetric mesh was resliced into 2mm thick SA sections with pixel spacing equivalent to the reconstructed pixel size (1-1.2 mm) of SA cine acquisition. In each voxel the KE was computed according to the following equation:

$$KE = \frac{1}{2}\, \rho_{blood} \cdot V_{voxel} \cdot v^2$$

Equation 4: Calculation of Kinetic Energy

ρ_{blood} = density of blood (1.06g/cm^3), V_{voxel} = volume of the voxel, v^2 = magnitude of velocity

Total KE was calculation by summation of the KE of each voxel for each phase. KE values were normalised to LVEDV (KEi_{EDV}) and reported as µJ/ml. The KE of the entire LV, systolic, diastolic, early diastolic filling (E-wave) and late diastolic filling (A wave) are reported. Finally the in-plane KE was calculated as percentage of the KE in the x-y direction from base to apex divided by the total KE of the LV.

4.3.7 Statistical analysis

Statistical analysis was performed using SPSS 25 (International Business Machines, Armonk, New York, USA). Data are presented as mean ± standard deviation, median (IQR: interquartile range) or frequency (%). For normally distributed variables, independent samples *t*-test was used for comparisons between groups and a paired samples *t*-test was comparisons within groups. For non-normally distributed variables, independent samples Mann-Whitney U test and the related samples Wilcoxon signed rank test were used. To compare categorical variables the Chi-squared test was used. Association between change in LVESVi and change in QRS duration was performed using Pearson product moment correlation test. P values <0.05 were considered significant.

4.4 Results

4.4.1 Demographic characteristics

A total of 34 patients were included in the final analysis. The mean age of the whole study population was 70±11 years (71% male) and the median time from device

implantation to the MRI was 431 days (IQR: 161-921). Patients were divided into two groups based on the presence or absence of left ventricular myocardial hyperenhancement assessed by LGE which was present in 18 (53%) patients. The baseline demographics for the study population are shown in Table 4-1.

Characteristic	All patients (n=34)	LGE - (n=16)	LGE + (n=18)	p-value
Male Sex – n (%)	24 (71%)	9 (56%)	15 (83%)	0.09
Age – years	69.5 ± 10.7	64.2 ± 12.6	74.2 ± 5.6	<0.01
BMI (IQR) – kg/m^2	28.3 (25.9-31.6)	28.2 (24.5-33.5)	28.3 (25.5-32.1)	0.93
Systolic BP, mmHg	139.8 ± 18.1	141.4 ± 20.1	138.3 ± 16.6	0.63
Diastolic BP, mmHg	81.6 ± 9.2	84.8 ± 10.4	78.8 ± 7.1	0.05
Time between device implant and scan (IQR) – days	431 (161-921)	219 (131-574)	618 (237-1337)	0.03
Medical history – n (%)				
Diabetes	4 (12%)	2 (13%)	2 (11%)	0.57
Hypertension	12 (35%)	7 (44%)	5 (28%)	0.33
MI	10 (29%)	0	10 (56%)	<0.01
Previous PCI	8 (24%)	1 (6%)	7 (39%)	0.03
Paroxysmal AF	7 (21%)	2 (13%)	5 (28%)	0.25
Baseline medications – n (%)				
ACE inhibitor	16 (47%)	4 (25%)	12 (67%)	0.02

ARB	5 (15%)	3 (19%)	2 (11%)	0.44
Statin	19 (56%)	5 (31%)	14 (78%)	<0.01
Anti-platelet	13 (38%)	2 (13%)	11 (61%)	<0.01
Antithrombotic	9 (26%)	4 (25%)	5 (28%)	0.58
β-blocker	17 (50%)	6 (38%)	11 (61%)	0.15
Calcium channel	3 (9%)	0	3 (17%)	0.14
Aldosterone antagonist	3 (9%)	0	3 (17%)	0.14

Table 4-1: Baseline Characteristics of all patients and then separated dependant on absence or presence of late gadolinium enhancement

Normally distributed continuous variables are expressed as mean±SD; non-parametric continuous variables are expressed as median (IQR) and categorical variables are expressed as counts (percent).

Abbreviations: ACE: angiotensin-converting enzyme, AF: atrial fibrillation ARB: angiotensin receptor blocker, BMI: body mass index, BP: blood pressure, IQR: interquartile range, LGE: late gadolinium enhancement, MI: myocardial infarction, PCI: percutaneous coronary intervention

4.4.2 Patient characteristics according to LGE status

4.4.2.1 Baseline characteristics

There were no significant differences in the sex, body mass index or blood pressure between those with and without LGE (Table 4-1). Late gadolinium enhancement positive patients were more likely to be older and have had a previous myocardial infarction (56% vs. 0%; $p<0.01$). Groups were matched for the presence of other diseases including diabetes, hypertension and AF. LGE positive patients were more often on angiotensin-converting enzyme inhibitors, anti-platelet drugs and statins. No significant differences were noted for other common cardiovascular medications.

4.4.2.2 Device and ECG parameters

In all of the study patients the RV lead was positioned in the apex. LGE positive patients had a significantly lower burden of ventricular pacing compared to those without LGE (0.2% vs 1.3%; $p<0.01$) (Table 4-2). There were no significant differences in the indication for the device or the atrial pacing burden. Importantly there was no significant difference between the groups in either the initial assigned pacing mode or the programmed pacing rate. The device and lead manufacturers and models for all patients in the study can be seen in Table 4-3

Characteristic		LGE – (n=16)	LGE + (n=18)	p-value
Device information				
Indication for device – no (%)				
Sinus node disease		12 (75%)	11 (61%)	
AV block		4 (25%)	3 (17%)	0.14
No pacing indication/ICD		0	4 (22%)	
Atrial pacing burden - %		4.4 (0.5-39.5)	11.8 (0.6-60.5)	0.46
Ventricular pacing burden - %		1.3 (0.5-4.5)	0.2 (0.2-0.5)	<0.01
Programmed pacing rate – bpm		80 (70-85)	80 (80-80)	0.60
First programmed mode AOO – n (%)		7 (44%)	9 (50%)	0.49
ECG parameters				
PR interval (ms)	AOO	206 (159-226)	202 (181-245)	0.53
	DOO	106 (98-115)	109 (98-113)	0.96
QRS duration (ms)	AOO	88 (79-96)	93 (86-108)	0.21
	DOO	147 (123-162)	160 (151-167)	0.11

Table 4-2: Baseline device characteristics and ECG parameters in AOO and DOO pacing modes dependant on absence or presence of late gadolinium enhancement.

Continuous variables are expressed as median (IQR) and categorical variables are expressed as counts (percent).

Abbreviations: AV: atrioventricular, BMI: body mass index, BPM: beats per minute, ECG: electrocardiogram, ICD: implantable cardioverter defibrillator, IQR: interquartile range, LGE: late gadolinium enhancement, ms: milliseconds

No significant differences were seen between the intrinsic PR interval (AOO mode) or programmed AV delay (DOO mode) between those with or without LGE (Table 4-2). QRS duration was shorter in AOO mode compared to DOO mode in the whole study population (95 vs. 151ms; $p<0.01$) but no significant differences were seen between those without or with LGE in either mode (AOO: 88 vs. 93ms; $p=0.21$, DOO: 147 vs. 160ms respectively; $p=0.11$).

Manufacturer	Model	LGE – (n=16)	LGE + (n=18)
IPG/ICD			
Boston Scientific®	Ingenio DR J177		1 (6%)
	Proponent MRI EL231	6 (38%)	3 (17%)
Medtronic®	Advisa DR A3DR01	1 (6%)	4 (22%)
	Azure W3DR01	1 (6%)	
	Ensura DR MRI EN1DR01	2 (13%)	4 (22%)
	Evera MRI S DR DDMC3D4		4 (22%)
St Jude Medical®	Assurity MRI PM2272	1 (6%)	2 (11%)
	Endurity MRI PM2172	5 (31%)	
Lead			
Boston Scientific®	Ingevity MRI (7731, 7732, 7735, 7736, 7741, 7742)	12 (38%)	8 (22%)
Medtronic®	Capsure Fix (5076)	8 (25%)	14 (39%)
	Capsure Sense (4574)		3 (8%)
	Capsure Sense (4074)		3 (8%)
	Sprint Quattro Secure (6935M)		3 (8%)
	Sprint Quattro Secure (6947M)		1 (3%)
St Jude Medical®	Isoflex (1944)	1 (3%)	3 (8%)
	Isoflex (1948)	1 (3%)	1 (3%)
	Tendril MRI (LPA1200M)	2 (6%)	
	Tendril STS (2088TC)	8 (25%)	

Table 4-3: Device and lead models in the study population.

Data are expressed as counts (percent).

ICD models are presented in *italics*.

Abbreviations: ICD: implantable cardioverter defibrillator, IPG: implantable pulse generator, LGE: late gadolinium enhancement

4.4.2.3 Baseline CMR data

LGE was present in 18 (53%) patients and was predominantly distributed in an infarct pattern (61%) with a mean scar burden of 7.2 ± 7.1% (Table 4-4). Those with LGE had significantly larger indexed left ventricular end-diastolic volume (LVEDVi) (77.5 ± 13.8 vs. 65.6 ± 12.4 ml/m^2; p=0.01) and LVESVi (37.6 ± 11.4 vs. 29.5 ± 9.8 ml/m^2; p=0.03) compared to those without LGE. There was no significant difference in LVEF between those with LGE and without (52.2 ± 8.0 vs. 56.0 ± 6.2%; p=0.13). Indexed LV mass was significantly higher in those with LGE (48.5 ± 9.1 vs. 40.5 ± 9.9 g/m^2; p=0.01). In the RV there was no significant difference between those with and without LGE in the indexed right ventricular end-diastolic (RVEDVi) and indexed right ventricular end-systolic volumes (RVESVi) or ejection fraction (RVEF) (58.3 ± 7.4 vs. 60.7 ± 5.8%; p=0.30).

Feature tracking analysis was successfully performed in all patients (Table 4-4). Global longitudinal strain was significantly lower in patients with LGE than those without (-12.4 ± 3.2 vs. -14.8 ± 2.8%; p = 0.03). Global circumferential and radial strain were also significantly lower in those with LGE (all p<0.05). MDI was significantly longer in those with LGE compared to those without (81.3 ± 17.6 vs. 61.3 ± 17.4 ms; p<0.01). Left ventricular contractility was also significantly lower in those with LGE (4.1 ± 1.4 vs. 5.2 ± 1.5 SBP/LVESVi; p=0.03).

Characteristic	LGE - (n=16)	LGE + (n=18)	p-value
Volumes			
LV end-diastolic volume index – ml/m^2	65.6 ± 12.4	77.5 ± 13.8	0.01
LV end-systolic volume index – ml/m^2	29.5 ± 9.8	37.6 ± 11.4	0.03
LV stroke volume index – ml/m^2	36.1 ± 3.4	39.9 ± 6.4	0.04
LV ejection fraction - %	56.0 ± 6.2	52.2 ± 8.0	0.13
LV mass index – g/m^2	40.5 ± 9.9	48.5 ± 9.1	0.01
RV end-diastolic volume index – ml/m^2	59.2 ± 9.9	69.8 ± 19.7	0.07
RV end-systolic volume index – ml/m^2	23.6 ± 7.2	29.9 ± 13.2	0.09
RV stroke volume index – ml/m^2	35.5 ± 3.9	39.9 ± 7.9	0.03
RV ejection fraction - %	60.7 ± 5.8	58.3 ± 7.4	0.30
Late gadolinium enhancement			
Infarct pattern of LGE (n)	NA	11 (61%)	NA
LGE FWHM – (g)	NA	2.9 ± 4.3	NA
LGE FWHM – (% of LV)	NA	7.2 ± 7.1	NA

Feature tracking parameters			
Global longitudinal strain - %	-14.8 ± 2.8	-12.4 ± 3.2	0.03
Global radial strain (long axis) - %	26.2 ± 6.8	20.5 ± 7.2	0.03
Global radial strain (short axis) - %	32.3 ± 9.3	23.6 ± 9.1	<0.01
Global circumferential strain - %	-18.3 ± 3.6	-14.6 ± 4.0	<0.01
MDI (ms)	61.3 ± 17.4	81.3 ± 17.6	<0.01
Contractility (SBP/$LVESV_i$)	5.2 ± 1.5	4.1 ± 1.4	0.03

Table 4-4: Baseline CMR data.

Continuous variables expressed as mean±SD. Categorical variables expressed as counts (percent)

Abbreviations: FWHM: full width half maximum, LGE: late gadolinium enhancement, MDI: mechanical dyssynchrony index, LV: left ventricle, LVESVi: left ventricular end-systolic volume index, RV: right ventricle, SBP: systolic blood pressure

4.4.3 Differences between AOO and DOO pacing modes

There were no significant differences noted between LVEDVi, RVEDVi and LV mass index between AOO and DOO pacing modes in either those with or without LGE (Table 4-5). In DOO pacing there was a significant increase in LVESVi when compared to AOO pacing resulting in a significant fall in LVEF in both those with and without LGE (all $p<0.01$). RVESVi increased between AOO and DOO pacing in those without LGE (23.6 ± 7.2 vs. 26.6 ± 8.0 ml/m^2; $p=0.03$) but no significant change was detected in those with LGE. RVEF fell between AOO and DOO pacing in both groups.

Variable	LGE - (n=16)			LGE + (n=18)			Unpaired p-value*
	AOO	DOO	p-value	AOO	DOO	p-value	
Volumes							
LV end-diastolic volume index – ml/m^2	65.6 ± 12.5	66.0 ± 12.8	0.67	77.5 ± 13.8	78.8 ± 13.4	0.34	0.53
LV end-systolic volume index – ml/m^2	29.5 ± 9.8	31.6 ± 8.9	<0.01	37.6 ± 11.4	43.0 ± 12.3	<0.01	<0.01
LV ejection fraction - %	56.0 ± 6.2	52.9 ± 5.4	<0.01	52.2 ± 8.0	46.5 ± 9.1	<0.01	0.02
LV mass index – g/m^2	40.5 ± 9.9	40.7 ± 11.4	0.88	48.5 ± 9.1	50.0 ± 7.9	0.17	NA
RV end-diastolic volume index – ml/m^2	59.2 ± 9.9	60.1 ± 11.4	0.54	69.8 ± 19.7	68.6 ± 19.4	0.29	0.19
RV end-systolic volume index – ml/m^2	23.6 ± 7.2	26.6 ± 8.0	0.03	30.0 ± 13.2	31.7 ± 12.4	0.07	0.83
RV ejection fraction - %	60.7 ± 5.8	58.2 ± 5.6	<0.01	58.3 ± 7.4	54.7 ± 7.6	<0.01	0.19
Feature tracking parameters							
Global longitudinal strain - %	-14.8 ± 2.8	-13.6 ± 4.0	0.04	-12.4 ± 3.2	-10.6 ± 2.9	<0.01	0.40
Mechanical Dyssynchrony Index (ms)	61.3 ± 17.4	71.0 ± 25.0	0.07	81.3 ± 17.6	88.8 ± 21.2	0.04	0.71
Other							
Contractility (SBP/LVESVi)	5.2 ± 1.5	4.5 ± 1.2	<0.01	4.1 ± 1.4	3.5 ± 1.2	<0.01	0.44

QRS duration (ms)	92.9 ± 24.1	145.1 ± 21.3	<0.01	96.8 ± 14.5	156.0 ± 16.4	<0.01	0.33

Table 4-5: CMR, contractility and QRS duration in AOO and DOO pacing modes in those with and without LGE.

Data expressed as mean±SD.

* LGE- vs. LGE+ (Absolute change between AOO and DOO)

Abbreviations: LGE: late gadolinium enhancement, LV: Left Ventricle, LVESVi: Left ventricular end-systolic volume index, RV: Right Ventricle, SBP: systolic blood pressure

Global longitudinal strain and LV contractility were significantly lower in DOO pacing compared to AOO pacing in those with and without LGE (all p<0.05) (Figure 4-9).

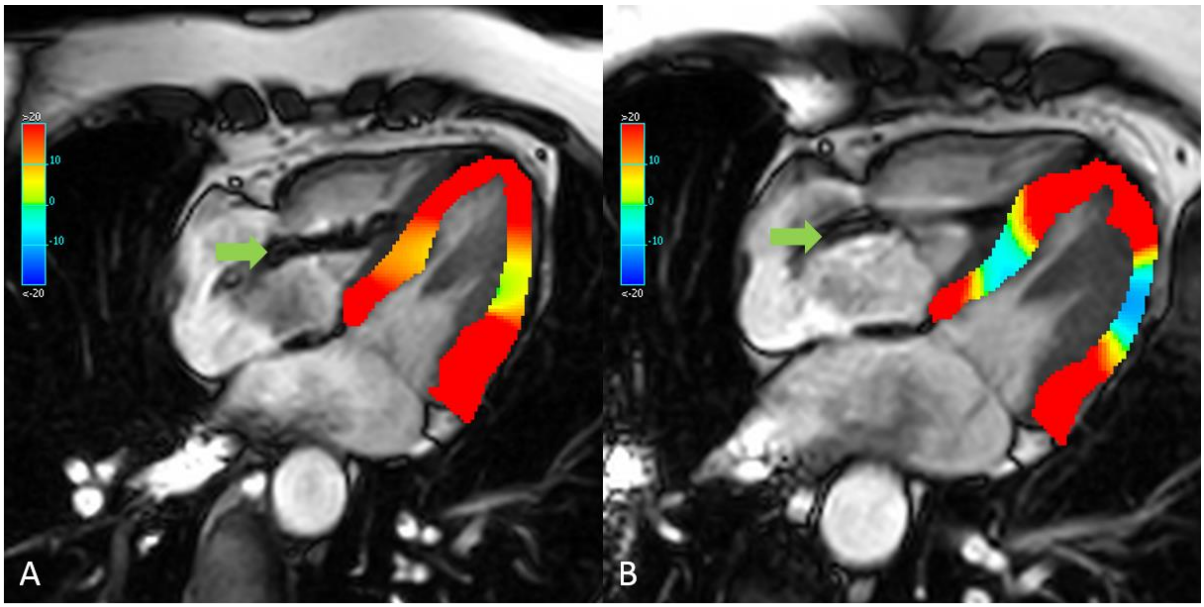


Figure 4-9: Global longitudinal strain in a patient with a pacemaker.

A visual example of the change in GLS at end-systole between AOO (Panel A) and DOO (Panel B) pacing modes. Susceptibility artefact from the pacing leads (green arrows) is demonstrated.

QRS duration increased significantly in both those with and without LGE from AOO to DOO pacing (LGE- : 92.9 ± 24.1 to 145.1 ± 21.3ms; p<0.01, LGE+ : 96.8 ± 14.5 to 156.0 ± 16.4 ms; p<0.01). MDI increased between AOO and DOO pacing modes in both groups although this was only significant in those with LGE (81.3 ± 17.6 vs. 88.8 ± 21.2 ms; p=0.04) (Figure 4-10).

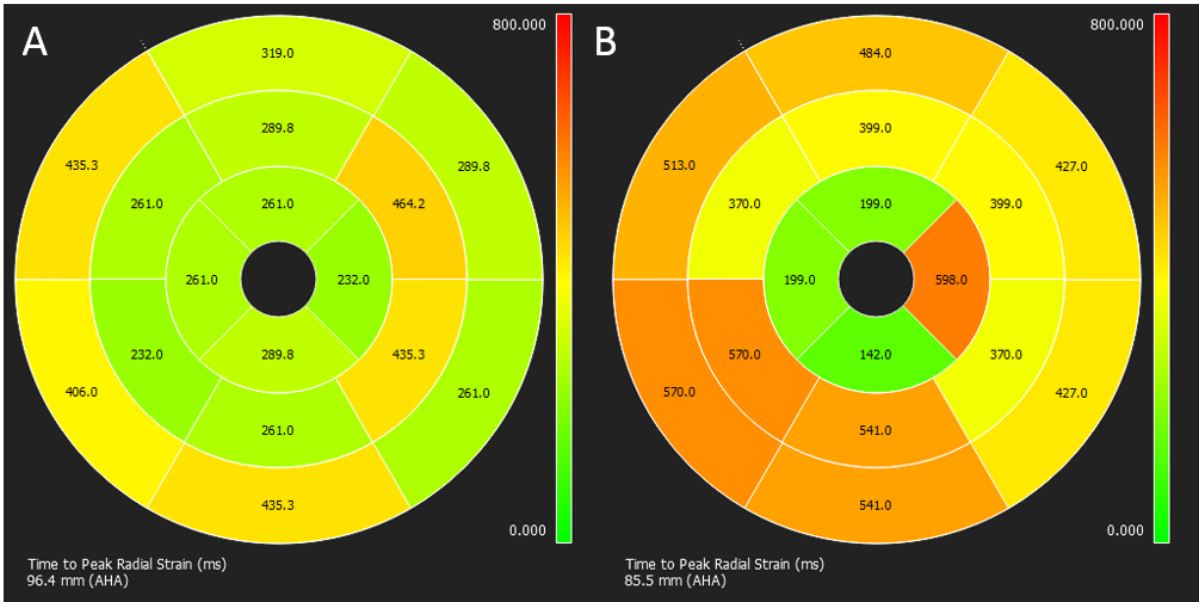


Figure 4-10: Time to peak radial strain in AOO and DOO pacing modes.

An example of the change in time to peak strain (ms) for all 16 AHA segments between AOO (Panel A) and DOO (Panel B) pacing modes.

4.4.4 Absolute change between pacing modes according to LGE status

The change in LVEDVi and LVESVi between AOO and DOO pacing modes for each individual patient can be seen in Figure 4-11. The graph illustrates that LVEDVi generally remains unchanged between pacing modes. LVESVi increased in both those with and without LGE with a greater increase in LVESVi in those with LGE.

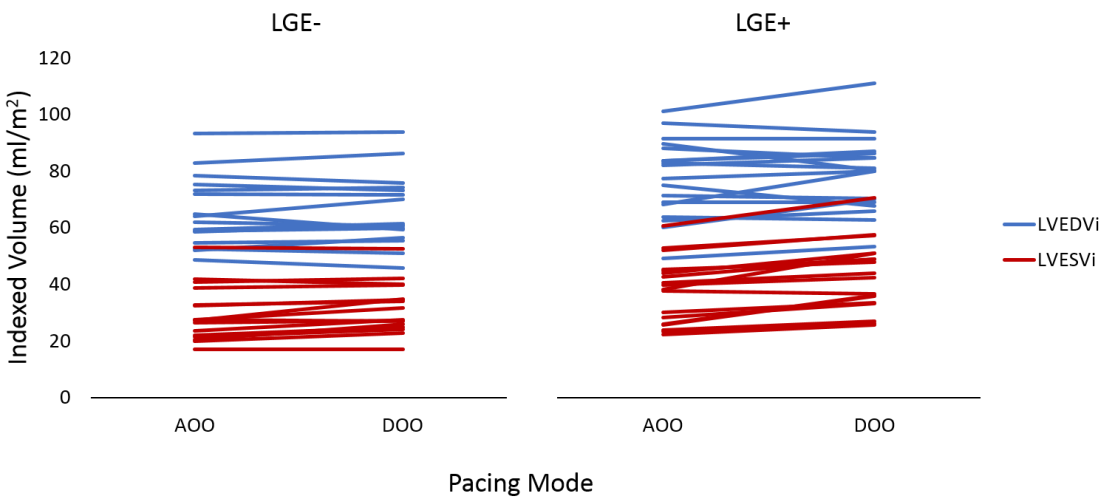


Figure 4-11: Change in left ventricular volumes between pacing modes.

Change in left ventricular end-diastolic (blue lines) and left ventricular end-systolic (red lines) indexed volumes between AOO and DOO pacing mode in those with (right) and without (left) LGE.

Abbreviations: LGE: late gadolinium enhancement, LVEDVi: Left ventricular end-diastolic volume index, LVESVi: Left ventricular end-systolic volume index

The absolute change in LVESVi between AOO and DOO pacing modes was significantly higher in those with LGE compared to those without (5.3 ± 3.5 vs. 2.1 ± 2.4 ml/m^2; $p<0.01$) (Figure 4-12) and those with LGE had a significantly greater drop in LVEF (-5.7 ± 3.4 vs. -3.2 ± 2.6%; $p=0.02$). The absolute changes in LVEDVi, RVEDVi and RVESVi were not significantly different between those with and without LGE.

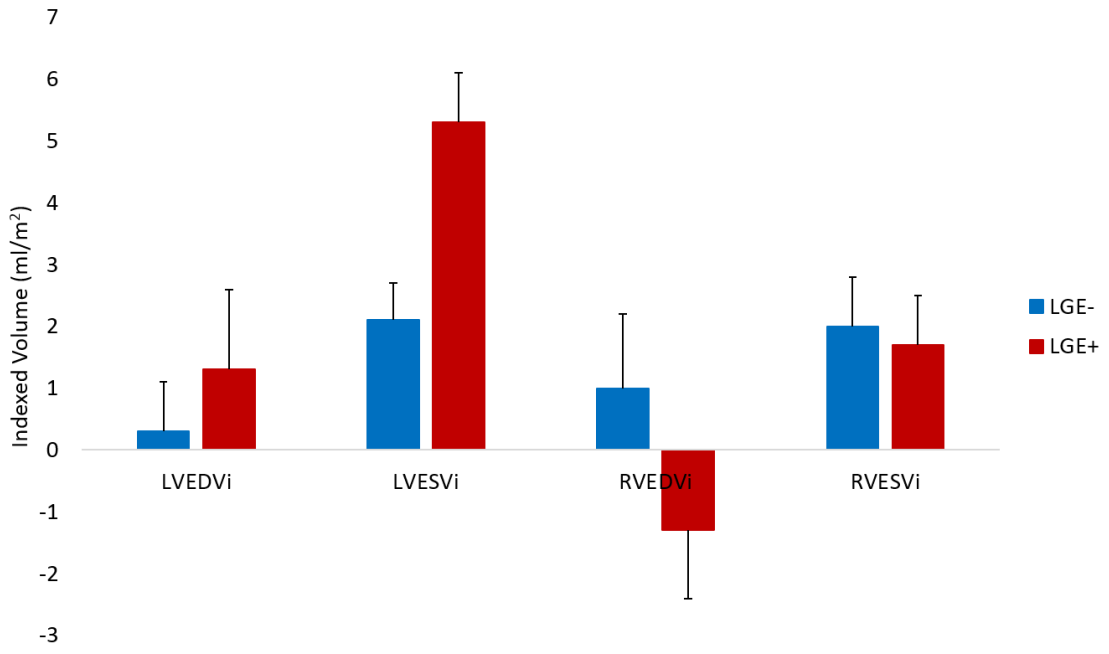


Figure 4-12: Change in ventricular volumes between AOO and DOO pacing modes.

Absolute change in left and right ventricular volumes between AOO and DOO pacing modes in those with (red) and without (blue) LGE. Values are mean ± SE.

Abbreviations: LGE: late gadolinium enhancement, LVEDVi: Left ventricular end-diastolic volume index, LVESVi: Left ventricular end-systolic volume index, RVEDVi: Right ventricular end-diastolic volume index, RVESVi: Right ventricular end-systolic volume index

No significant difference was noted in the absolute change in QRS duration between AOO and DOO pacing modes in those with and without LGE (59.2 ± 18.6 vs. 52.3 ± 20.8 ms; p=0.33). However in those without LGE the change in QRS duration between AOO and DOO pacing showed a moderate positive correlation between the change in LVESVi which was statistically significant (r=0.55; p=0.03) (Figure 4-13). There was no correlation between the change in QRS duration and LVESVi between pacing modes in those with LGE (r=0.07; p=0.79).

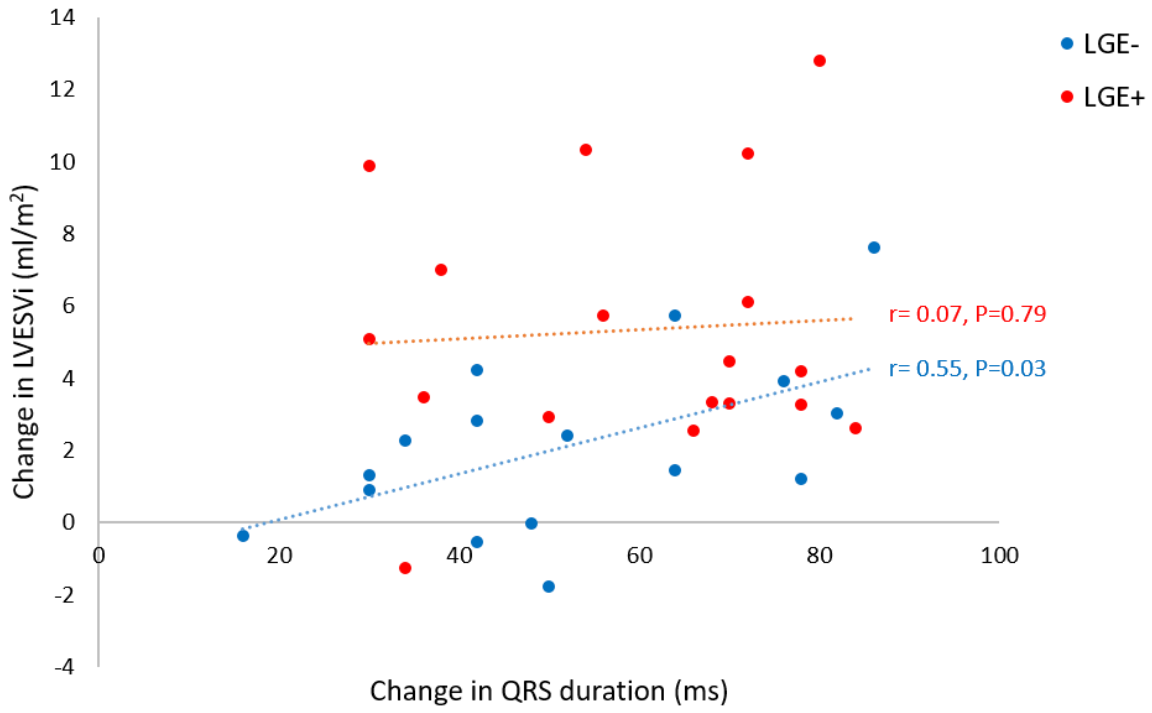


Figure 4-13: Scatterplot of change in LVESVi and QRS duration between AOO and DOO pacing modes.

Abbreviations: LGE: late gadolinium enhancement, LVESVi: Left ventricular end-systolic volume index

4.4.5 4D flow derived LV kinetic energy

4.4.5.1 Baseline characteristics according to LGE status

4D flow reconstructions failed in one patient so analysis was performed in 33 patients. The baseline 4D flow KE parameters for patients with and without LGE can be seen in Table 4-6. There was no significant difference in any of the measures of global LV KE in either those with or without LGE.

4.4.5.2 Differences between AOO and DOO pacing modes in those with and without LGE

There was a non-significant trend for KEi_{EDV} over the entire cardiac cycle to fall between AOO and DOO pacing in both groups (p>0.05) (Table 4-7). There was no change in the average systolic KEi_{EDV} between pacing modes. Average diastolic KEi_{EDV} was significantly lower during DOO pacing in patients with LGE (14.5 ± 5.6 vs. 12.0 ± 4.3 μJ/ml; p=0.028). There was a fall in peak late filling (A-wave) KEi_{EDV} between pacing

modes in both groups although the change was non-significant ($p>0.05$). In-plane KE increased significantly during DOO pacing compared to AOO pacing in those with LGE (37.3 ± 9.2 vs. 43.3 ± 8.8%; $p=0.003$). No differences were observed between those with and without LGE in the absolute change between pacing modes (Table 4-7).

Characteristic	LGE – (n=16)	LGE + (n=17)	p-value
Global LV kinetic energy (µJ/ml)			
Total Left Ventricle	11.9 ± 3.7	13.1 ± 4.0	0.393
Systolic	10.9 ± 2.1	11.6 ± 3.8	0.490
Diastolic	13.3 ± 2.4	14.5 ± 5.6	0.562
Peak E-wave	10.6 ± 6.7	10.7 ± 5.8	0.958
Peak A-wave	19.8 ± 11.9	23.8 ± 10.0	0.127
In-plane KE (%)	34.2 ± 8.3	37.3 ± 9.2	0.326

Table 4-6: Baseline values for mapping of left ventricular kinetic energy in patients with and without late gadolinium enhancement. Continuous variables expressed as mean±SD.

Abbreviations: KE: kinetic energy LGE: late gadolinium enhancement, LV: Left ventricle,

Characteristic	LGE – (n=16)		p-value	LGE + (n=17)		p-value	Unpaired p-value*
	AOO	DOO		AOO	DOO		
Global LV kinetic energy (µJ/ml)							
LV	11.9 ± 3.7	10.5 ± 2.4	0.150	13.1 ± 4.0	11.7 ± 4.2	0.062	0.545
Systolic	10.9 ± 2.1	10.3 ± 5.9	0.381	11.6 ± 3.8	11.4 ± 4.7	0.653	0.405
Diastolic	13.3 ± 2.4	11.0 ± 3.9	0.098	14.5 ± 5.6	12.0 ± 4.3	0.028	0.708
Peak E-wave	10.6 ± 6.7	8.7 ± 3.6	0.163	10.7 ± 5.8	9.0 ± 4.3	0.149	0.624
Peak A-wave	19.8 ± 11.9	16.5 ± 9.1	0.326	23.8 ± 10.0	20.0 ± 11.8	0.076	0.790
In-plane KE (%)	34.2 ± 8.3	37.3 ± 9.7	0.255	37.3 ± 9.2	43.3 ± 8.8	0.003	0.360

Table 4-7: Left ventricular kinetic energy in AOO and DOO pacing modes in those with and without LGE.

Continuous variables expressed as mean±SD.

*Unpaired P-Value comparing absolute change between AOO and DOO pacing in those with and without LGE.

Abbreviations: KE: kinetic energy LGE: late gadolinium enhancement, LV: Left ventricle

4.4.6 Device parameters

All thirty four patients completed the full protocol safely with no adverse clinical events. Devices were interrogated before and after the MRI (Table 4-8). No significant changes to lead impedance, atrial or ventricular capture threshold, P- and R- wave amplitude or battery voltage were noted. One patient with an ICD experienced a minor drop in battery voltage after the MRI scan and the information was conveyed to the cardiac physiology department responsible for further follow up. No clinically significant changes in lead parameters were detected.

Parameter	Pre MRI value (n=34)	Post MRI value (n=34)	p-value
Pacing lead impedance - Ohms			
- Atrial lead	487 (437-555)	489 (439-551)	0.24
- Ventricular lead	570 (488-749)	588 (460-692)	0.12
Pacing lead threshold – V@0.4ms			
- Atrial lead	0.5 (0.5-0.8)	0.6 (0.5-0.8)	0.49
- Ventricular lead	0.8 (0.5-1.0)	0.8 (0.5-1.0)	0.40
Battery Voltage* - V	3.02 (3.01-3.02)	3.02 (3.01-3.02)	NA
P-wave amplitude - mV	3.8 (2.5-4.8)	3.8 (2.4-5.0)	0.86
R-wave amplitude - mV	12 (7.4-15.3)	12 (7.9-16.5)	0.67

Table 4-8: Comparison of device parameters before and immediately after the CMR examination

The data are expressed as median (IQR).

*Boston Scientific® devices were excluded as the programmer does not given a numerical value for battery voltage (n=8).

4.5 Discussion

This study investigated the effect of forced RV pacing compared with intrinsic AV conduction on cardiac haemodynamics in patients with and without focal myocardial fibrosis. The study demonstrated that:

1. Patients with focal myocardial fibrosis, compared to those without, have a greater decline in left ventricular systolic function and a greater increase in LV dyssynchrony during forced RV pacing.
2. Forced RV pacing leads to an acute deterioration in left and right ventricular function compared to intrinsic AV conduction in those with and without focal myocardial fibrosis.
3. Forced RV pacing is associated with a reduction in global longitudinal strain and left ventricular contractility in patients with and without focal fibrosis.
4. Forced RV pacing is associated with changes to the in-plane LV KE in patients with myocardial fibrosis.

4.5.1 Influence of myocardial fibrosis on left ventricular volumes during forced RV pacing

To our knowledge this is the first study to evaluate changes in ventricular volumes and function between intrinsic AV conduction and forced RV pacing in patients with MRI conditional pacemakers using CMR. Our study set out to assess the influence of myocardial fibrosis, confirmed by LGE imaging, on immediate changes in ventricular performance during RV pacing.

In our study changing from intrinsic AV conduction to forced RV pacing was associated with a decline in LVEF in patients with and without myocardial fibrosis. In both groups the observed change in LV function was predominantly mediated by a significant increase in LVESVi during RV apical pacing with no change in LVEDVi between pacing modes. The magnitude of change in LV volumes with initiation of RV pacing was greater in those with underlying myocardial fibrosis than those without myocardial fibrosis. The increase in LVESVi in those with fibrosis led to nearly a 6% fall in LVEF.

The observed changes in LVESVi between pacing modes within our study suggests that initiation of apical pacing may directly alter LV contractility assuming a constant preload and afterload. Indeed we have shown that LV contractility was significantly lower in DOO rather than AOO pacing in both groups. Overall the findings are in keeping with previous studies where initiation of RV pacing leads to an increase in LVESV and subsequent reduction in LVEF (101, 258, 280). Interestingly our study demonstrates that the magnitude of change in LVESVi is greater in those with myocardial fibrosis suggesting they are particularly susceptible to the potential haemodynamic consequences of RV pacing.

In our study LVEDVi did not change between pacing modes, which is likely due to minimal changes to the preload between pacing modes. We aimed to minimise variation in LV filling time by pacing at the same heart rate during both pacing modes. LVEDV has been shown to fall between intrinsic rhythm and RV apical pacing performed during electrophysiology studies (50) (281). These observations may be because AV synchrony was not maintained during RV pacing. The loss of atrial systole during late diastole may therefore compromise LV filling. Zile *et al.* have shown in anaesthetised dogs that sequential AV pacing, compared to asynchronous RV pacing, minimises changes in ventricular loading and preload (end-diastolic dimensions) and is similar to that during right atrial pacing (91). In patients it has been shown that LVEDV does not change, if heart rate is constant, in patients with pacemakers when intrinsic AV conduction is compared to sequential AV conduction with forced ventricular pacing (99, 101, 258, 282).

There were differences in baseline CMR parameters for those with and without myocardial fibrosis. Despite similar LVEF between the groups those with myocardial fibrosis had significantly larger LVEDVi and LVESVi. These findings suggest that those with myocardial fibrosis have undergone a degree of adverse remodelling with resultant changes in LV volumes. Indeed the presence of late gadolinium enhancement in patients with other cardiovascular diseases, such as aortic stenosis or dilated cardiomyopathy, is associated with higher LVEDVi and LVESVi than those without LGE (283, 284). In patients with non-ischaemic cardiomyopathy the presence of midwall fibrosis is associated with a greater degree of ventricular dilatation and systolic impairment compared to those without fibrosis (285). The effect of increased baseline volumes on the immediate effects of RV apical pacing have not previously been evaluated. However a lower initial LVEF and higher LVESV have been found on univariate analysis to be associated with decline in both LVEF (≥5%) at 12 months and heart failure death or

hospitalisation in the longer term (follow up mean duration: 6.7±3.9 years) (138, 286). Pastore *et al.* have previously shown across a wide range of LVEF that baseline LVEF and baseline volumes (LVEDV and LVESV) correlate with the amount of intra-LV dyssynchrony induced after 24 hours of RV pacing and that on multivariate linear regression baseline LVESV correlated with intra-LV dyssynchrony after pacing (B = 0.60, $p<0.001$) (199).

4.5.2 Influence of myocardial fibrosis on right ventricular volumes during forced RV pacing

At baseline in our study there was no significant difference between those with and without myocardial fibrosis in RVEDVi or RVESVi. In a similar trend to LV function we observed that RV function declined significantly after initiation of RV pacing in both groups. Indeed mirroring the changes on the left side of the heart during pacing the RVEDV remained unchanged. There was an increase in RVESV which only reached significance in those without fibrosis. There was no significant difference in the observed changes between those with and without myocardial fibrosis.

Although the right ventricle displayed a similar pattern in response to right ventricular apical pacing as the left ventricle, the magnitude of the change was much less. This may be a reflection of RV activation occurring prior to left ventricular activation and perhaps overall a shorter time to total endocardial activation in the RV due to its smaller myocardial mass. The lack of difference between those with and without fibrosis could be attributed to the absence of right ventricular fibrosis with the propagation of the electrical wavefront throughout the RV not differing between the two groups. However assessment of right ventricular fibrosis, using LGE, is challenging as the RV is thin walled and can be surrounded by epicardial fat and pericardium.

Data on the effects of right ventricular pacing on right ventricular volumes and function are limited with the majority evaluating the long term outcomes of pacing on the RV. Friedberg *et al.* evaluated the acute effects of AOO and DOO pacing in children with structurally normal hearts and found no acute compromise of RV function or haemodynamics (287). Nunes *et al.* found no detrimental effect to RV pacing on RV dimensions or strain compared to controls (288). Even in the long term RV systolic function and strain do not appear to change following RV pacing (288-291). The fact that

we have demonstrated a change in RV function with pacing may be a reflection of the improved reproducibility of CMR compared to echocardiography (292).

4.5.3 Effect of Pacing on Electromechanical Synchrony and Strain

Both groups had a significant fall in LVEF between pacing modes with an increase in LVESVi during DOO pacing which is presumably mediated by the electromechanical dyssynchrony induced by RV pacing. During normal sinus rhythm electrical activation occurs through the His-Purkinje system with near simultaneous activation of both ventricles leading to a narrow QRS complex on the surface ECG. However in RV apical pacing the activation wavefront propagates from the site of earliest activation at the RV apex with myocyte to myocyte spread to the site of latest activation at the infero-posterior base of the LV giving rise to a prolonged QRS duration and left superior axis on the 12 lead ECG (84, 293). In our study electrical dyssynchrony, as denoted by the QRS duration, increased significantly in both groups between AOO and DOO pacing modes (LGE- : 88ms vs. 147ms; $p<0.01$, LGE+ : 93ms vs. 160ms; $p<0.01$). There was no significant difference in either the intrinsic or paced QRS duration between those with or without fibrosis. The electrical dyssynchrony induced by RV apical pacing in our study led to changes in LV mechanics in both groups with significant decreases in GLS and LV contractility. Initiation of apical pacing in those with fibrosis led to the development of significant mechanical dyssynchrony and although a trend to mechanical dyssynchrony was observed in those without fibrosis this did not reach significance. These results suggest that the presence of fibrosis leads to increased mechanical dyssynchrony and decline in LV function.

Numerous studies in patient populations have demonstrated the acute effects of RV pacing on LV mechanics. The use of advanced echocardiographic techniques such as STE or TDI have shown RV apical pacing can lead to an immediate reduction in LVEF through reduced global strain, regional contraction and LV twist together with an increase in mechanical dyssynchrony (50, 99, 100, 198, 265). However electrical dyssynchrony cannot be the sole explanation for the change in LV performance. Greater acute haemodynamic change was observed in those with fibrosis where the degree of electrical dyssynchrony did not correlate with changes in ESV suggesting a more complex relationship between electrical activation and mechanical performance (electromechanical coupling).

The presence of electrical dyssynchrony does not necessarily lead to the development of significant mechanical dyssynchrony. In patients with LBBB the presence of septal flash, a rapid pre-ejection leftward septal motion, as a marker of dyssynchrony, was only present in 52% of patients (294). Furthermore the surface ECG may not be the best predictor of subsequent mechanical dyssynchrony as Yu *et al.* have previously shown using TDI that mechanical dyssynchrony is present over half of patients of heart failure patients with a narrow QRS duration (295). Indeed acute LV dyssynchrony was only seen in half of patients with SND after initiation of RV pacing despite a significant increase in QRS duration in all patients (95 ± 17 vs. 162 ± 34 ms; $p<0.001$) (101). LVESV increased in both groups between V- sense and V-paced rhythms but the absolute change was greater in those who developed dyssynchrony compared to those that did not (2.9 ± 2.4 vs 1.0 ± 2.1 ml; $p<0.001$). This demonstrates that electrical dyssynchrony does not necessarily equate to significant mechanical dyssynchrony but it is the latter that predominantly determines LV performance after pacing.

4.5.4 Left Ventricular Kinetic Energy

In our study we have demonstrated subtle changes in LV KE after initiation of RV pacing particularly in patients with myocardial fibrosis. These patients experienced a significant reduction in the diastolic LV KE and an increase in the in-plane KE with RV pacing.

First of all it is important to note that the total LV KE in our cohort was greater than has been previously shown in healthy volunteers and in patients with myocardial infarction (255, 296). The increase in the total LV KE in our population must reflect an increase in diastolic KE as the values we observed for LV systolic KE are in keeping with values previously demonstrated in healthy volunteers (296). We speculate that the increase in diastolic KE is related to a greater degree of diastolic dysfunction in our patient population and advancing age. Interestingly the observed reduction in diastolic KE and peak A wave with initiation of RV pacing was greater in those with LGE. These changes may be due to the AV delay during DOO pacing. The shorter AV delay may lead to premature closure of the mitral valve with subsequent truncation of the A wave and a reduction in the KE (297). The fact that these changes were more pronounced in patients with LGE may reflect a greater level of baseline diastolic dysfunction. This could reflect underlying fibrosis, increasing myocardial stiffness, as the A wave during AOO pacing was higher than that seen in patients without fibrosis.

In the present study we have also demonstrated changes in the in-plane KE in those with fibrosis during RV pacing. Garg *et al.* have previously demonstrated that in-plane KE increases as LVEF declines and postulated this was due to LV impairment and dilatation altering flow conditions within the LV cavity leading to the development of a large swirling vortex within the LV (255, 298). Development of this vortex is translated as a greater in-plane KE as transversal shunts within the vortex are interpreted as in-plane KE. Recent work by Bianco *et al.* using echocardiography techniques has shown that RV apical pacing is associated with multiple dysfunctional vortexes and it may be that we are detecting these as a greater proportion of in-plane KE (258). They also demonstrated during RV apical pacing that there was higher diastolic KE dissipation as myocardial contraction became dyssynchronous. The greater dyssynchrony in those with fibrosis may lead to more dysfunctional vortices and greater KE dissipation with a subsequent reduction in cardiac output.

4.5.5 Safety and feasibility

Undertaking CMR in patients with pacemakers and ICDs was feasible in both AOO and DOO pacing modes in the same visit. Analysable image quality was obtained in all patient with pacemakers and the majority of patients with ICDs. All patients were scanned in accordance with manufacturer's instructions and no lead related parameter changes were detected. A small decline in battery voltage was noted in one patient. These findings suggest that the CMR protocol used in this study did not pose any additive risk, though long-term device follow-up is needed to confirm this.

4.5.6 Limitations

To avoid intrinsic AV node conduction, it was essential to programme the AV delay to be shorter than the intrinsic PR interval in AOO pacing. It is possible this may have affected cardiac function. If the AV delay is too short then atrial systole can occur against a closed mitral valve thus reducing LV filling (299). However the data on the optimal AV delay are conflicting (300-302). Occhetta *et al.* found no differences in stroke volumes across a range of AV delays (90-240ms) in pacemaker recipients programmed to atrial-triggered ventricular pacing and atrioventricular sequential pacing at rest (303). Conversely other studies have shown that optimising the AV delay can improve immediate systolic function (304, 305). The programmed AV delay was consistent between groups in those with and without fibrosis and AV timing alone cannot be solely responsible for the haemodynamic changes observed.

Susceptibility artefact due to the presence of the IPG or ICD may also have influenced contouring of epicardial and endocardial contours and even feature tracking results, although studies without clear delineation between blood pool and the endocardium where excluded from analysis. Furthermore the presence of artefact between AOO and DOO scanning should be relatively consistent minimising the impact on intra-patient comparisons. Feature tracking has also previously been shown to be feasible with good intra- and inter-observer variability performed on SSFP acquisitions in patients with pacemakers (209).

Importantly the groups were not matched at baseline as LGE positive patients were significantly older, more often taking certain cardiovascular medications (i.e. angiotensin-converting enzyme inhibitors) and had greater baseline LV volumes. Future work with a greater sample size could potentially address the effect of these factors on an individual's response to forced ventricular pacing.

4D flow CMR sequences used in our study did not use respiratory navigation which may have affected KE parameters. However studies evaluating whole heart 4D flow sequences with and without respiratory navigation have demonstrated comparable values for KE quantification (261). In addition, LV geometry was defined using the LV cine stack acquired during breath holding as opposed to the free breathing 4D flow acquisitions. Despite correcting for spatial miss-registration, issues such as differing physiology remain.

4.5.7 Future implications

Both patient groups experienced a deterioration in left ventricular systolic performance with RV apical pacing. Those with myocardial fibrosis had a greater increase in LVESV and developed worsening mechanical dyssynchrony compared to intrinsic rhythm.

The findings are important because in patients with chronic RV pacing the presence of early (one month) pacing induced dyssynchrony is a strong predictor of reduction of ejection fraction at 12 months (286). Induction of LV dyssynchrony in the short term (median 13 months) has also been demonstrated to be associated with mortality and heart failure hospitalisation in the long term. Further work is needed to evaluate whether

the acute changes in LV performance with initiation of RV pacing portend patients to a greater long term risk of heart failure.

Finally we have demonstrated subtle changes in blood flow KE during RV pacing particularly in those with myocardial fibrosis. These changes in LV blood flow KE could be due to alterations in the AV interval between pacing modes or by changing LV mechanics during RV pacing. Further work in larger studies using 4D flow CMR is needed to: 1) identify novel biomarkers that may provide further mechanistic insight into development of heart failure after RV pacing and 2) evaluate its ability to aid in device optimisation.

4.6 Conclusions

Forced right ventricular pacing leads to immediate changes in left ventricular systolic performance compared to intrinsic atrioventricular conduction. The presence of myocardial fibrosis during ventricular pacing is associated with greater adverse haemodynamic change. The observed changes seem to be mediated by the electromechanical dyssynchrony and alterations in LV mechanics that occur with right ventricular pacing. Whether these acute changes will be reflective of longer term left ventricular adverse remodelling in the bradycardia pacemaker population is unknown but further investigation is warranted.

Chapter 5 Impact of myocardial fibrosis on long term ventricular remodelling in patients with atrioventricular block undergoing permanent pacemaker implantation (BLOCK MR)

5.1 Abstract

Background: Right ventricular pacing induces electrical and mechanical dyssynchrony which can lead to LV dysfunction and heart failure. Cardiovascular magnetic resonance enables accurate serial assessment of cardiac function and detection of myocardial fibrosis. The aim of the study was to determine if the presence of myocardial fibrosis altered cardiac haemodynamics after 6 months of RV pacing.

Methods: 67 patients with AV block were prospectively recruited. Patients underwent clinical assessment and CMR before and 6 months after pacemaker implantation.

Results: 50 patients (mean age 79 ± 9 years; 80% male) were included in the final analysis and myocardial fibrosis was present in 62%. At six months LVESV index increased significantly in those with fibrosis compared to those without (8.0 ± 10.4 vs. -0.6 ± 7.3 ml/m^2; p=0.008). Those with fibrosis had a greater fall in LVEF (-12.3 ± 7.9 vs. -6.7 ± 6.2%; p=0.012) despite a smaller decrease in LVEDV index (-7.1 ± 13.8 vs. -14.6 ± 13.9 ml/m^2; p=0.077). Paced QRS duration was longer in those with fibrosis (171.7 ± 13.1 vs. 163.5 ± 12.1 ms; p=0.031). Significant mechanical dyssynchrony (83.7 ± 29.7 vs. 97.6 ± 31.2 ms; p=0.029) and impaired LV contractility developed between baseline and 6 months in those with fibrosis but not in those without fibrosis. No adverse clinical events occurred during the study. Small but significant changes to the ventricular lead impedance and pacing capture threshold were observed immediately after MRI.

Conclusion: Focal myocardial fibrosis is common in patients with AV block undergoing pacemaker implantation. The presence of fibrosis in patients with right ventricular pacing is associated with greater electromechanical dyssynchrony and consequent decline in LV function compared to those without fibrosis.

5.2 Introduction

Right ventricular pacing is a long established treatment for symptomatic bradycardia and has been shown to normalise life expectancy and improve quality of life (30, 262, 263). Right ventricular apical pacing induces electrical and mechanical dyssynchrony which over the longer term may led to progressive LV dysfunction and heart failure (80, 126, 254, 306). Indeed the BLOCK-HF trial demonstrated improved outcomes with biventricular pacing over RV pacing in patients with AV block and LVEF less than 50% (127). However biventricular pacing is associated with a greater financial cost and higher rate of complications than RV pacing and data on its utility in patients with preserved or mildly impaired LV function are less robust (159, 161, 162). Alternate strategies such as right ventricular septal pacing or ventricular pacing avoidance algorithms, have also failed to improve hard clinical end points (168, 182). Observational data suggest that a proportion of patients with preserved LVEF will develop heart failure or have a significant decline in LVEF with long term RV pacing (11, 115, 118, 124). Therefore there is a need to improve the understanding of the pathophysiology of ‘pacing induced cardiomyopathy’ (PICM) and be able to identify individuals at greatest risk to whom upfront physiological pacing may prevent development of heart failure.

Cardiovascular magnetic resonance provides accurate serial assessment of cardiac volumes, evaluation of LV synchrony through feature tracking and tissue tagging techniques and enables detection of myocardial fibrosis (203-205, 210, 218, 267). It is therefore a valuable tool to assess not only cardiac remodelling but also potentially to identify myocardial tissue characteristics that are associated with LV adverse remodelling with long term RV pacing.

We hypothesise that long term RV pacing in the presence of focal myocardial fibrosis leads to greater adverse cardiac remodelling compared to those without myocardial fibrosis.

Therefore, the main aims of the study were to:

1. Evaluate the association of myocardial fibrosis on LVESV in patients with AV block before and 6 months after pacemaker implantation
2. Evaluate the effect of RV pacing on left and right ventricular volumes and function at 6 months

3. Assess the impact of RV pacing on electrical synchrony and LV mechanics in those with and without focal myocardial fibrosis.

5.3 Methods

5.3.1 Study Design and Population

Between February 2018 and January 2019, Sixty seven patients with acquired AV block scheduled to undergo single or dual chamber pacemaker were prospectively recruited from the cardiology in-patient and out-patient departments at a tertiary cardiology centre (Leeds General Infirmary, Leeds, United Kingdom).

Inclusion criteria: Adults (aged over 18), Class I or IIa indication for a pacemaker due to atrioventricular block and planned insertion of a MRI conditional pacemaker

Exclusion criteria: Prior diagnosis of heart failure, Current or recent (<7 days) use of temporary pacing system, acute coronary syndrome within the last 30 days, severe valvular heart disease, Class 1 CRT indication, contraindication to MRI, pregnant or breastfeeding, estimated glomerular filtration rate <30ml/min, obesity where girth exceeds the scanner bore and inability to give informed consent

Decision to proceed to pacemaker implantation was taken by the patient's clinical team. The type of pacemaker (single or dual chamber) implanted was taken by the consultant cardiologist at the time of implantation. Patients were initially recruited and underwent baseline CMR prior to pacemaker implantation. Patients with AV block had a Class I or IIa indication for permanent pacemaker insertion as defined by ESC guidelines (30). The only exception was for patients with first degree AV block who were only included if the PR interval was over 300ms when paced over 100 bpm. The rationale for this is based on previously published work in patients with AV block and the assumption that these patients would likely have a long term high burden of RV pacing (127). The patient recruitment pathway can be seen in Figure 5-1.

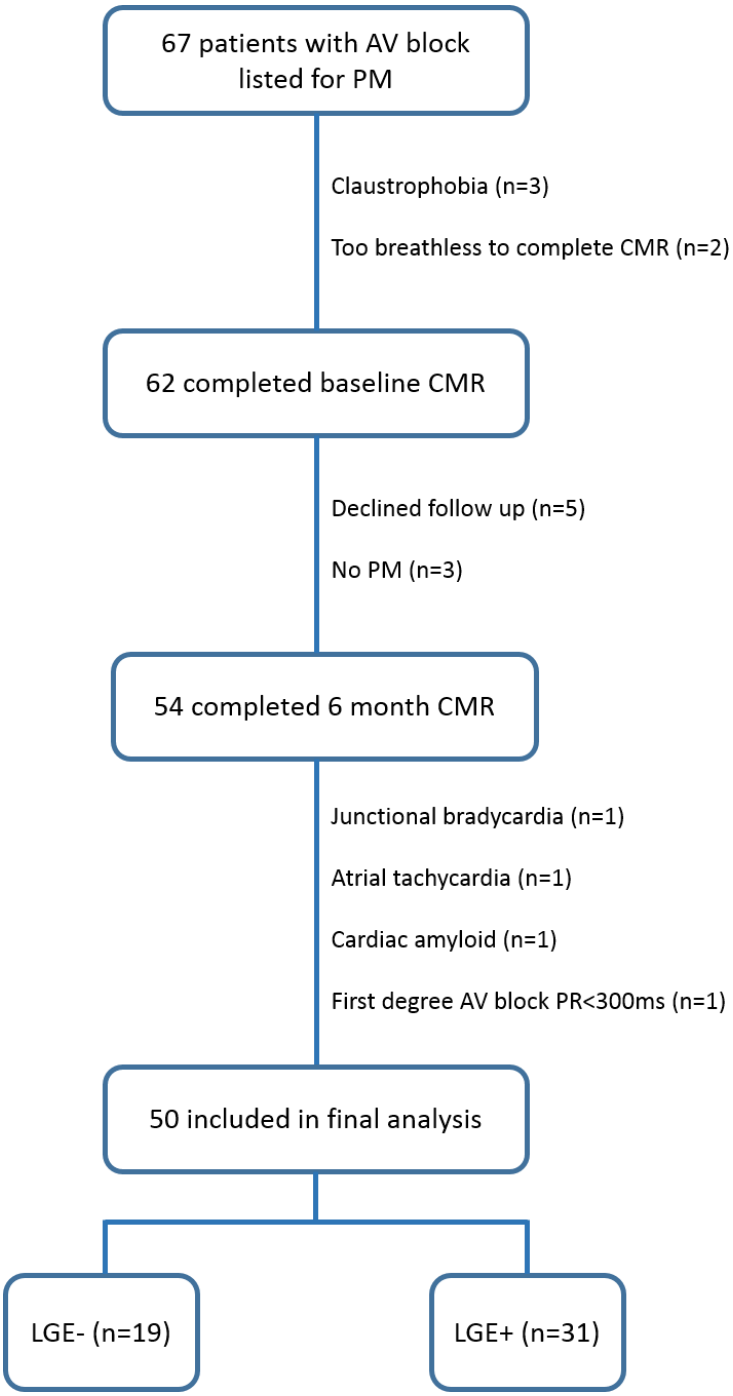


Figure 5-1: Patient recruitment pathway

Abbreviations: AV: atrioventricular, CMR: cardiovascular magnetic resonance, LGE: late gadolinium enhancement, PM: pacemaker

CMR scans were performed prior to pacemaker implantation (baseline) and six months after pacemaker implantation. Baseline and follow up clinical and demographic data were

recorded for all patients. Furthermore the following clinical assessments were conducted at both visits (Figure 4-2):

1. Electrocardiograms to record the heart rate, type of AV block (at baseline visit) and QRS duration (MAC3500, General Electric Medical Systems, Milwaukee, WI, USA or CT8000i, Seca, Hamburg, Germany).
2. Blood samples were taken for full blood count (for measurement of haematocrit) and stored for future measurement of high sensitivity troponin and BNP at the time of intravenous cannulation prior to CMR study
3. New York Heart Association (NYHA) Class
4. Quality of life (EQ-5D questionnaire)
5. New clinical events, including atrial fibrillation, new onset heart failure and death, were recorded at 6 months and will be recorded at 12 months then yearly for a total of 5 years.

5.3.2 Primary Endpoint

The primary endpoint in our study was a change in LVESVi at six months. LVESVi was selected as the primary endpoint as it has been shown to be a powerful predictor of clinical outcomes after myocardial infarction and coronary revascularisation over and above either LVEDV or LVEF (129, 307). A reduction in LVESV with angiotensin converting enzyme inhibitors and CRT has been demonstrated to correlate with an improvement in clinical response and cardiovascular outcomes (145, 308). Furthermore change in LVESVi has been linked to clinical endpoint in patients with AV block. In the BLOCK-HF study the risk of morbidity and mortality after pacing increased by 1% for every 1ml/m^2 increase in LVESVi (156).

5.3.3 Power Calculation

To detect a clinically meaningful (10ml) change in LVESV between those with and without LV scar based on interstudy standard deviation of 5.4% a minimum of 7 patients with LV scar are required (α 5%, β 10%) (204). The prevalence of LV scar in patients undergoing pacemaker implantation is unknown and a sample size of 50 allows for a minimum prevalence of 14% which is similar to the prevalence of unrecognised scar in similarly aged populations (309). Increasing the sample size to 55 allows for a dropout of 10%.

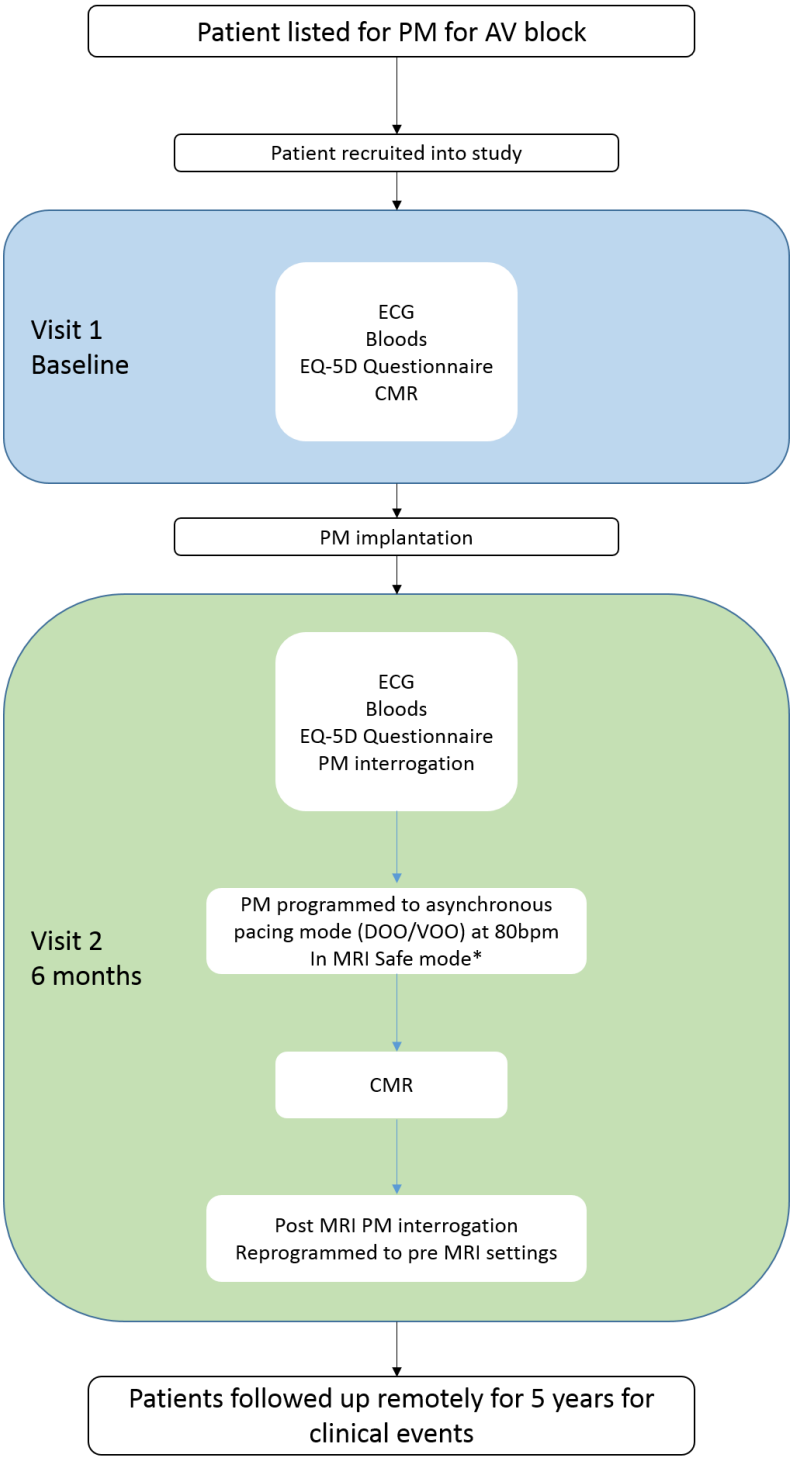


Figure 5-2: Study protocol

* Patients were programmed at a minimum base rate 80bpm or 10bpm above intrinsic rate

Abbreviations: DOO: dual chamber pacing, AV: atrioventricular, CMR: cardiovascular magnetic resonance, ECG: electrocardiogram, LGE: late gadolinium enhancement, MRI: magnetic resonance imaging, PM: pacemaker, VOO: ventricular pacing

The pacing and lead parameters were evaluated at the time of device implantation, at a 6 week clinically scheduled check and at the 6 month visit. The following quantitative parameters were obtained: 1. Ventricular lead R wave and thresholds. 2. Percentage of atrial and ventricular pacing. 3. Significant atrial or ventricular high rate episodes. Individual device programming at implant and follow up was at the discretion of the clinical team.

5.3.4 Ethics Approval

The study complied with the Declaration of Helsinki (October 2000) and the study protocol was approved by the National Research Ethics Service (Ref 17/EM/0475). All patients recruited in the study gave written informed consent. Ethical approval, patient information sheets and consent forms are available in the Appendix.

5.3.5 Device Programming

Before entering the MRI room, patients underwent full device interrogation which included determination of lead impedance, pacing thresholds and P- and R-wave sensing amplitude and battery voltage. Devices were then programmed into manufacturer specific MRI safe mode. Patients were programmed to asynchronous pacing at a base rate of 80 bpm; typically dual chamber (DOO) pacing but patients with a single chamber pacemaker or in atrial fibrillation at the time of the scan were programmed to ventricular (VOO) pacing. If the patient's sinus rate was greater than 80bpm they were programmed to DOO at 10 beats per minute above intrinsic heart rate to avoid competition and ensure sequential AV pacing. During the MRI examination patients were monitored using non-invasive blood pressure and VCG signal. A device check was performed assessing the lead impedance, pacing thresholds, P- and R-wave sensing amplitudes and battery voltage immediately after the MRI. Given lead parameters vary on repeated measurements we recorded the following absolute changes in keeping with previous large MRI studies in patients with pacemakers: pacing lead capture threshold increase of ≥0.5V, P- or R-wave amplitude decrease of ≥50%, lead impedance change of ≥50 Ohms and battery voltage decrease of ≥0.04V (23, 46). Patients were reprogrammed to pre scan settings before discharge.

5.3.6 Quality of Life assessment

The EQ-5D instrument was completed before and 6 months after pacemaker implantation to evaluate health related quality of life. EQ-5D assesses a respondent's self-reported health state on the day of completion in five different domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (310). Responses provide an index (quality of life weighting) between 0 and 1 where 0 reflects death and 1 full health. It is scored using the UK population time-trade-off valuation exercise (311). EQ-5D also includes a visual analogue scale (VAS) where patients score their health state from 0 (worst imaginable health) to 100 (best imaginable state).

5.3.7 Cardiovascular Magnetic Resonance

Participants underwent CMR imaging at 1.5T (Ingenia, Philips, Best, The Netherlands) with a phased array receiver coil (24-channel equipped with Philips dStream digital broadband MR architecture technology). At the 6 month follow up scan all patients were scanned in normal operating mode (Upper limit of SAR level 2 W/kg body weight) with maximised gradient slew rate up to 200T/m/s and according to any other specific manufacturer's device instructions. All scans were supervised by a Cardiology Registrar with valid Advanced Life Support certification and a Cardiac Physiologist with expertise in cardiac devices was present at the follow up.

When possible at follow up (dependent on manufacturer specific device instructions and patient comfort) the patients arm was positioned arm their head (ipsilateral to location of the implantable pulse generator) to minimise susceptibility artefact over the heart from the pacemaker. Repositioning of the arm moved the susceptibility artefact further away from the heart thus improving overall image quality and delineation of endocardial and epicardial borders (Figure 1-2 & Figure 4-4).

5.3.8 Image Acquisition

The CMR protocol was as follows:

1. Survey images
2. Cine imaging: Acquired using SSFP in a single slice breath-hold sequence. Images obtained included a LV volume contiguous short axis stack as well as two, three and four chamber views. Typical image parameters were as follows: Slice thickness 10mm, TE 1.5 ms, TR 3 ms, flip angle 60°, SENSE factor 2 with 30 phases per cardiac cycle.
3. T1 mapping: Acquired using a breath held Modified Look-Locker Inversion recovery (MOLLI) technique (ECG triggered 5s(3s)3s, single-shot, prepulse delay 350ms, trigger delay set for end-diastole (adaptive), SENSE factor 2, flip angle 35°, matrix 152 x 150, slice thickness 10mm, reconstructed voxel size of 1.17 x 1.17mm. Three short axis slices were acquired using the 3 of 5 technique (268).
4. Tissue tagging: SPAMM (spatial resolution 1.99 × 2.33 × 8 mm^3, tag separation 7 mm, ≥12 phases, TR 4.1ms, TE 1.8ms, flip angle 10°) was acquired in the three short axis slices identical to those acquired in T1 mapping.
5. Administration of an intravenous bolus of 0.15mmol/kg gadobutrol (Gadovist®, Bayer, Berlin, Germany) via a cannula followed by a 10ml saline flush.
6. TI scout (Look-locker sequence, single mid-ventricular slice, 10mm thickness, FoV 300x300mm) to determine the optimal TI to null the myocardium
7. Late gadolinium enhanced imaging:
    a. Performed using a T1-weighted PSIR gradient echo pulse sequence 10-15 minutes after contrast. Contiguous breath held short axis slices were planned to cover the entire left ventricle (Typically 10-12 slices: same geometry as LV cine imaging). Typical imaging parameters were as follows: 10mm thickness, no interslice gap, matrix 188 x 139, FoV 300 × 300 mm, TE 3.0 ms, TR 6.0 ms, flip angle 25°, acquired in-plane resolution 1.60 × 2.15 mm^2reconstructed to 0.89 × 0.89 mm^2, effective SENSE factor 1.8. Two, three and four chamber views were also typically acquired and cross cuts and phase swaps were performed as necessary to confirm the presence or absence of LGE.
    b. If patients were unable to complete breath holds then patients were instructed to free-breathe and a respiratory echo-based navigator was placed on the right hemi diaphragm with a gating window of 6mm with continuous gating level drift activated.

c. If the above steps were unsuccessful at obtaining diagnostic images then a single shot inversion recovery SSFP sequence was performed. Typical imaging parameters were as follows: 10mm thickness, no interslice gap, matrix 192 x 144, TE 2.1 ms, TR 4.4 ms, flip angle 20°, acquired in-plane resolution $1.82 \times 2.44\ mm^2$ reconstructed to $1.22 \times 1.22\ mm^2$, effective SENSE factor 2.

8. Post contrast T1 mapping: performed 15 minutes following contrast injection with identical positioning to the native T1 map using a 4s(3s)3s(3s)2s MOLLI acquisition.

5.3.9 Image Analysis

Cardiac magnetic resonance analysis was performed quantitatively offline by a single operator (CS) blinded to clinical data. Analysis was performed using commercially available software (Cvi42, Circle Cardiovascular Imaging, Calgary, Canada). Endocardial contours were traced on the short axis cine stack at end-diastole and end-systole to calculate LV and RV end-diastolic volume, end-systolic volume, stroke volume and ejection fraction (summation of disks methodology). Papillary muscle and LV trabeculation were excluded from analysis. Epicardial contours were performed for the left ventricle at end-diastole to calculate LV mass (epicardial volume − endocardial volume multiplied by myocardial density [1.05 g/cm^3]). Left atrial volume was calculated using the formula below (Equation 5) where $A2_{Ch}$ and $A4_{Ch}$ are the left atrial area at end-systole in 2- and 4-chamber views respectively and L is the shorter of the two atrial length measurements (274). Pulmonary veins and left atrial appendage were excluded from segmentation (Figure 5-3).

$$\text{Left atrial volume} = \frac{8(A2_{Ch})\,(A4_{Ch})}{3\pi L}$$

Equation 5 : Left atrial volume calculation.

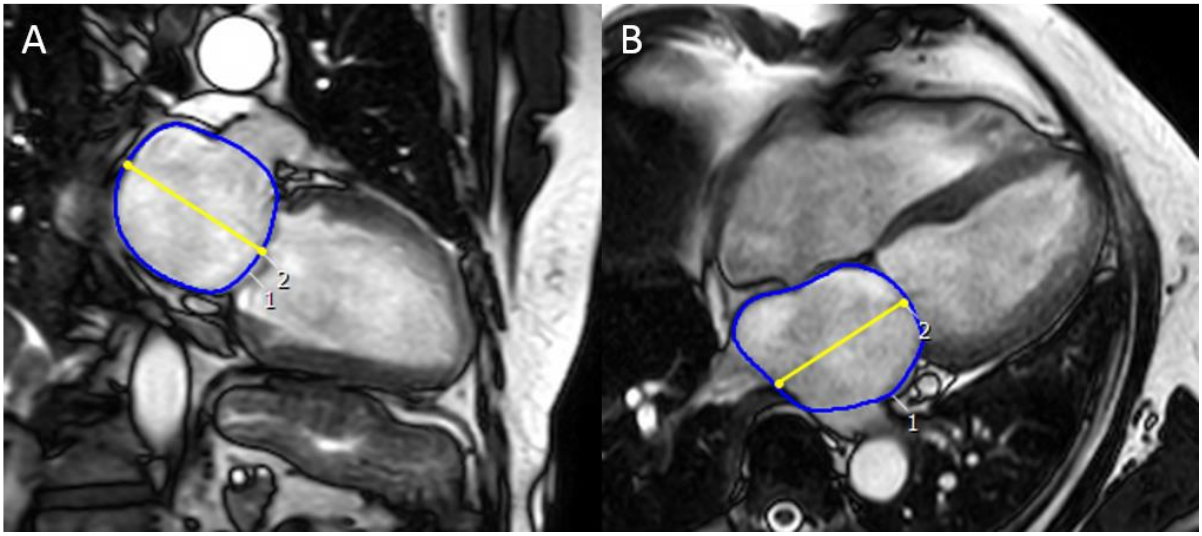


Figure 5-3: Measurement of left atrial parameters at end-systolic phase of cardiac cycle.

Measurement of left atrial parameters at end-systolic phase of cardiac cycle. Left atrial area (1: blue line) and length (2: yellow line) were measured in 2- (Panel A) and 4- (Panel B) chamber views.

Indexed parameters were divided by body surface area calculated using the Mosteller equation (269).

Late gadolinium images were visually reviewed at visit 1 and 2 for the presence or absence of late gadolinium enhancement (LGE) by two physicians with at least 2 years' experience in CMR. If present then LGE was categorised as being either an infarct (subendocardial) or non-infarct (midwall/subepicardial) pattern (Figure 5-4). Semi-automated quantification of LGE was then performed using the full-width half maximum method (threshold of 50% of the maximum intensity within areas of LGE) (270). Endocardial and epicardial contours were manually contoured on the LV short axis images and two user defined regions of interest (ROI) were defined when LGE was present. ROI 1 (remote myocardium - no LGE present) and ROI 2 (hyperenhanced myocardium - LGE present). Manual correction was then performed to exclude any blood pool, artefact and pericardial partial volume effect (270). Calculations of the total late gadolinium enhanced mass (grams) and the percentage of LGE relative to the entire LV mass were then performed.

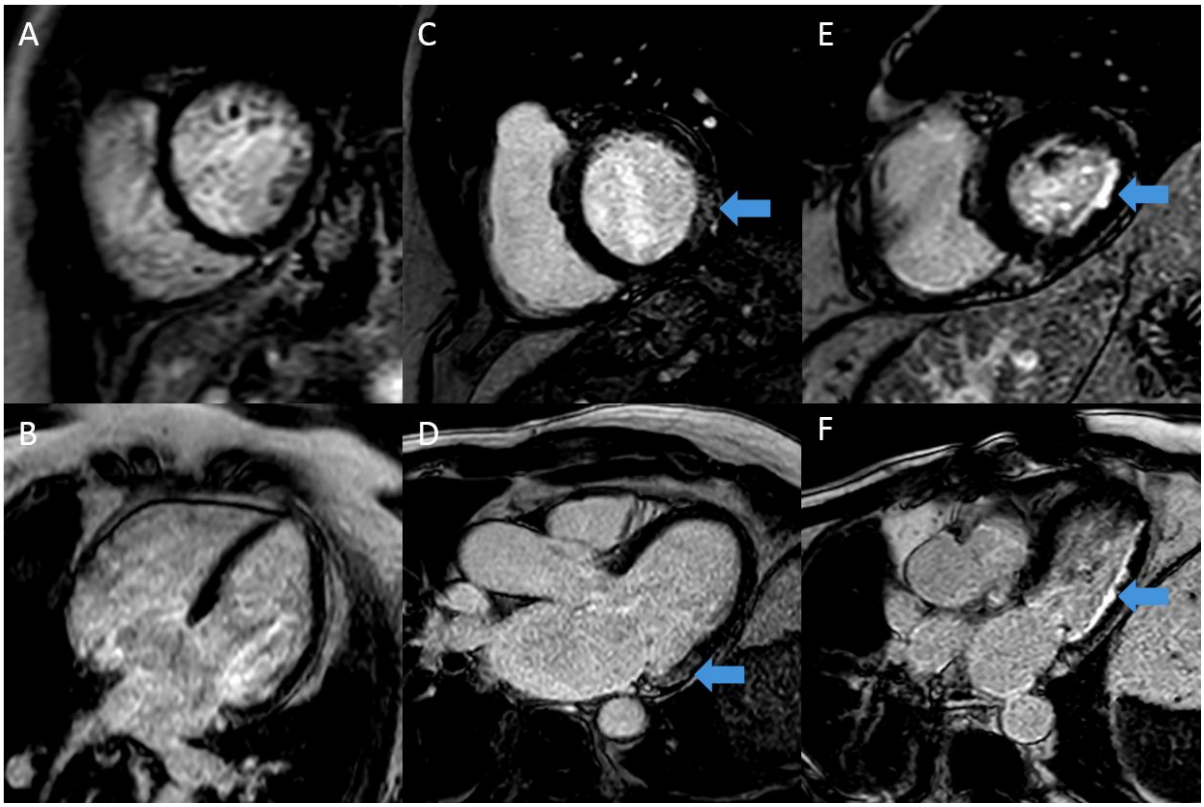


Figure 5-4: Late gadolinium enhancement images in two orthogonal planes in study patients.

Patients were initially grouped according to the absence (Panel A-B) or presence (Panels C-F) of hyperenhancement (blue arrows). Patient 1 (Panel A-B) had no evidence of LGE, Patient 2 (Panel C-D) had a non-infarct (midwall) pattern of LGE and Patient 3 (Panel E-F) had an infarct (subendocardial) pattern of LGE.

Average myocardial T1 values were recorded both pre and post contrast with a 3-parameter exponential fit with Look-Locker correction on short axis slices within the septum excluding areas where LGE was present. Apical slices were not used as the decreased wall thickness made the measurement vulnerable to partial volume effects (312). Extracellular volume was subsequently calculated from the native and post contrast T1 values from myocardium and blood pool together with haematocrit (313).

Analysis of strain parameters was performed using feature tracking software (Cvi42, Circle Cardiovascular Imaging, Calgary, Canada) from the short axis LV and 2-, 3- and 4-chamber SSFP cine acquisitions. Brightness and contrast settings were adjusted to optimise differentiation between the endocardium and blood pool. Epicardial and endocardial borders were traced manually at end-diastole and the software then tracked

the voxel features of the myocardium to quantify myocardial motion and calculate strain values (271). The anterior RV insertion point was used as the reference point for differentiating anterior wall and septum on the short axis analysis. Basal segments and slices with through-plane distortion of the outflow tract during the cardiac cycle and apical slices with no clear blood pool in systole were not analysed (272, 273). The global longitudinal strain and the time to peak radial strain for 16 segments of the 17 segment model (apex was excluded) proposed by the AHA were recorded (Figure 5-10) (274). A mechanical dyssynchrony index (MDI) was then calculated from the standard deviation of the segmental time (ms) to maximum radial strain for the 16 AHA segments similar to a technique previously described (275).

A surrogate of left ventricular contractility was calculated by dividing the systolic blood pressure by the indexed LV end-systolic volume which has been previously validated against invasive methods (276, 277).

5.3.10 Statistical analysis

Statistical analysis was performed using SPSS 25 (International Business Machines, Armonk, New York, USA). Data are presented as mean ± standard deviation, median (IQR: interquartile range) or frequency (%). For normally distributed variables, independent samples *t*-test was used for comparisons between groups and a paired samples *t*-test for comparisons within groups. For non-normally distributed variables, independent samples Mann-Whitney U test and the related samples Wilcoxon signed rank test were used. To compare categorical variables the Chi-squared test was used. Association between baseline ventricular volumes and heart rate was performed using Pearson product moment correlation test. Univariate linear regression analysis was used to identify associations between clinical or imaging parameters and the percentage change of LVESVi between baseline and follow up. All significant variables ($p<0.05$) and those with a $p<0.1$ on univariate analysis were included in multivariate linear regression. P-values <0.05 were considered significant.

5.4 Results

67 patients were recruited into the study and 62 patients completed the baseline CMR scan. No adverse events secondary to bradycardia were observed during the CMR scan and imaging was feasible in all patients despite significant bradycardia in a large proportion of patients. 54 patients completed the 6 month follow up scan (Figure 5-1). One patient with CMR features suggestive of cardiac amyloidosis (n=1) and three patients with negligible ventricular pacing at 6 months due to first degree AV block with PR<300ms when paced at 100bpm (n=1), persistent atrial tachycardia with 2:1 AV conduction (n=1) and initial junctional bradycardia rather than AV block (n=1) were excluded from the final analysis. 50 patients were included in the final analysis (Table 5-1).

5.4.1 Baseline characteristics

5.4.1.1 Entire cohort

The mean age of the whole study population was 79±9 years and 80% of patients were male (Table 5-1). The median time from baseline CMR to pacemaker implantation was 1 day (IQR: 0-7 days). Patients were subsequently separated into groups based on the presence or absence of LV myocardial hyperenhancement assessed by LGE imaging. Hyperenhancement was present in 31 (62%) of patients.

Characteristic	All patients (n=50)	LGE - (n=19)	LGE + (n=31)	p-value
Male Sex – n (%)	40 (80%)	12 (63%)	28 (90%)	0.020
Age – years	79.5 ± 9.1	77.3 ± 9.9	80.9 ± 8.5	0.173
BMI – kg/m^2	24.3 ± 4.3	22.7 ± 4.2	25.3 ± 4.2	0.024
BSA – m^2	1.96 ± 0.23	1.86 ± 0.22	2.01 ± 0.21	0.040
Systolic BP (IQR) – mmHg	147 (18)	142 (24)	150 (39)	0.944
Diastolic BP (IQR) – mmHg	76.5 (15)	78 (19)	75 (15)	0.904
Medical history – n (%)				
Atrial fibrillation	14 (28%)	2 (10%)	12 (39%)	0.031
Diabetes	18 (36%)	4 (21%)	14 (45%)	0.085
Hypertension	33 (29%)	12 (63%)	21 (68%)	0.740
History of MI	11 (22%)	0	11 (35%)	0.003
Previous PCI	2 (4%)	1 (5%)	1 (3%)	0.721
Previous CABG	10 (20%)	0	10 (32%)	0.006
Previous stroke	3 (6%)	1 (5%)	2 (7%)	0.864
NYHA functional class – n (%)				

I	14 (28%)	6 (32%)	8 (26%)	
II	28 (56%)	11 (58%)	17 (55%)	0.693
III	8 (16%)	2 (10%)	6 (19%)	
Baseline medications – n (%)				
ACE inhibitor	18 (36%)	7 (37%)	11 (35%)	0.923
ARB	12 (24%)	2 (10%)	10 (32%)	0.081
Statin	19 (56%)	8 (42%)	25 (81%)	0.005
Anti-platelet	16 (32%)	2 (10%)	14 (45%)	0.011
Antithrombotic	15 (30%)	4 (21%)	11 (35%)	0.280
β-blocker	6 (12%)	0	6 (19%)	0.041
Aldosterone antagonist	2 (4%)	0	2 (7%)	0.258

Table 5-1: Baseline Characteristics (whole cohort and then dependent on absence or presence of late gadolinium enhancement)

Normally distributed continuous variables are expressed as mean±SD; non-parametric continuous variables are expressed as median (IQR) and categorical variables are expressed as counts (percent).

Abbreviations: ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, BMI: body mass index, BP: blood pressure, BSA: body surface area, CABG: coronary artery bypass grafting, IQR: interquartile range, LGE: late gadolinium enhancement, MI: myocardial infarction, NYHA: New York Heart Association, PCI: percutaneous coronary intervention

5.4.1.2 Baseline characteristics according to LGE status

Patients with LGE were more often male (90% vs. 63%; p=0.020) and had a higher body mass index (BMI) than those without LGE (Table 5-1). There were no significant differences in age or baseline blood pressure (BP) between the groups. Those who were LGE positive were more likely to have AF (39% vs. 10%; p=0.031), a previous myocardial infarction (35% vs. 0%; p=0.003) and undergone coronary artery bypass grafting (10% vs. 0%; p=0.006). The groups were matched for the presence of other diseases including diabetes, hypertension and previous stroke. No difference was observed in the baseline NYHA Class between groups. LGE positive patients were more often on angiotensin receptor blockers, anti-platelets, beta–blockers and statins. No differences were noted for other common cardiovascular medications.

5.4.2 Baseline CMR data

The baseline CMR data for the entire study population and then separated according to LGE status are presented in Table 5-2. LGE was present in 62% of patients and in those with LGE there was a near equal split of infarct and non-infarct patterns of enhancement (45% vs. 55%). The distribution of LGE according to the AHA LV segments can be seen in Figure 5-5. The distribution of LGE in patients with an infarct pattern was predominantly in the basal to mid inferior and inferolateral segments. LGE in patients with a non-infarct pattern was most frequently observed in the basal to mid inferoseptum and basal inferolateral segments.

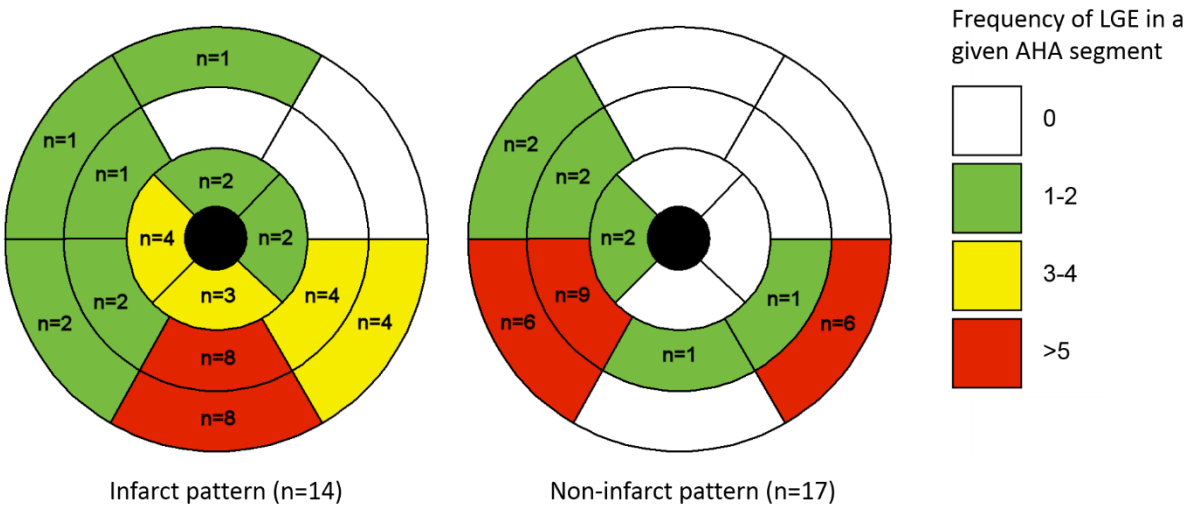


Figure 5-5: Distribution of late gadolinium enhancement.

Bullseye diagrams representing the 16 AHA evaluated segments demonstrate the distribution of LGE in patients with an infarct and non-infarct pattern of LGE.

Abbreviations: AHA: American Heart Association, LGE: late gadolinium enhancement

Mean LVEF was normal in both groups although it was significantly lower in those with LGE compared to those without LGE (55.5 ± 7.9% vs. 60.2 ± 5.4%; p=0.027). No patients in the study had a LVEF of less than 35%. Global longitudinal strain was significant lower in those with LGE (LGE -13.4±2.5 vs. No LGE- -16.2±1.8%; p<0.001). The groups were otherwise matched on LV and RV volumes, LV contractility, mechanical dyssynchrony index, Native T1 and ECV.

Variable	All patients (n=50)	LGE- (n=19)	LGE+ (n=31)	p-value
Volumes & Function				
LV end-diastolic volume index – ml/m^2	89.4 ± 19.2	87.8 ± 21.0	90.3 ± 18.3	0.418
LV end-systolic volume index – ml/m^2	38.6 ± 12.5	34.9 ± 9.3	40.9 ± 13.7	0.103
LV stroke volume index – ml/m^2	50.8 ± 11.1	52.9 ± 13.7	49.5 ± 9.2	0.624
LV ejection fraction – %	57.3 ± 7.4	60.2 ± 5.4	55.5 ± 7.9	0.027
LV mass index – g/m^2	54.2 ± 17.1	51.7 ± 17.4	55.8 ± 17.0	0.234
RV end-diastolic volume index – ml/m^2	78.5 ± 19.3	80.5 ± 22.9	77.2 ± 17.0	0.564
RV end-systolic volume index – ml/m^2	33.5 ± 10.8	35.0 ± 12.6	32.5 ± 9.6	0.429
RV stroke volume index – ml/m^2	46.9 ± 11.1	48.8 ± 12.9	45.7 ± 9.9	0.727
RV ejection fraction – %	59.8 ± 5.1	60.2 ± 5.3	59.5 ± 5.0	0.618
Left atrial volume index – ml/m^2	59.8 ± 23.2	58.3 ± 29.8	60.8 ± 18.6	0.267
Feature tracking and contractility				
Global longitudinal strain – %	-14.4 ± 2.6	-16.2 ± 1.8	-13.4 ± 2.5	<0.001
Mechanical dyssynchrony index – ms	78.8 ± 29.9	70.3 ± 29.1	83.7 ± 29.7	0.081

Contractility (SBP/LVESVi)	4.2 ± 1.3	4.5 ± 1.0	4.0 ± 1.5	0.254
Tissue Characterisation				
Native T1 – ms	1011.7 ± 32.5	1009.9 ± 38.9	1012.7 ± 28.8	0.860
ECV – %	27.8 ± 4.0	26.8 ± 3.6	28.3 ± 4.2	0.204
LGE present – n (%)	31 (62%)	NA	31 (100%)	NA
Infarct pattern	14 (28%)	NA	14 (45%)	NA
Non-infarct pattern	17 (34%)	NA	17 (55%)	NA
LGE mass – grams	NA	NA	4.9 ± 5.3	NA
LGE mass – %	NA	NA	6.2 ± 5.6	NA

Table 5-2: Baseline CMR data of all patients and then separated dependant on absence or presence of late gadolinium enhancement

Continuous variables expressed as mean±SD. Categorical variables expressed as counts (percent)

Abbreviations: ECV: extracellular volume, LGE: late gadolinium enhancement, LV: Left ventricle, LVESVi, left ventricular end-systolic volume index, NA: not applicable, RV: Right ventricle, SBP: systolic blood pressure

The relationships between the baseline heart rate and the LV end-diastolic volume index (LVEDVi) and the LV end-systolic volume index (LVESVi) can be seen in Figure 5-6. There was a moderate, negative correlation between LVEDVi and baseline heart rate, which was statistically significant (r = -0.40; p =0.004). There was no significant correlation between LVESVi and the baseline heart rate (r= -0.06; p=0.668).

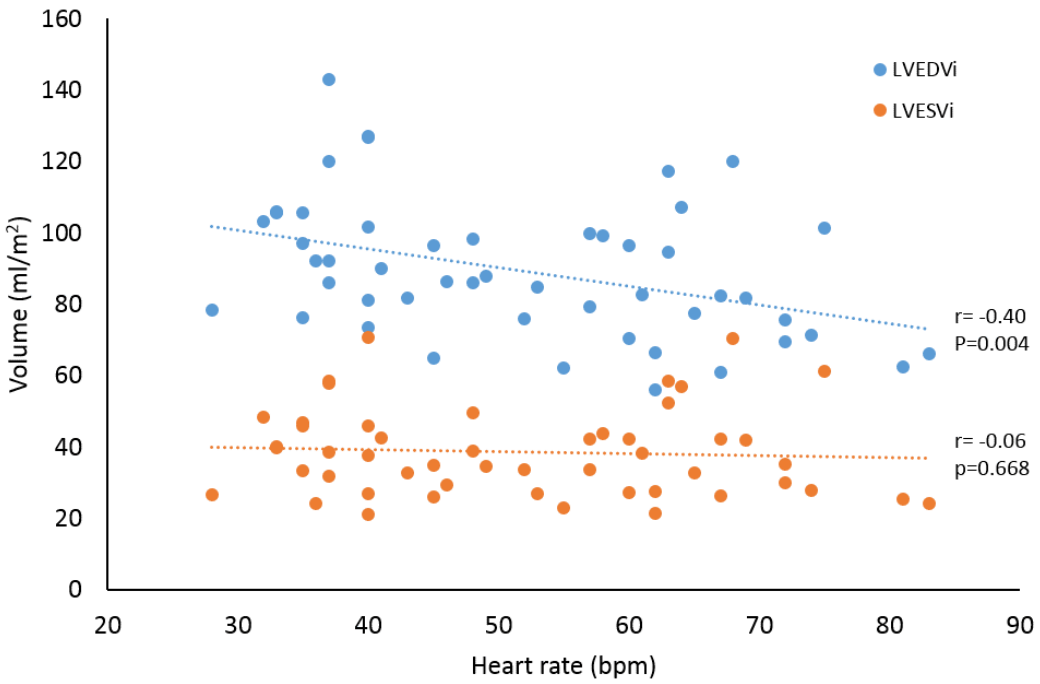


Figure 5-6: Scatter plots of baseline LV volumes and heart rate.

LV end-diastolic volume index (blue dots) correlated with heart rate but no correlation was demonstrated between LV end-systolic volume index (orange dots) and heart rate.

Abbreviations: LVEDVi: left ventricular end-diastolic volume index, LVESVi, left ventricular end-systolic volume index

5.4.3 Device and pacing characteristics

There were no significant differences in the type of AV block necessitating pacemaker implantation between those with and without LGE (p=0.948) (Table 5-3). The majority of study participants had 3rd degree AV block (44%) as the indication for pacemaker implantation. Over three quarters of the patients had a dual chamber pacemaker implanted (82%). No significant difference was observed between the number of single

and dual chamber devices between those with and without LGE. One patient had a RV septal lead with the remainder implanted in the RV apex.

Characteristic	All patients (n=50)	LGE– (n=19)	LGE+ (n=31)	p-value
Indication for device - no (%)				
Type 1 AV block	6 (12%)	2 (10%)	4 (13%)	
Type 2 AV block (Mobitz 1)	6 (12%)	2 (10%)	4 (13%)	0.948
Type 2 AV block (Mobitz 2)	16 (32%)	7 (37%)	9 (29%)	
Type 3 AV block	22 (44%)	8 (43%)	14 (45%)	
Pacemaker type - no (%)				
Single chamber	9 (18%)	1 (5%)	8 (26%)	0.066
Dual chamber	41 (82%)	18 (95%)	23 (74%)	
Right ventricular lead position - no (%)				
Apex	49 (98%)	18 (95%)	31 (100%)	0.197
Septum	1 (2%)	1 (5%)	0	
Atrial pacing burden – %	0 (10)	0 (14)	1 (11)	0.553
Ventricular pacing burden – %	94 (71)	96 (72)	85 (70)	0.711

Pacing mode for scan				
DOO	39 (78%)	17 (90%)	22 (71%)	0.125
VOO	11 (22%)	2 (10%)	9 (29%)	
Time from baseline scan to PPM (IQR) – days	1 (7)	1 (11)	1 (3)	0.511
Time from PM to follow up scan (IQR) – days	182 (10)	186 (11)	182 (10)	0.026

Table 5-3: Device implantation and follow up parameters of all patients and then separated based on absence or presence of late gadolinium enhancement

Continuous variables are expressed as median (IQR) and categorical variables are expressed as counts (percent).

Abbreviations: AV: atrioventricular, bpm: beats per minute, DOO: dual chamber asynchronous pacing, IQR: interquartile range, LGE: late gadolinium enhancement, PM: pacemaker, VOO: ventricular asynchronous pacing

There was no difference between the groups in the time for the CMR to pacemaker implantation. The device and lead manufacturers and models for all patients in the study grouped according to the presence or absence of LGE can be seen in Table 5-4.

Manufacturer	Model	LGE – (n=19)	LGE + (n=31)
IPG			
Boston Scientific®	Essentio SR L110	0	4 (13%)
	Proponent DR EL231	8 (42%)	15 (48%)
Medtronic®	Ensura EN1SR01	0	1 (3%)
	Azure W3DR01	1 (5%)	3 (10%)
St Jude Medical®	Assurity MRI PM2272	1 (5%)	0
	Endurity MRI PM1172	1 (5%)	3 (10%)
	Endurity MRI PM2172	8 (42%)	5 (16%)
Lead			
Boston Scientific®	Ingevity MRI (7731, 7732, 7735, 7736, 7740, 7741, 7742)	16 (43%)	34 (63%)
Medtronic®	Capsure Fix (5076)	0	6 (11%)
	Capsure Sense (4074, 4574)	2 (5%)	1 (2%)
St Jude Medical®	Isoflex (1944, 1948)	6 (16%)	3 (5%)
	Tendril STS (2088TC)	13 (35%)	10 (19%)

Table 5-4: Device and lead models in the study population

Data are expressed as counts (percent).

Abbreviations: IPG: implantable pulse generator, LGE: late gadolinium enhancement, MRI: magnetic resonance imaging

The median time from pacemaker implantation to follow up CMR was 182 days (IQR: 178-188 days) (Table 5-3). The median time to follow up was significantly shorter in those with LGE compared to those without (186 days, IQR: 175-186 vs. 182 days, IQR: 180-

191; p=0.026). Device interrogation at follow up showed a median overall atrial pacing burden of 0% and a ventricular pacing burden of 94%. No significant difference in pacing burden was noted between the groups. A total of 39 (78%) of patients were programmed DOO for the follow up scan and 11 (22%) patients programme VOO due to single ventricular lead pacemakers or presence of AF at the time of the scan.

5.4.4 Electrocardiographic characteristics

There was no significant difference in the baseline heart rate (56.4 ± 14.5 bpm vs. 50.5 ± 15.3 bpm; p=0.443) or the baseline QRS duration (111.4 ± 21.0 ms vs. 115.7 ± 29.4 ms; p=0.920) between those with and without LGE (Table 5-5). There was no difference in the programmed pacing base rate between groups with a median of 80 bpm in both groups. Although those with LGE had a longer paced QRS duration than those without LGE (171.7 ± 13.1 ms vs. 163.5 ± 12.1 ms; p=0.031).

Characteristic	All patients (n=50)	LGE– (n=19)	LGE+ (n=31)	p-value
Baseline heart rate - bpm	53.8 ± 14.9	50.5 ± 15.3	56.4 ± 14.5	0.443
Native QRS duration - ms	113.0 ± 24.3	115.7 ± 29.4	111.4 ± 21.0	0.920
Programmed pacing rate for follow up scan - bpm	80 (10)	80 (20)	80 (10)	0.181
Paced QRS duration - ms	168.6 ± 13.2	163.5 ± 12.1	171.7 ± 13.1	0.031

Table 5-5: Follow up electrocardiogram parameters of all patients and then separated dependant on absence or presence of late gadolinium enhancement

Normally distributed continuous variables are expressed as mean±SD and non-parametric continuous variables are expressed as median (IQR).

Abbreviations: bpm: beats per minute, IQR: interquartile range, LGE: late gadolinium enhancement, ms: milliseconds

5.4.5 Changes in CMR parameters between baseline and follow up

5.4.5.1 Entire cohort

The CMR parameters before and after pacemaker implantation for all the patients are shown in Table 5-6. There was a significant reduction in LVEF before and after

pacemaker implantation in the entire cohort (57.3 ± 7.4 vs. 47.1 ± 11.3%; $p<0.001$). The change in LVEF was driven by a significant reduction in LVEDVi (89.4 ± 19.2 vs. 79.4 ± 19.0 ml/m^2; $p<0.001$) and a significant increase in LVESVi (38.6 ± 12.5 vs. 43.3 ± 18.7 ml/m^2; $p=0.006$). There was also a significant reduction in RVEF (59.8 ± 5.1 vs. 53.9 ± 8.4%; $p<0.001$) driven by a reduction in RVEDVi (78.5 ± 19.3 vs. 69.2 ± 16.0; $p=0.001$). There was also a significant decrease in left atrial volume index (59.8 ± 23.2 vs. 50.7 ± 21.3 ml/m^2; $p<0.001$).

Variable	All patients (n=50)		
	Pre-PM	Post-PM	p-value
LV end-diastolic volume index – ml/m²	89.4 ± 19.2	79.4 ± 19.0	<0.001
LV end-systolic volume index – ml/m²	38.6 ± 12.5	43.3 ± 18.7	0.006
LV stroke volume index – ml/m²	50.8 ± 11.1	36.0 ± 7.6	<0.001
LV ejection fraction – %	57.3 ± 7.4	47.1 ± 11.3	<0.001
LV mass index – g/m²	54.2 ± 17.1	51.4 ± 11.0	0.342
Left atrial volume index – ml/m²	59.8 ± 23.2	50.7 ± 21.3	<0.001
RV end-diastolic volume index – ml/m²	78.5 ± 19.3	69.2 ± 16.0	0.001
RV end-systolic volume index – ml/m²	33.5 ± 10.8	32.6 ± 12.5	0.437
RV stroke volume index – ml/m²	46.9 ± 11.1	36.6 ± 7.4	<0.001
RV ejection fraction – %	59.8 ± 5.1	53.9 ± 8.4	<0.001

Table 5-6: CMR parameters of all patients pre and 6 months after pacemaker implantation.

Variables expressed as mean±SD.

Abbreviations: LV: Left ventricle, PM: pacemaker, RV: Right ventricle

5.4.5.2 Volumetric data according to LGE status

In both groups there was a decline in ejection faction before and after pacemaker implantation (LGE-: 60.2 ± 5.4 vs. 53.5 ± 6.8%; p<0.001 and LGE+: 55.5 ± 7.9 vs. 43.2 ± 11.7%; p<0.001) (Table 5-7). The absolute change in LVEF was greater in those with LGE (-12.3 ± 7.9 vs. -6.7 ± 6.2%; p=0.012) (Figure 5-7). The reduction in LVEF was due a significant decrease in LVEDVi in both groups. The greater absolute reduction of LVEF in those with LGE occurred due to an increase in LVESVi which was not seen in those without LGE (LGE 8.0 ± 10.4 vs. No LGE- -0.6 ± 7.3 ml/m^2; p=0.008) as the change in mean LVEDVi did not differ between groups.

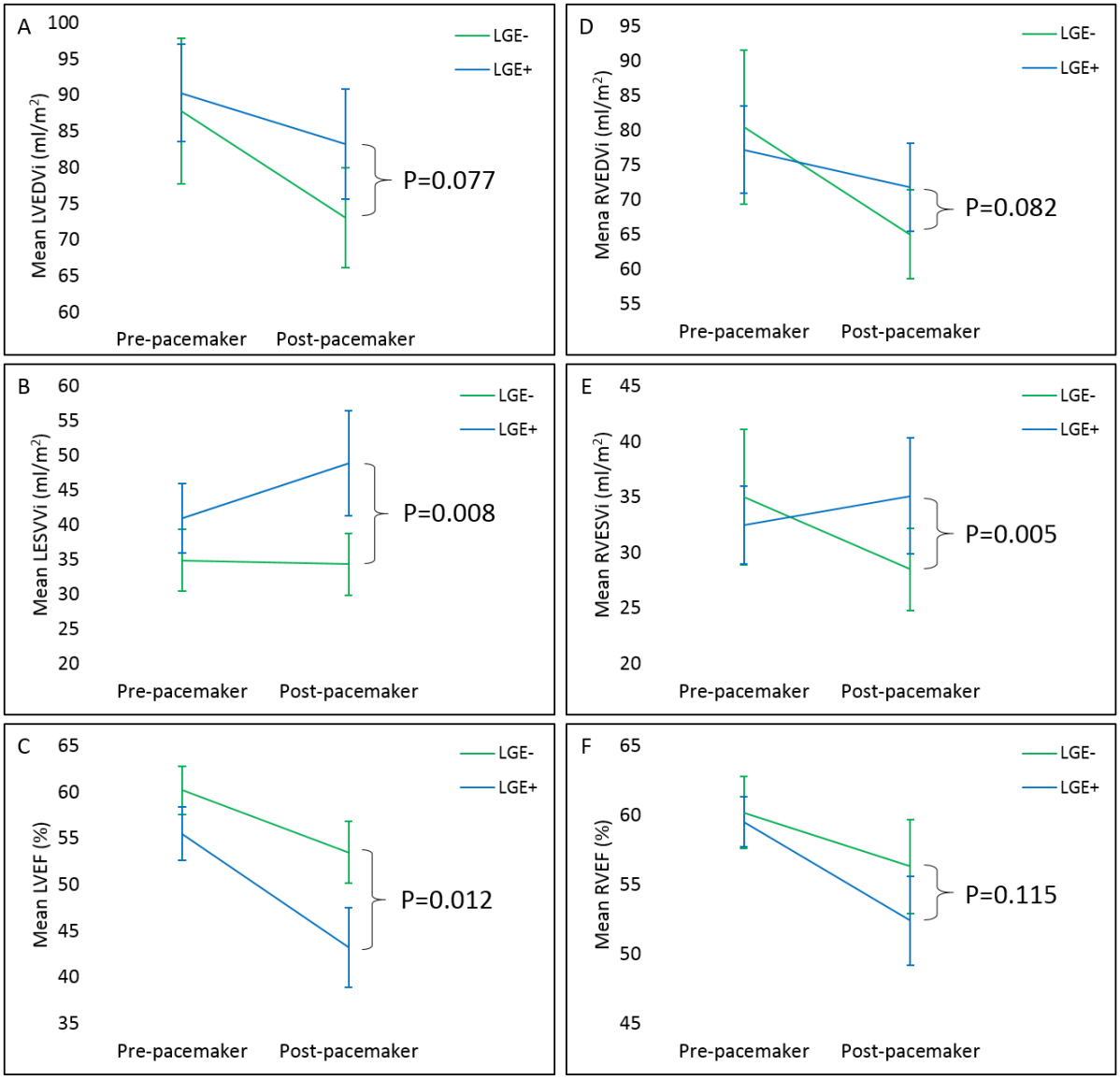


Figure 5-7: Line graphs demonstrating changing in volumes and function before and 6 months after pacing.

Line graphs depicting change in LVEDVi (Panel A), LVESVi (Panel B), LVEF (Panel C), RVEDVi (Panel D), RVESVi (Panel E) and RVEF (Panel F) before and 6 months after pacemaker implantation according to absence or presence of late gadolinium enhancement. The vertical lines represent the 95% confidence intervals. p-values depict comparisons of the absolute change in parameters between baseline and 6 months in those with and without LGE.

Abbreviations: LGE: late gadolinium enhancement, LVEDVi: left ventricular end-diastolic volume index, LVEF: left ventricular ejection fraction, LVESVi, left ventricular end-systolic volume index, RVEDVi: right ventricular end-diastolic volume index, RVEF: right ventricular ejection fraction, RVESVi, right ventricular end-systolic volume index

The change in LVEDVi and LVESVi between AOO and DOO pacing modes for each individual patient can be seen in Figure 5-8.

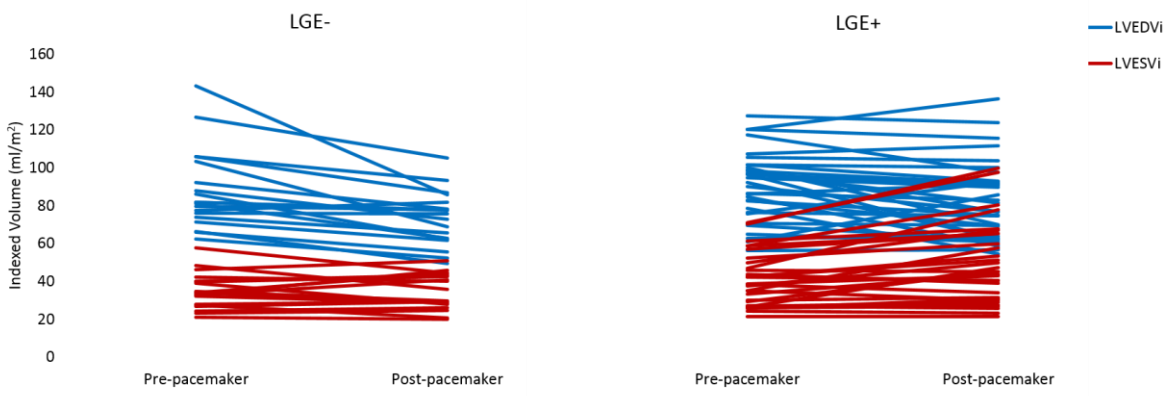


Figure 5-8: Line graphs depicting change in left ventricular volume for each patient before and 6 months after pacing.

Change in left ventricular end-diastolic (blue lines) and left ventricular end-systolic (red lines) indexed volumes before and 6 months after pacemaker implantation in those without (left) and with (right) late gadolinium enhancement.

Abbreviations: LGE: late gadolinium enhancement, LVEDVi: left ventricular end-diastolic volume index, LVEF: left ventricular ejection fraction, LVESVi, left ventricular end-systolic volume index

Pre- and post-pacemaker implantation values for all CMR characteristics can be seen in Table 5-7. No significant change in LV mass index occurred within or between groups. Left atrial volume declined in both groups from pre to post pacemaker scans (No LGE: 58.3 ± 29.8 vs. 47.0 ± 24.7 ml/m^2; p=0.003 and LGE: 60.8 ± 18.6 vs. 52.9 ± 18.9 ml/m^2; p=0.006) although there was no significant change between the groups (p=0.147). RVEF fell between pre- and post-scans in both those with and without LGE. The absolute change in RVEF although not significant was greater in those with LGE (No LGE: -3.9 ± 6.9 vs. LGE: -7.1 ± 6.9%; p=0.115) despite a greater fall in RVEDVi in those without LGE (No LGE: -15.5 ± 21.2 vs. LGE: -5.4 ± 18.4 ml/m^2; p=0.082) (Figure 5-7). The magnitude of the observed change in RVEF was also mediated by an increase in RVESVi in those with LGE whereas RVESVi fell in those without LGE (2.6 ± 10.6 vs. -6.6 ± 9.4 ml/m^2 respectively; p=0.005).

Variable	LGE- (n=19)			LGE+ (n=31)			Unpaired p-value‡
	Pre-PM	Post-PM	p-value*	Pre-PM	Post-PM	p-value†	
LV end-diastolic volume index – ml/m^2	87.8 ± 21.0	73.1 ± 14.3	<0.001	90.3 ± 18.3	83.2 ± 20.6	0.007	0.077
LV end-systolic volume index – ml/m^2	34.9 ± 9.3	34.3 ± 9.3	0.709	40.9 ± 13.7	48.9 ± 20.9	0.001	0.008
LV stroke volume index – ml/m^2	52.9 ± 13.7	38.9 ± 7.9	<0.001	49.5 ± 9.2	34.3 ± 7.0	<0.001	0.529
LV ejection fraction – %	60.2 ± 5.4	53.5 ± 6.8	<0.001	55.5 ± 7.9	43.2 ± 11.7	<0.001	0.012
LV mass index – g/m^2	51.7 ± 17.4	47.5 ± 9.2	0.494	55.8 ± 17.0	53.7 ± 11.5	0.624	0.682
Left atrial volume index – ml/m^2	58.3 ± 29.8	47.0 ± 24.7	0.003	60.8 ± 18.6	52.9 ± 18.9	0.006	0.147
RV end-diastolic volume index – ml/m^2	80.5 ± 22.9	65.0 ± 13.3	0.005	77.2 ± 17.0	71.8 ± 17.2	0.092	0.082
RV end-systolic volume index – ml/m^2	35.0 ± 12.6	28.5 ± 7.8	0.007	32.5 ± 9.6	35.1 ± 14.2	0.272	0.005
RV stroke volume index – ml/m^2	48.8 ± 12.9	36.5 ± 8.5	<0.001	45.7 ± 9.9	36.7 ± 6.8	<0.001	0.341
RV ejection fraction – %	60.2 ± 5.3	56.3 ± 6.9	0.024	59.5 ± 5.0	52.4 ± 8.9	<0.001	0.115
Global longitudinal strain – %	-16.2 ± 1.8	-11.4 ± 3.3	<0.001	-13.4 ± 2.5	-9.1 ± 3.3	<0.001	0.768
Mechanical dyssynchrony index – ms	70.3 ± 29.1	80.8 ± 21.6	0.145	83.7 ± 29.7	97.6 ± 31.2	0.029	0.662
Contractility (SBP/LVESVi)	4.5 ± 1.0	4.7 ± 1.4	0.417	4.0 ± 1.5	3.3 ± 1.4	0.000	0.001

LGE mass§ - grams	NA	NA	NA	4.9 ± 5.3	5.0 ± 5.7	0.914	NA
LGE mass§ - %	NA	NA	NA	6.2 ± 5.6	5.7 ± 5.4	0.265	NA

Table 5-7: Changes in CMR characteristics of patients with and without late gadolinium enhancement from baseline to follow up.

Abbreviations: ECV: extracellular volume, LGE: late gadolinium enhancement, LV: Left ventricle, LVESVi, left ventricular end-systolic volume index, NA: not applicable, PM: Pacemaker, RV: Right ventricle, SBP: systolic blood pressure

* Pre vs. Post (LGE-)

† Pre vs. Post (LGE+)

‡ LGE- vs. LGE+ (Absolute change between Pre and Post)

§ 2 patients did not undergo LGE imaging at follow up

In those patients with LGE there was no significant difference in LGE mass before and after pacemaker implantation (6.2 ± 5.6 vs. 5.7 ± 5.4%; p=0.265). Unfortunately two patients were excluded from the comparison due to a possible contrast reaction at baseline scan in one patient and another patient requesting to terminate the scan prior to contrast administration.

5.4.5.3 According to pattern of LGE

We performed sub-group analysis to investigate whether changes related to long term pacing were different between those with ischaemic and non-ischaemic patterns of LGE. When separated according to the pattern of LGE no significant differences were observed in baseline heart rate, paced QRS duration or ventricular pacing burden. However baseline electrical dyssynchrony, measured by QRS duration, was greater in those with an infarct pattern of LGE compared to those with a non-infarct pattern (120.4 ± 22.2 vs. 103.9 ± 17.2ms respectively; p=0.026) (Table 5-8).

Variable	Infarct pattern (n=14)	Non-infarct pattern (n=17)	p-value
Baseline heart rate – bpm	57.8 ± 13.7	49.5 ± 14.4	0.109
Baseline QRS duration – ms	120.4 ± 22.2	103.9 ± 17.2	0.026
Paced QRS duration – ms	173.7 ± 14.5	170.1 ± 12.1	0.467
Ventricular pacing burden – %	85 (65)	92 (72)	0.597
Volumes & Function			
LV end-diastolic volume index – ml/m^2	97.0 ± 11.7	84.9 ± 17.3	0.065
LV end-systolic volume index – ml/m^2	48.4 ± 12.2	34.6 ± 11.9	0.002
LV stroke volume index – ml/m^2	48.6 ± 8.7	50.2 ± 9.8	0.623
LV ejection fraction – %	50.5 ± 5.8	59.6 ± 7.1	0.001
LV mass index – g/m^2	50.6 ± 13.0	60.0 ± 18.9	0.173
RV end-diastolic volume index – ml/m^2	79.1 ± 16.6	75.7 ± 17.7	0.591
RV end-systolic volume index – ml/m^2	32.8 ± 8.3	32.3 ± 10.8	0.899
RV stroke volume index – ml/m^2	46.3 ± 10.2	45.2 ± 10.0	0.762
RV ejection fraction – %	58.7 ± 5.3	60.1 ± 4.7	0.429

LGE mass – %	8.7 ± 5.8	4.2 ± 4.3	0.013
Feature tracking and contractility			
Global longitudinal strain – %	-12.7 ± 2.1	-13.9 ± 2.7	0.154
Mechanical dyssynchrony index – ms	91.9 ± 24.9	76.9 ± 32.3	0.167
Contractility (SBP/LVESVi)	3.2 ± 0.9	4.8 ± 1.5	0.143

Table 5-8: Baseline Device, Electrocardiographic and CMR data of late gadolinium enhancement positive patients separated dependant on pattern of late gadolinium enhancement.

Variables expressed as mean±SD or median (IQR).

Abbreviations: bpm: beats per minute, ECV: extracellular volume, LGE: late gadolinium enhancement, LV: Left ventricle, LVESVi, left ventricular end-systolic volume index, RV: Right ventricle, SBP: systolic blood pressure

At baseline patients with an infarct pattern of LGE also had significantly higher LVESVi (48.4 ± 12.2 vs. 34.6 ± 11.9 ml/m^2; p=0.002) and lower LVEF (50.5 ± 5.8 vs. 59.6 ± 7.1%; p=0.001). At follow up LVEDVi was unchanged (97.0 ± 11.7 vs. 94.3 ± 18.5 ml/m^2; p=0.517) in those with an infarct pattern but LVESVi increased (48.4 ± 12.2 vs. 61.7 ± 16.9 ml/m^2; p=0.002) whereas a significant decline in LVEDVi (84.9 ± 17.3 vs. 74.1 ± 18.0 ml/m^2; p=0.002) was seen in patients with a non-infarct pattern with no change in LVESVi (34.6 ± 11.9 vs. 38.4 ± 17.9 ml/m^2; p=0.163) (Table 5-9). Mean LVEF fell to a greater extent in those with an infarct pattern of LGE pre and post pacemaker (Infarct: 50.5 ± 5.8 to 35.3 ± 7.5%; p<0.001 and Non-infarct: 59.6 ± 7.1 to 49.8 ± 10.5%; p=0.001) although the difference in absolute change was not significant (15.2 vs. 9.8% respectively; p=0.054). The LGE mass was significantly greater in those with an infarct pattern compared to those with a non-infarct pattern (8.9 ± 6.0 vs. 4.0 ± 4.4%: p=0.013). However there was no correlation between the LGE mass and the change in LVESVi in either group (Figure 5-9).

Variable	Infarct pattern (n=14)			Non-infarct pattern (n=17)			Unpaired p-value‡
	Pre-PM	Post-PM	p-value*	Pre-PM	Post-PM	p-value†	
LV end-diastolic volume index – ml/m²	97.0 ± 11.7	94.3 ± 18.5	0.517	84.9 ± 17.3	74.1 ± 18.0	0.002	0.106
LV end-systolic volume index – ml/m²	48.4 ± 12.2	61.7 ± 16.9	0.002	34.6 ± 11.9	38.4 ± 17.9	0.163	0.013
LV stroke volume index – ml/m²	48.6 ± 8.7	32.6 ± 8.3	<0.001	50.2 ± 9.8	35.7 ± 7.4	<0.001	0.720
LV ejection fraction – %	50.5 ± 5.8	35.3 ± 7.5	<0.001	59.6 ± 7.1	49.8 ± 10.5	0.001	0.054
Global longitudinal strain – %	-12.7 ± 2.1	-7.9 ± 2.7	<0.001	-13.9 ± 2.7	-10.1 ± 3.4	<0.001	0.395
Mechanical dyssynchrony index –ms	91.9 ± 24.9	105.4 ± 34.7	0.193	76.9 ± 32.3	91.2 ± 27.3	0.088	0.951
Contractility (SBP/LVESVi)	3.2 ± 0.9	2.3 ± 0.7	0.001	4.8 ± 1.5	4.1 ± 1.2	0.007	0.445
LGE mass§ - %	8.9 ± 6.0	8.1 ± 6.3	0.421	4.0 ± 4.4	3.7 ± 3.7	0.278	0.666

Table 5-9: CMR parameters of all late gadolinium enhancement positive patients' pre and 6 months after pacemaker implantation according to the pattern of late gadolinium enhancement.

Variables expressed as mean±SD.

Abbreviations: ECV: extracellular volume, LGE: late gadolinium enhancement, LV: Left ventricle, LVESVi, left ventricular end-systolic volume index, NA: not applicable, PM: Pacemaker, RV: Right ventricle, SBP: systolic blood pressure

* Pre vs. Post (Infarct pattern)

† Pre vs. Post (Non-infarct pattern)

‡ LGE- vs. LGE+ (Absolute change between Pre and Post)

§ 2 patients did not undergo LGE imaging at follow up

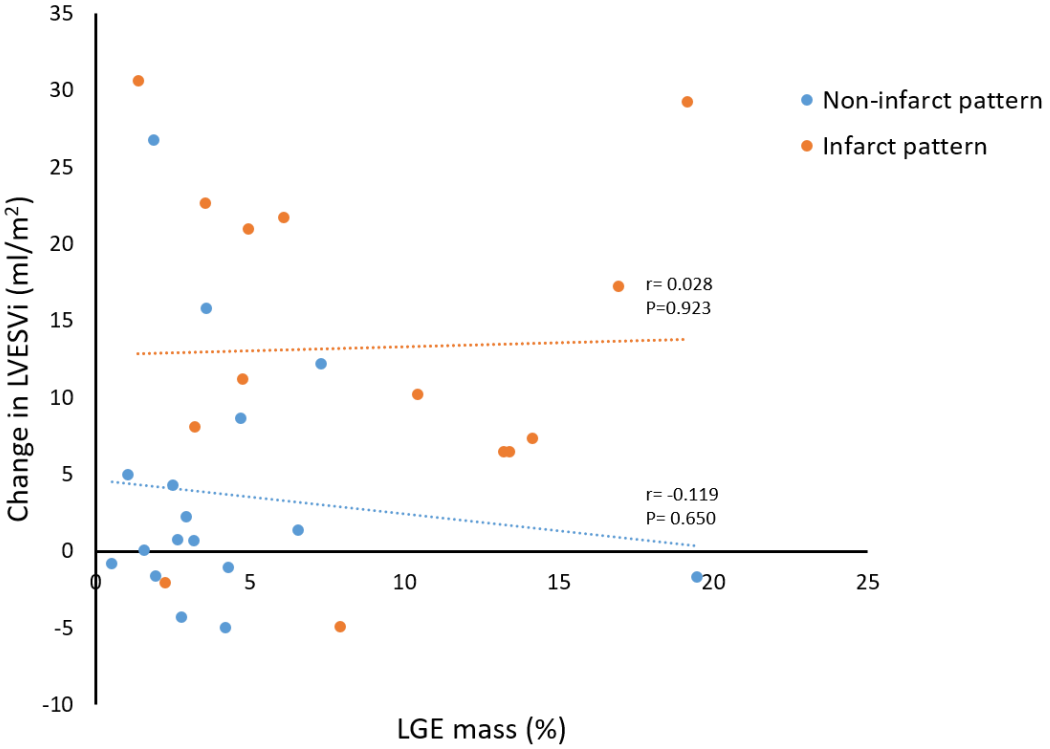


Figure 5-9: Scatter plots of baseline LGE mass and change in LVESVi from baseline to 6 months.

No correlation was demonstrated for either patients with an infarct (orange dots) or non-infarct (blue dots) pattern between LGE mass and change in LVESVi.

Abbreviations: ECV: extracellular volume, LGE: late gadolinium enhancement, LV: Left ventricle, LVESVi, left ventricular end-systolic volume index, NA: not applicable, RV: Right ventricle, SBP: systolic blood pressure

5.4.6 Contractility, dyssynchrony and strain

SPAMM tagging sequences were acquired in all patients but long breath holds, particularly in patients with significant bradycardia, and fading of tags meant images were of insufficient quality to analyse in most patients. Therefore, we used feature tracking, which has a better spatial and temporal resolution, for assessment of strain and dyssynchrony. Global longitudinal strain fell significantly in both groups at follow up (No LGE: -16.2 ± 1.8 vs -11.4 ± 3.3%; p<0.001 and LGE: -13.4 ± 2.5 vs. -9.1 ± 3.3%; p<0.001) but there was no significant difference in the fall between the groups (p=0.768) (Table 5-7). There was evidence of significant mechanical dyssynchrony and impaired LV

contractility in those with LGE between baseline and 6 months after pacing (MDI: 83.7 ± 29.7 vs. 97.6 ± 31.2ms; p=0.029 and Contractility: 4.0 ± 1.5 vs. 3.3 ± 1.4; p<0.001) which was not seen in those without LGE. An example of the change in GLS and time to peak strain of the AHA segments in a patient with LGE can be seen in Figure 5-10. No significant difference was observed between the absolute change in contractility, GLS or mechanical dyssynchrony between patients with different patterns of LGE (Table 5-9).

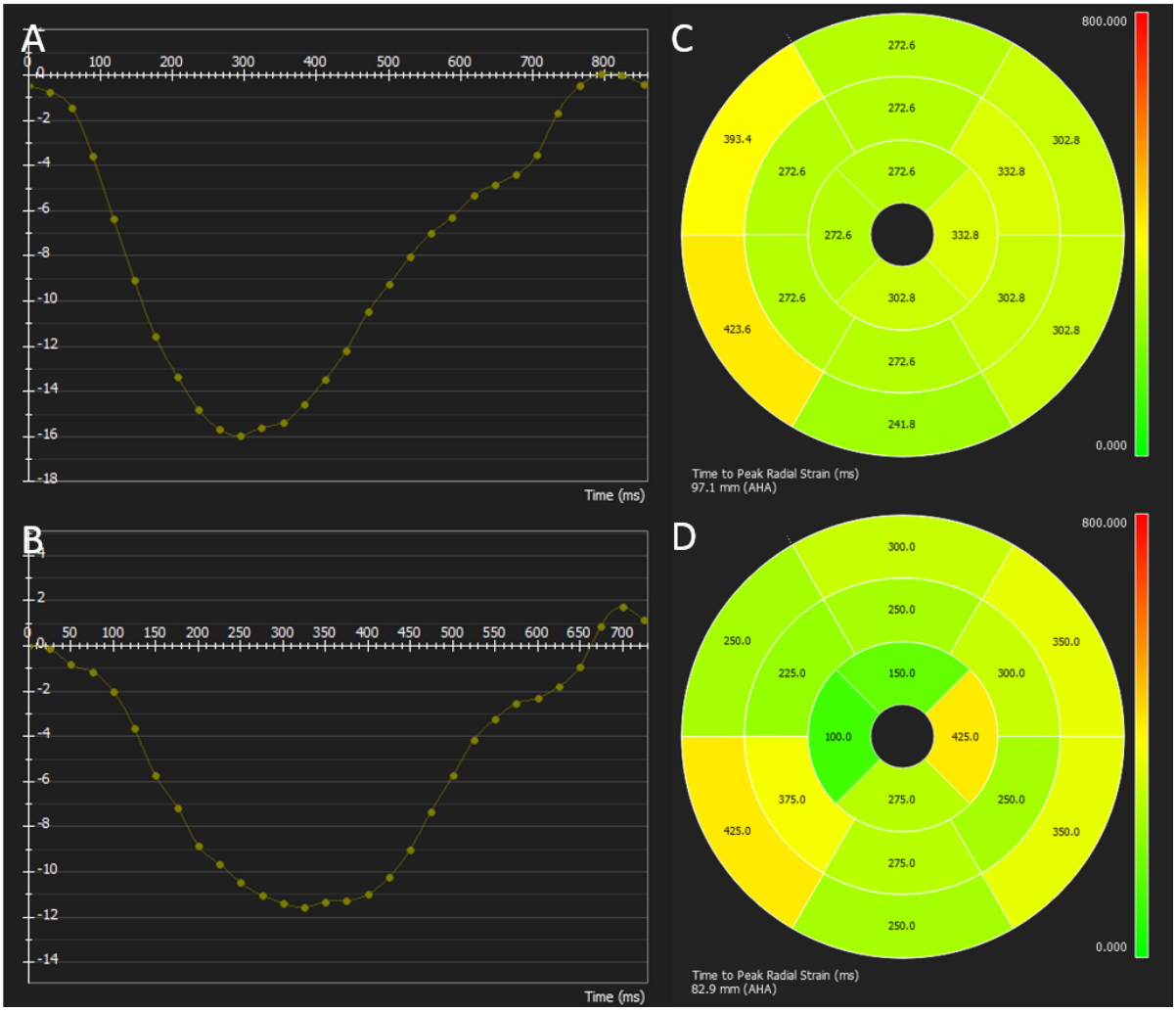


Figure 5-10: Feature tracking parameters before and 6 months after pacemaker implantation.

Global longitudinal strain is reduced from baseline (Panel A) to 6 month follow up (Panel B). Time to peak strain for all segments changes from baseline (Panel C) to 6 month follow up with early activation of the apical septum (Panel D).

5.4.7 Predictors of change in LVESVi

Variables which may influence adverse cardiac reverse remodelling following pacemaker implantation were analysed to determine univariate predictors of the percentage change in LVESVi at 6 months (Table 5-10). Presence of an infarct pattern LGE (beta 0.442; p=0.001) and a history of atrial fibrillation (beta 0.334; p=0.018) were associated with a change in LVESVi and remained significant independent predictors on multiple regression analysis. No other variables significantly impacted on the post pacemaker change in LVESVi at 6 months.

	Coefficient B	Standard Error	p-value	Coefficient B	Standard Error	p-value
	Univariate analysis -% change in LVESVi			**Multiple regression analysis -% change in LVESVi**		
Infarct pattern of LGE	19.070	5.592	0.001	16.125	5.470	0.005
Non-infarct pattern of LGE	-0.041	5.907	0.995			
Baseline LVEF	-0.577	0.374	0.130			
Baseline QRS duration	-0.033	0.116	0.777			
Paced QRS duration	0.207	0.211	0.331			
Age	0.164	0.309	0.597			
Gender	-2.640	6.986	0.707			
History of AF	14.434	5.874	0.018	11.132	5.377	0.044
Native T1	0.108	0.083	0.199			
ECV	1.1115	0.663	0.099	0.320	0.633	0.616
Ventricular pacing %	-0.087	0.073	0.243			

Table 5-10: Univariate and multivariate analysis of percentage change in LVESVi.

Abbreviations: AF: atrial fibrillation, ECV: extracellular volume, LGE: late gadolinium enhancement, LVEF: Left ventricular ejection fraction, LVESVi: left ventricular end-systolic volume index

5.4.8 Quality of life and NYHA Class

Visual analogue scale scores increased significantly from baseline to 6 month follow up in the whole study population (64 ± 20 vs. 70 ± 18; p=0.016) with a non-significant increase in EQ-5D scores (Table 5-11). When separated by LGE status only those without evidence of LGE had a significant increase in VAS scores at follow up (70 ± 15 vs. 78 ± 16; p=0.010) (Table 5-12).

Variable	UK Norm*	Baseline (n=50)	6 months (n=50)	p-value
EQ-5D index	0.73	0.77 ± 0.24	0.81 ± 0.18	0.439
EQ VAS	73.8	64 ± 20	70 ± 18	0.016
NYHA Class				
I		14 (28%)	24 (48%)	
II	NA	28 (56%)	20 (40%)	0.119
III		8 (16%)	6 (12%)	

Table 5-11: Quality of life scores and NYHA Class for the entire study population at baseline and 6 month follow up.

*UK norms are reported for a UK population stratified according to age (>75 years). (314)

Abbreviations: NA: not applicable, NYHA: New York heart association, UK: United Kingdom, VAS: Visual analogue scale

Overall NYHA Class did not change significantly from baseline to 6 month follow up (p=0.119) (Table 5-11). However when stratified according to LGE status those without LGE showed a significant change in NYHA Class at follow up (p=0.024) which was not observed in those with LGE (p=0.841) (Table 5-12). The change in NYHA Class between baseline and follow up stratified according to LGE status can be seen in Figure 5-11. Six patients in the LGE- group and eight patients in the LGE+ were NYHA Class I at baseline and therefore could not show an improvement at follow up.

Variable	LGE- (n=19)			LGE+ (n=31)		
	Pre-PM	Post-PM	p-value	Pre-PM	Post-PM	p-value
EQ-5D index	0.85 ± 0.13	0.85 ± 0.18	0.887	0.72 ± 0.27	0.79 ± 0.17	0.326
EQ VAS	70 ± 15	78 ± 16	0.010	61 ± 22	66 ± 18	0.211
NYHA Class						
I	6 (32%)	14 (74%)		8 (26%)	10 (32%)	
II	11 (58%)	5 (26%)	0.024	17 (55%)	15 (49%)	0.841
III	2 (10%)	0		6 (19%)	6 (19%)	

Table 5-12: Quality of life scores and NYHA Class stratified according to absence or presence of late gadolinium enhancement at baseline and 6 month follow up.

Abbreviations: LGE: late gadolinium enhancement, NYHA: New York heart association, PM: Pacemaker, VAS: Visual analogue scale

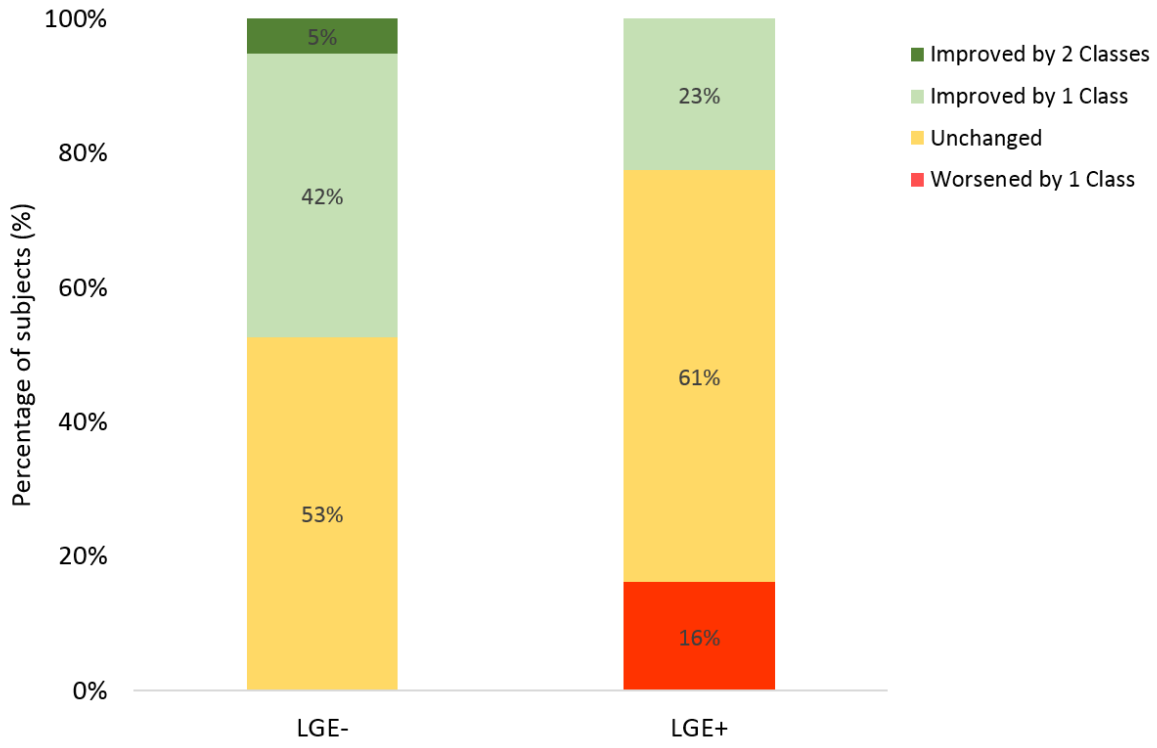


Figure 5-11: Change in NYHA Class.

Bar graph depicting change in NYHA Class between baseline and follow up stratified according to LGE status. No significant change was seen in the change in NYHA Class between the groups (p=0.13).

Abbreviations: LGE: late gadolinium enhancement

5.4.9 Adverse events

There was no overall significant difference in any of the procedural or clinical adverse events between those with and without LGE (Table 5-13). There was a trend towards new onset atrial fibrillation and new onset heart failure in those with LGE (Both: 4 vs. 0 events respectively; p=0.103). No sustained episodes of high ventricular rates were noted in either group.

Adverse event	LGE- (n=19)	LGE+ (n=31)	p-value
Procedure related			
Lead displacement	1	1	0.721
DVT	1	0	0.197
Clinical outcomes			
New onset AF	0	4	0.103
New development of HF	0	4	0.103

Table 5-13: Comparison of procedure related and clinical adverse events in patients with and without late gadolinium enhancement.

Data are expressed as counts (percent).

Abbreviations: AF: atrial fibrillation, DVT: deep vein thrombosis, HF: heart failure, LGE: late gadolinium enhancement

5.4.10 Device parameters

All fifty patients completed the full protocol safely with no adverse clinical events related to the implanted device. Pacemakers were interrogated before and immediately after the MRI protocol (Table 5-14). No significant changes in atrial lead impedance or capture threshold, P- and R- wave amplitude or battery voltage were noted. Small but significant changes were observed before and after MRI with numerically small decreases in ventricular lead impedance (722 ± 170 vs. 704 ± 150 Ohms; p=0.006) and increases in ventricular lead pacing capture threshold (0.72 ± 0.26 vs. 0.78 ± 0.25 V; p=0.005).

Parameter	Pre MRI value (n=50)	Post MRI value (n=50)	p-value
Pacing lead capture threshold – V@0.4ms			
- **Atrial lead*†**	0.72 ± 0.26	0.73 ± 0.20	0.573
- **Ventricular lead**	0.72 ± 0.26	0.78 ± 0.25	0.005
P-wave amplitude* - mV	4.9 ± 2.8	4.8 ± 2.5	0.803
R-wave amplitude§ - mV	15.6 ± 6.6	15.8 ± 6.5	0.553
Pacing lead impedance - Ohms			
- **Atrial lead***	549 ± 147	558 ± 128	0.963
- **Ventricular lead**	722 ± 170	704 ± 150	0.006
Battery Voltage‡ - V	3.04 ± 0.06	3.04 ± 0.06	NA

Table 5-14: Comparison of device parameters before and immediately after the CMR examination.

The data are expressed as mean±SD.

* No atrial lead (n=9)

† Unable to assess atrial lead threshold and P-wave amplitude due to AF (n=2)

§ No R wave (n=12)

‡ Boston Scientific® devices excluded as no numerical value for battery voltage is available on the programmer (n=8).

Abbreviations: MRI: magnetic resonance imaging, ms: milliseconds, mV: millivolts, V: Volts

The increase in the ventricular lead pacing capture threshold was deemed not to be clinically significant and in no patients did it increase by more than 50% (Table 5-15). However a significant number of patients experienced an immediate change in lead impedance of ≥50 Ohms (26%) and these changes occurred predominantly in patients with Boston Scientific® devices (21 of 24 incidences; 88%).

Device parameter change	All patients *number/total number (%)*
PCT increase ≥0.5V *†	0/89
Decrease in P-wave amplitude ≥50% *†	0/39
Decrease in R-wave amplitude ≥50% §	0/38
Lead impedance change ≥50 Ohms*	24/91 (26%)

Table 5-15: Clinically significant changes in device parameters from pre and immediately post MRI.

* No atrial lead (n=9)

† Unable to assess atrial lead threshold and P-wave amplitude due to AF (n=2)

§ No R wave (n=12)

Abbreviations: PCT: pacing capture threshold, mV: millivolts, V: Volts

5.5 Discussion

This study investigated the effect of right ventricular pacing on cardiac haemodynamics at 6 months in patients with advanced AV block and focal myocardial fibrosis. To our knowledge this is the first study using CMR to evaluate longitudinal changes following pacemaker implantation in patients with AV block. The study demonstrates that after 6 months of right ventricular pacing in patients with AV block:

1. The presence of myocardial fibrosis was associated with increased electrical and mechanical dyssynchrony.
2. There was an increase in LVESV and decline in both left and right ventricular function in these individuals.
3. Patients with fibrosis did not experience an improvement in quality of life after pacing and some patients experienced a decline in functional class.
4. Myocardial fibrosis, in both infarct and non-infarct patterns, was prevalent in patients with AV block.

5.5.1 Left Ventricular End-Systolic Volume after right ventricular pacing in patients with and without myocardial fibrosis

In our study we have demonstrated that in patients with myocardial fibrosis there was a significant increase in LVESVi after 6 months of right ventricular pacing. No interval change in LVESVi was observed in patients without myocardial fibrosis. LVESV is a strong predictor of LV remodelling and subsequent heart failure risk in patients with prior myocardial infraction and in patients with AV block and LVEF <50% (129, 156). It is likely that changes in LVESVi in patients with scar reflect a combination of mechanical dyssynchrony and remodelling.

Fang *et al.* have previously shown using echocardiography that development of dyssynchrony after acute initiation of RV pacing leads to immediate increases in LVESV (101). It is possible that the change in LVESV in those with myocardial fibrosis may simply be due to the development of dyssynchrony. However, the degree of change in LVESV after 6 months in this study was greater than the immediate changes observed in the previous Chapter. Additionally, the greater change in LVESVi in this experiment may be due to LV remodelling in the presence of RV pacing. Indeed previous studies evaluating longer term changes in left ventricular volumes after right ventricular pacing have shown significant increases in LVESV (159, 168). Furthermore sub-analysis of the BLOCK-HF study has shown that LVESVi is predictive of morbidity and mortality and the estimated risk of these events increases by 1% for every 1 ml/m^2 increase in LVESVi (156). It is therefore likely that those with myocardial fibrosis are at greater risk of developing significant LV dyssynchrony with RV pacing with consequent long-term remodelling.

5.5.2 Left ventricular volumes and function after right ventricular pacing in patients with myocardial fibrosis

At baseline there were no significant differences between the left ventricular volumes in patients with and without myocardial fibrosis, although those with myocardial fibrosis had a significantly lower baseline LVEF. Mean LVEF was normal in both groups and not at a level where a change in medication or even CRT would be considered. At 6 month follow up there was an increase in LVESVi in patients with myocardial fibrosis that was not seen in those without fibrosis. In both groups we observed a significant decline in LVEF after pacemaker implantation with the absolute change being greater in those with LGE (LGE: -12.3±7.9 vs. No LGE: -6.7±6.2%; p=0.012). The change in LVEF in both groups

was accompanied by a significant fall in LVEDVi at 6 months, although the magnitude of the fall was twice as great in those without LGE (No LGE: -14.6 ± 13.9 vs. LGE: -7.1 ± 13.8 ml/m^2: p=0.077). Therefore the greater decline in LVEF in those with focal fibrosis is mediated not only by a fall in LVEDVi but also an increase in LVESVi.

The change in LVESVi may also explain the differential changes in LVEDVi between those with and without fibrosis. The decline in LVEDVi in those with fibrosis at follow-up was doubled compared those without despite baseline and follow-up heart rates being matched between groups. Therefore, this suggests that diastolic filling period and preload alone do not account for the observed differences in LVEDVi. It could be that alterations in contractility induced by RV pacing, which were predominantly observed in those with LGE, trigger a compensatory increase in LVEDV. As cardiac output declines due to the impaired contractility the LV end-diastolic pressure (LVEDP) increases causing greater myocardial stretch in order to maintain cardiac output. In the long term this could lead to neurohormonal activation and further ventricular remodelling which hastens myocardial dysfunction.

5.5.3 Left and right ventricular volumes after right ventricular pacing in entire cohort

Our study demonstrates that in all patients with advanced AV block permanent pacemaker implantation and subsequent RV pacing is associated with a decline in LVEF at 6 months. Indeed, LVEF fell by approximately 10% from pre-pacemaker to 6 months post-pacemaker in the entire study population. The fall in LVEF was mediated by a significant decline in LVEDVi and an increase in LVESVi. LVEDV is significantly influenced by ventricular preload and therefore we would expect it to increase in the presence of bradycardia where LV filling time is increased. Bradycardia prior to pacemaker implantation leads to prolongation of LV filling time, greater LVEDV and subsequent increase in LV stroke volume by the Frank Starling mechanism. In our patients the baseline heart rate had a significant negative correlation with LVEDVi. At follow-up patients were paced at 80 bpm so diastolic filling time was reduced, resulting in a lower LVEDV, despite reintroduction of AV synchrony, with a consequent fall in LVEF. Hung *et al.* have previously shown that cardiac output in normal subjects is increased by incremental atrial stimulation with a linear and inverse relationship between heart rate, stroke volume and LVEDV (315). Our observed changes in the LVEDV have been previously demonstrated in animal models of AV block where LVEDV increases to compensate for the low ventricular rate in order to maintain stroke volume whereas left

ventricular systolic volume remains unchanged (316-318). Furthermore increasing the ventricular rate from a mean of 39 to 78 beats per minute by pacing in patients with complete heart block has been shown to lead to an immediate decrease in LVEDV (242 ± 60 vs. 180 ± 43 ml respectively; $p<0.001$) (319).

Our data shows that LVESVi was not correlated with the baseline heart rate and previous studies have shown LVESV to be relatively insensitive to loading (320-322). Park *et al.* have previously shown using pressure volume loops that acute RV pacing induces LV dyssynchrony which shifts the end-systolic pressure volume relationship to the right (323). This highlights that ventricular pacing can depress ventricular function and contractility. Clinical trials comparing RV pacing with biventricular pacing suggest that LVEDV does not alter with pacing although importantly these studies performed baseline echocardiography after pacemaker implantation presumably to account for heart rate mediated changes in volumes (156, 160, 161). The absolute changes in LVESV following RV pacing are conflicting. In the PACE trial an increase in LVESV of 7.1 ml between baseline and 12 months was observed which is in keeping with the findings in the present study. Conversely, no significant change was observed in the PREVENT-HF trial where echocardiography was performed after initiation of right ventricular pacing. It is therefore difficult to conclude the extent to which changes in LVESVi in our study were due to dyssynchrony, changes in LV contractility and adverse LV remodelling.

Left atrial volumes fell after 6 months of pacing and this likely reflects the changes seen in the left ventricle where reductions in LVEDVi may be accompanied by a fall in LVEDP. Indeed Rosenquist *et al.* have demonstrated a significant fall in LVEDP and subsequently LA pressure on initiation of pacing in individuals with complete heart block (324). Furthermore transient increases in LA pressure have been shown to occur when atrial systole occurs against a closed AV valve which may have exacerbated LA dilatation at baseline in our patients (318).

A similar fall in RVEF was observed before and after pacing in our cohort which was driven by a reduction in RVEDVi at follow up. Unlike the left ventricle, there was no change in RVESVi at follow up. These findings suggest that RV function is determined primarily by heart rate and diastolic filling time and the RV may be less susceptible, perhaps as it is activated earlier during RV pacing, to the electromechanical alterations induced by ventricular pacing.

5.5.4 Electromechanical dyssynchrony and left ventricular contractility after right ventricular pacing in patients with myocardial fibrosis

Before pacemaker implantation there was no difference in either LV contractility, mechanical dyssynchrony or intrinsic QRS duration between those with and without myocardial fibrosis. Global longitudinal strain was significantly lower at baseline in those with myocardial fibrosis. The differences we observed in these parameters may reflect subtle changes in LV mechanics caused by the presence of myocardial fibrosis that do not result in a significant reduction in LVEF. Fent *el al.* have previously shown that myocardial infarction, detected by LGE imaging, is associated with lower GLS despite preservation of LVEF meaning this 'subclinical' dysfunction may not be distinguished using standard echocardiographic techniques (140).

At follow-up the mean paced QRS duration was significantly longer in those with myocardial fibrosis. We also observed alterations in LV mechanics between baseline and 6 months in patients with fibrosis with worsening of contractility and GLS and greater mechanical dyssynchrony. In contrast those without fibrosis only had a reduction in GLS. These data suggest that patients with underlying myocardial fibrosis experience greater electrical dyssynchrony and are susceptible to development of mechanical dyssynchrony over the long term. We propose that the presence of myocardial fibrosis slows the propagation of the electrical activation wavefront during RV pacing to a greater extent than those without fibrosis thus prolonging the time to mechanical activation and consequently increasing mechanical dyssynchrony.

Vassolo *et al.* have previously shown that total endocardial activation time during RV pacing was significantly longer in patients with previous anteroseptal myocardial infarction compared to patients without infarction (118 ± 30 vs. 76 ± 14 ms respectively; $p<0.001$) (84). Furthermore Park *et al.* have demonstrated during acute ventricular pacing that greater QRS duration and time to endocardial activation lead to greater proportional increase in the end-systolic pressure volume relationship (323). Long term, the presence of LV mechanical dyssynchrony in chronic RV pacing is associated with LV remodelling (83, 106, 325). These studies suggest patients with fibrosis are potentially at a heightened risk of LV remodelling due to the greater degree of electromechanical dyssynchrony.

5.5.5 Effect of distribution and burden of myocardial fibrosis on change in left ventricular volumes and function

We separately analysed patients with different patterns of LGE to evaluate the relationship between LGE and volumetric and functional changes at 6 months. At baseline patients with an infarct pattern had significantly greater LVESVi and lower LVEF than those with a non-infarct pattern. Those with an infarct pattern also had more pronounced underlying conduction disease with a longer baseline QRS duration. At follow up those with an infarct pattern had a much greater increase in LVESVi and decline in LVEF. LVEDVi did not fall in the infarct group with a significant drop observed in those with a non-infarct pattern.

The changes in LVESVi in those with an infarct pattern are likely not only to represent a greater degree of mechanical dyssynchrony but also adverse LV remodelling at follow up. The reason for the static LVEDVi in this group may just represent adaptive LV dilatation in response to an increased LVESVi in order to maintain cardiac output. Importantly those with an infarct pattern of LGE also had a significantly higher LGE mass. It is possible that greater mass of LGE leads to greater subsequent electromechanical dyssynchrony as the activation wavefront during RV pacing propagates more slowly through a larger volume of infarcted tissue. Our data suggest the relationship between patterns of fibrosis and remodelling is more complex as we did not identify any difference in the paced QRS duration at follow up and we failed to identify any correlation between the LGE mass and the change in LVESVi.

These findings suggest that there is a complex relationship between RV pacing and development of significant dyssynchrony in an individual. It seems likely that pacing factors, such as the pacing burden and paced QRS duration, may be additive to the risk of dyssynchrony and remodelling in the presence of fibrosis. Indeed on multi-variate a background of atrial fibrillation as well as an infarct pattern of LGE were found to be associated with the change in LVESVi highlighting other patient related factors that may impact on the development of dyssynchrony or remodelling in any individual. Recent work by Aalen *et al.* in animals has demonstrated that inducement of LBBB dyssynchrony by ablation caused pre-ejection shortening and rebound stretch of the septum which is then followed by reduced septal systolic shortening (326). The inducement of lateral wall dysfunction by circumflex occlusion caused a loss of rebound stretch and therefore improved septal work. However, in left anterior descending territory occlusion rebound stretch was increased. It may be that the presence, burden and location of fibrosis, in

tandem with RV pacing, exacerbates pre-existing regional changes in contraction causing a greater reduction in myocardial efficiency.

5.5.6 NYHA Class, Quality of Life and Adverse events after pacemaker implantation

After pacemaker implantation we found that patients with myocardial fibrosis did not experience an improvement in NHYA functional class or their perception of their own health state. This was in contrast to patients without fibrosis where significant improvements in NYHA Class and self-assessed health were observed. Neither group experienced a change in EQ-5D quality of life scores after pacemaker implantation.

The baseline NYHA Class was not significantly different between the groups and therefore despite restoration of a more 'physiological' heart rate and AV synchrony those with fibrosis did not improve after pacing. At baseline NYHA class will presumably be determined not only by bradycardia but also by co-morbidities. Patients with LGE had a greater burden of AF and coronary artery disease which may have contributed to NYHA class and these factors may not directly be augmented by pacing. In addition, the greater volumetric changes observed in those with fibrosis may offset any improvements made by restoring physiological heart rates. In the BLOCK HF trial biventricular pacing was associated with less adverse LV remodelling as well as better clinical outcomes and improved functional class over the long term when compared to RV pacing (127, 155).

Patients with myocardial fibrosis did not experience any improvement in their perceived quality of life after pacing in contrast to those without fibrosis. Clearly the reasons for this may be complex and QoL may have been influenced by many factors in this study including bradycardia, hospitalisation at time of initial assessment and co-morbidities. However, it must be considered whether the changes in LV volumes and function in those with fibrosis are linked to QoL and, if so, whether this can be augmented at presentation by the use of interventions such as biventricular pacing.

Neither group experienced a change in EQ-5D quality of life scores. The EQ-5D is a relatively blunt tool and only assesses QoL over five domains and may not adequately assess the impact of pacing alone on QoL. Perhaps the use of a different questionnaire such as the AQUAREL questionnaire, which was developed for patients with rhythm disorders requiring pacing, would have been better suited to our study (327).

The lack of improvement in QoL is at odds with the FOLLOWPACE study which demonstrated a significant improvement in quality of life measured by EQ-5D in a Dutch population of pacemaker recipients (328). Their population had a lower baseline score and significantly larger sample size, included all indications for pacemaker implantation and not just AV block. Perhaps most importantly, they added the following question to the score: “How would you consider your change in health after your pacemaker implantation?” which may have significantly influenced the results. Interestingly the baseline quality of life scores in the whole cohort in our study were higher than the UK norm suggesting our study population on average had a good quality of life. It may therefore be difficult to detect small incremental improvements especially given the modest sample size.

At follow-up we also observed four new incidences of AF and heart failure which all occurred in patients with myocardial fibrosis. The study was not powered to detect changes in clinical endpoints, these findings are perhaps not surprising. Right ventricular pacing has been shown in large pacemaker and defibrillator trials to be associated with an increased incidence of atrial fibrillation and heart failure (80, 126). Furthermore the presence of LGE has been shown to be associated with an increased risk of heart failure hospitalisation across a spectrum of LVEF and heart failure stage (329). Whether RV pacing in patients with myocardial fibrosis hastens the development of heart failure or even increases an individual’s risk clearly warrants further investigation.

5.5.7 Prevalence of myocardial fibrosis

We have found that focal and replacement cardiac fibrosis is prevalent in this population with nearly two thirds of patients having evidence of late gadolinium enhancement. In those with LGE there was nearly an even split between those with infarct and non-infarct patterns. Only 11 of the 14 patients had a known history of myocardial infarction, which meant we identified previously unknown myocardial infarction in three patients. The distribution of LGE was predominantly in the basal to mid inferior and basal inferolateral segments consistent with the right coronary artery territory. It is possible that the development of AV block in these individuals results from long term ischaemic damage to the AV nodal artery. In those with a non-infarct pattern of LGE the distribution tended to be in the basal to mid inferoseptum and basal inferolateral segments. The relatively high prevalence of non-infarct LGE can be explained by the high mean age and burden

of co-morbidities in the study population. Recent evidence suggests that nearly a third of unselected older adults have evidence of non-ischaemic LGE (330). The presence of basal septal LGE in some individuals may also have led directly to the development of AV block through disruption of conduction through the His bundle as it traverses the septum.

5.5.8 Feasibility of imaging in patients with bradycardia and permanent pacemakers

CMR was feasible in all subjects despite significant bradycardia in some participants at baseline assessment and presence of pacemaker at 6 month follow up. Image quality was of diagnostic quality in all patients and LGE imaging for assessment of focal fibrosis was possible with a flexible approach utilising respiratory navigated and single shot sequences in cases where standard segmented breath held LGE images were non-diagnostic. Unfortunately, SPAMM tagging sequences were often uninterpretable due to long breath holds and tag fading meaning they could not be analysed.

5.5.9 Device Safety

No adverse clinical events related to the scanning of MRI conditional devices during the study were noted. A small but significant increase in the ventricular pacing lead capture threshold and a small but significant decrease in the ventricular lead impedance were noted on device check immediately after CMR. However no clinically significant changes were noted in any device parameters except in the ventricular lead impedance although a mean change in lead impedance of 18 Ohms would not result in clinical intervention or device reprogramming. Furthermore changes in lead parameters occur irrespective of whether a patient is undergoing an MRI (42). The majority of changes in lead impedance were noted in Boston Scientific® devices and previously published data with these devices have demonstrated an immediate reduction in the mean lead impedance of 15Ω which returned to pre-MRI levels at device check one week later (331).

5.5.10 Limitations

Our study had a few important limitations. Firstly, this was an observational study and type of pacemaker as well as device programming were managed by the patient's clinical team. This may have led to individual variations in management that may have

influenced cardiac function at 6 months. However clinical teams were blinded to the LGE status of patients minimising differences in pacing programming between groups. Secondly, all patients were scanned in a pacing mode that mandated ventricular pacing to ensure safety whilst in the MRI scanner, by avoiding inadvertent inhibition of pacing, and to ensure consistency across all patients. In patients with a low RV pacing burden acute dyssynchrony may have been induced and therefore may not be reflective of these patients' usual ventricular function. Although, this would only be relevant in a small number of patients as the median RV pacing burden was over 80% in both groups. Thirdly, identifying whether changes in LVESV are due to adverse remodelling or pacing-induced dyssynchrony is challenging as CMR was performed prior to pacemaker implantation. CMR was performed prior to implantation in our study to confirm the presence of LGE before implantation, evaluate the presence of LGE as an upfront risk factor and assess feasibility of LGE imaging in this population. Another limitation to performing CMR prior to pacemaker implantation is that both arrhythmia and bradycardia may prolong breath holds and impact on image quality. Although we attempted to overcome this by using single shot techniques to offset poor breath holding and arrhythmia these sequences have inherent lower signal to noise ratio resulting in a potentially lower sensitivity for detecting LGE (332).

We did not assess for development of mitral regurgitation which has been recognised in patients after pacemaker implantation (112). This may led to a reduction in the effective stroke volume and may contribute to development of heart failure or a change in NYHA Class. In future studies, echocardiographic measurement of mitral regurgitation or indirect CMR calculation using aortic valve phase contrast imaging would help in evaluating this aspect. (333).

Lastly the sample size was a relatively small with a small event rate and with predominantly inferior distribution of myocardial fibrosis Therefore the results may be hard to generalise to all patients with these disease processes and all patients needing pacemakers. Furthermore a larger sample size is needed to evaluate whether other confounding factors, such as the presence of atrial fibrillation between the groups, influenced the long term changes in LV haemodynamics.

5.5.11 Future implications

To our knowledge this is the first study using CMR to evaluate the prevalence of myocardial fibrosis in patients with AV block and its impact on the longitudinal changes

in ventricular volumes and function following pacemaker implantation. Those with fibrosis seem to be most susceptible to development of dyssynchrony and LV remodelling suggesting that the underlying myocardial substrate is potentially an important determinant of deterioration in LV function and development of heart failure after pacing. Hopefully this study could pave the way for further CMR studies examining the relationship between myocardial fibrosis and pacing induced heart failure.

We believe that in future studies perhaps serial changes in response to pacing should be guided by LVESV rather than LVEF. Changes in LVEF are the current standard for assessment of pacing-induced cardiomyopathy and baseline LVEF is used in guidelines to determine the upfront pacing device (117, 191). LVEF is mediated to a significant extent by LVEDV and both metrics may largely depend on diastolic filing time and preload. This may lead to two issues: firstly LVEF may be 'falsely' elevated during bradycardia where LVEDV is increased due to a long diastolic filling period, so LV function may be overestimated; secondly, a subsequent drop in LVEF at follow up may be heart rate dependent rather than reflecting a true decline in cardiac function. We have shown that LVESV is heart rate independent and it may therefore be a better parameter for both upfront and serial measurement of LV remodelling. Indeed a 10 ml/m^2 increase in LVESVI after pacing has been shown to be associated with a 7% increased risk of death and a 10% increased risk of hospitalisation from heart failure (156). CMR is uniquely placed to evaluate serial changes in LVESV due to its high inter-study reproducibility. To detect a 10ml change in LVESV in heart failure patients sample size can be reduced by 85% compared to echocardiography (204). One factor we did not address in the study was whether changes in LVESV were due to dyssynchrony caused by acute RV pacing or long term remodelling and perhaps an additional scan immediately after pacing in future studies could help answer that question.

Clearly there are drawbacks to using CMR in a cohort of patients with AV block. These patients are often elderly and have significant bradycardia which means they are at risk of further arrhythmias. Furthermore arrhythmia and long breath holds due to bradycardia may impact image quality as well as resulting in a prolonged scan time. Some of these issues can be overcome with utilisation of newer sequences and post processing techniques. These can allow free breathing, potentially reduce scan times and improve image quality as well as patient tolerance and comfort during the scan. Good quality cine imaging can now be obtained in a single breath hold for an entire LV SA stack using compressed sense acceleration or even using free breathing real time cine with motion correction and retrospective binning which is comparable to standard segmented cine

imaging (334, 335). Furthermore free-breathing, motion-corrected, single shot LGE imaging provides at least comparable image quality to breath held sequences, and can reduce scan times and has been validated in conjunction with wide band LGE in patients with cardiac devices (70, 336, 337).

We have shown that the presence of myocardial fibrosis is associated with worsening cardiac function at 6 months compared to those without fibrosis. Importantly this means we have the potential to identify high risk patients before device implantation. The incorporation of newer CMR techniques can facilitate scanning, by reducing scan time and breath holding, in patients with AV block prior to pacemaker implantation. Indeed, the identification of fibrosis using CMR could be used to guide upfront device selection, particularly in those with preserved LVEF. We advocate a clinical trial where those with fibrosis are randomised to either physiological pacing with CRT or His bundle pacing or standard ventricular pacing. His bundle pacing may alleviate some of the pacing mediated factors, particularly electrical dyssynchrony induced by RV pacing, by the maintenance of physiological conduction and has shown promise in reducing clinical events compared to RV pacing (176, 338).

5.6 Conclusion

To our knowledge this is the first study using CMR to evaluate longitudinal changes following pacemaker implantation in patients with AV block. Focal myocardial fibrosis is common in patients with AV block undergoing pacemaker implantation. The presence of fibrosis, compared to those without fibrosis, in patients with RV pacing at 6 month follow-up is associated with:

1. A significant increase in LVESVi and greater decline in LVEF
2. Greater electrical and mechanical dyssynchrony with reduced LV contractility
3. A lack of improvement in quality of life and functional class.
4. A possible signal for development of new onset heart failure and atrial fibrillation.

Further work is needed to determine the longer term effect of cardiac fibrosis in this population and identify whether upfront interventions such as cardiac resynchronisation therapy or His bundle pacing in this cohort can prevent dyssynchrony and adverse LV remodelling.

Chapter 6 Short and long term effects of right ventricular pacing in patients with myocardial fibrosis

The advent of implantable permanent pacemakers has helped normalise life expectancy and restore quality of life in patients with symptomatic bradycardia (262, 263). However large clinical trials have demonstrated that long term RV pacing can be associated with an increased risk of hospitalisation for heart failure (79, 80). Individuals with baseline impairment of left ventricular function appear to be at the greatest risk but even those with preserved LVEF can experience a decline in LVEF and develop heart failure (117, 126). Hospitalisation for heart failure is expensive and impacts significantly on long term prognosis of patients (339, 340). Current strategies such as alternate right ventricular pacing sites and biventricular pacing in patients with normal LV function have had limited success and are not routinely recommended in guidelines (30, 161, 168, 191). There is a need to identify upfront factors that can predict subsequent decline in LV function and risk of heart failure in order to individualise therapy prior to pacemaker implantation. This is particularly important as the rates of pacemaker implantation in Europe continue to increase year on year (239).

The aim of this project was to utilise CMR to evaluate the effect of acute and chronic RV pacing on biventricular function. To our knowledge this work is the first use of CMR to explore the effects of RV pacing. Previous work has predominantly used echocardiography to evaluate to changes in cardiac function. Multi-parametric CMR has several inherent advantages over other cardiac imaging modalities. In particular it enables accurate and reproducible serial assessment of cardiac volume and function as well as detecting myocardial fibrosis with unparalleled spatial resolution (203, 204, 210). The presence of myocardial fibrosis, detected by LGE imaging, is a powerful prognostic marker of cardiovascular mortality, ventricular arrhythmia and hospitalisation for heart failure independent of LVEF in both ischaemic and non-ischaemic cardiomyopathy (67, 68). In patients with RV pacing the presence of previous myocardial infarction is associated with future risk of heart failure (10, 134). We set out to evaluate how the presence of myocardial fibrosis, detected by late gadolinium enhanced imaging, affected acute cardiac haemodynamics and longer-term LV remodelling in patients with pacemakers. Furthermore we also evaluated the use of 4D flow CMR, in patients with CIEDs, in assessment of transvalvular and intracardiac flow in different pacing modes.

This body of work utilising CMR in pacemaker recipients has demonstrated that:

1. Performing CMR in patients with significant bradycardia and high degree AV block is feasible.
2. Myocardial fibrosis is relatively common in device recipients particularly in patients with AV block.
3. The presence of myocardial fibrosis in patients with AV block is associated with an increase in LVESV and a greater decline in LV function at 6 months compared to those without fibrosis.
4. Initiation of RV pacing in patients with preserved AV conduction and myocardial fibrosis is associated with greater mechanical dyssynchrony and consequent increase in LVESV compared to those without fibrosis.
5. 4D flow CMR in patients with MRI conditional pacemakers is feasible and allows accurate and consistent assessment of transvalvular flow.

6.1 Acute and chronic effect of right ventricular apical pacing in patients with myocardial fibrosis

The absolute changes observed in left ventricular volumes and function with both acute and chronic right ventricular pacing in those with and without myocardial fibrosis can be seen in Figure 6-1**.** Right ventricular pacing induces both acute and chronic changes in LV function regardless of the presence of myocardial fibrosis. Importantly, in both study cohorts, the magnitude of the decline in LV function during right ventricular pacing was greater in those with myocardial fibrosis.

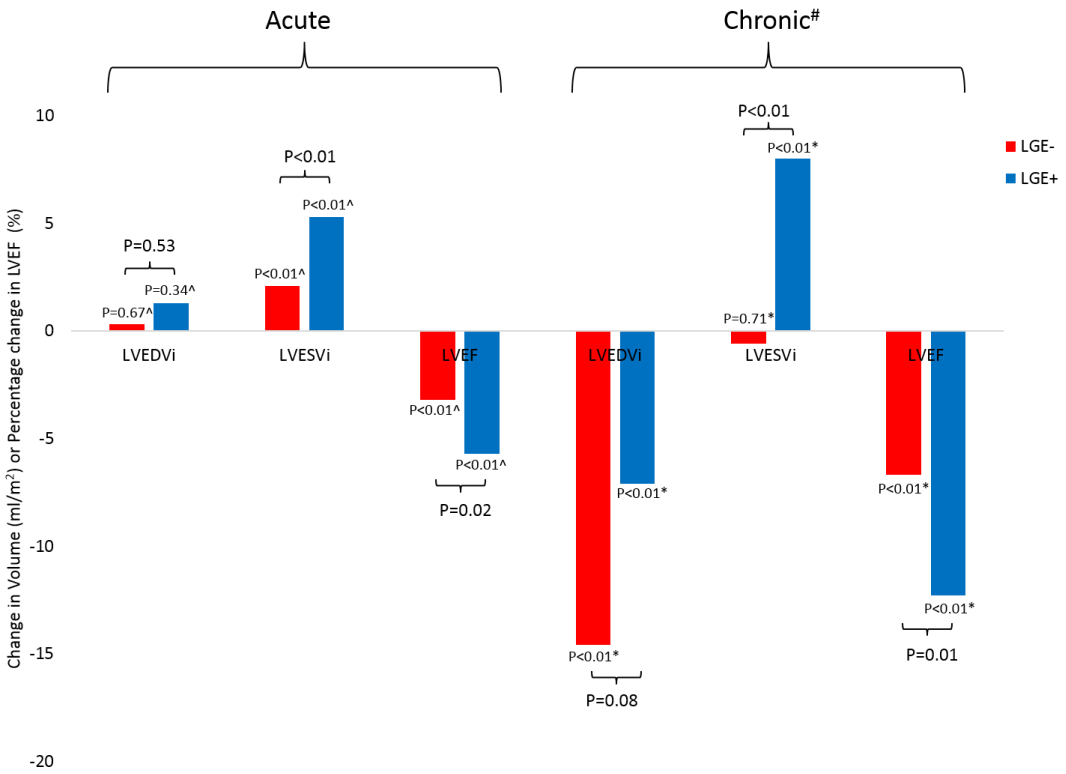


Figure 6-1: Changes in Left Ventricular Volumes with initiation of Right Ventricular pacing.

Left ventricular volumes and function after either acute (immediate - left side) or chronic (6 months – right side) right ventricular pacing in patient with (blue bars) and without (red bars) myocardial fibrosis.

^ P-value comparing values obtained during AOO and DOO pacing modes

* P-value comparing values obtained before and 6 months after pacemaker implantation

In the chronic group baseline and follow up scans were performed at different heart rates making comparison of LVEDVi and LVEF data challenging

Abbreviations: LGE: late gadolinium enhancement, LVEDVi: left ventricular end-diastolic volume index, LVEF: left ventricular ejection fraction, LVESVi, left ventricular end-systolic volume index, RVEDVi: right ventricular end-diastolic volume index, RVEF: right ventricular ejection fraction, RVESVi, right ventricular end-systolic volume index

6.1.1 Left Ventricular End-Systolic Volume

We have observed that initiation of RV pacing causes an acute increase in LVESV in all patients which is also seen over the long term in those with myocardial fibrosis. LVESV is relatively insensitive to loading and indeed our data show that LVESV does not have any correlation with heart rate (321, 322, 341). We therefore postulate that acute changes in LVESV are due to direct effects of pacing on LV contractility. Long term changes in LVESV are likely a combination of acute pacing induced dyssynchrony and LV remodelling.

6.1.1.1 Patients with myocardial fibrosis

A greater acute change was observed in those with myocardial fibrosis suggesting that its presence has an additive effect on the electromechanical dyssynchrony induced by RV pacing. Indeed, mechanical dyssynchrony was significantly worse in those with myocardial fibrosis and though a trend to worsening dyssynchrony was observed in those without fibrosis it was non-significant. A similar pattern was observed over the long term in those with myocardial fibrosis with reductions in contractility and deteriorations in mechanical synchrony occurring between baseline and follow-up. In addition, greater electrical dyssynchrony was present in those with fibrosis at follow-up. The presence of fibrosis may therefore delay electrical propagation of the delivered ventricular stimulation through the myocardium, which we believe contributes to increased mechanical dyssynchrony and a decline in LV function.

Patients with myocardial fibrosis are clearly more susceptible to developing electromechanical dyssynchrony after RV pacing. In the longitudinal study it was not possible to ascertain whether changes in LV volumes and function were due to the dyssynchrony induced by RV pacing or reflected underlying LV remodelling. Unfortunately the majority of MRI conditional pacemakers are not licensed to undergo MRI until 6 weeks post implantation so immediate imaging using CMR would not have been possible. The impact of this limitation may be minimal as the presence of LV dyssynchrony after RV pacing has been shown to be associated with LV remodelling, worsening heart failure symptoms and increased heart failure hospitalisation over the longer term (83, 142). Additionally, the magnitude of change in LVESV in those with fibrosis was greater at 6 months than what we observed acutely. We conclude that the differential change in LVESVi most likely represents adverse remodelling in the long term. Furthermore the smaller reduction in LVEDVi in those with myocardial fibrosis may

be explained by compensatory ventricular dilatation as a response to decreased contractility, increases in LV end-diastolic pressure and neurohormonal activation. Indeed RV pacing has previously been shown to induce sympathetic activation, alter myocardial oxygen demand and lead to long term changes in myocardial perfusion (89, 108, 110). It may be that these mechanisms are hastened in patients with myocardial fibrosis particularly in those with an infarct pattern who may already have some impairment to perfusion.

6.1.1.2 Patients without myocardial fibrosis

In patients without fibrosis there was a small immediate increase in LVESVi with initiation of RV pacing. However, over the long term there was no significant change in LVESVi. These findings are interesting as clearly RV pacing induces electrical dyssynchrony with both an acute and chronic increase in the QRS duration. Unlike in those with fibrosis this electrical dyssynchrony does not appear to lead to detectable mechanical dyssynchrony as no significant change in MDI was observed after initiation of RV pacing either immediately or at 6 months. Perhaps the healthier underlying myocardium can compensate over the long term for the immediate changes in contractility in a way that is not feasible in those with underlying myocardial fibrosis.

6.1.2 Left Ventricular End-Diastolic Volume

In the longitudinal study the observed fall in LVEF was heavily influenced by a marked drop in LVEDVi. In acute pacing however we did not observe any change in LVEDVi. LVEDV is preload dependent and has been shown to have an inverse relationship with heart rate during atrial pacing (315). In Chapter 5 CMR was performed prior to pacemaker implantation when profound bradycardia was present in a proportion of patients. Bradycardia prolongs diastolic filling time and thereby increases preload leading to a greater LVEDV. This is compatible with the significant fall in LVEDVi at follow up where the heart rate was programmed at 80bpm. The fall in LVEDV was much less in those with myocardial fibrosis despite there being no difference in either baseline or follow up heart rates. Given there was no significant difference between the groups in the baseline or follow up heart rate we conclude that the difference in LVEDV between those with and without fibrosis is related to adverse remodelling in those with fibrosis. We did not observe any change in LVEDV between intrinsic conduction and acute initiation of ventricular pacing because preload was relatively constant as there was no change in heart rate and AV synchrony was maintained during ventricular pacing.

6.1.3 Discussion

Acute RV pacing leads to a small increase in LVESV through reduced contractility and mechanical dyssynchrony. Patients with myocardial fibrosis are particularly susceptible to developing mechanical dyssynchrony after RV pacing. In chronic RV pacing there is decrease in LVEF in all patients predominantly due to increase in heart rate and decline in LVEDV. In patients with myocardial fibrosis there is a greater decline in LVEF due to mechanical dyssynchrony and adverse LV remodelling. A proposed mechanism for the pathophysiology underpinning the development of heart failure in those with myocardial fibrosis is shown in Figure 6-2.

The presence of fibrosis alone cannot be the sole risk factor for the development of dyssynchrony and remodelling. We can see from the individual data points in Chapters 4 and 5 that many patients with fibrosis did not experience a significant change in LVESV after pacing. It may be that pacing mediated factors such as pacing burden and paced QRS duration heighten risk and perhaps the location or burden of the fibrosis play a role. Further work is needed in a larger population to further define this relationship.

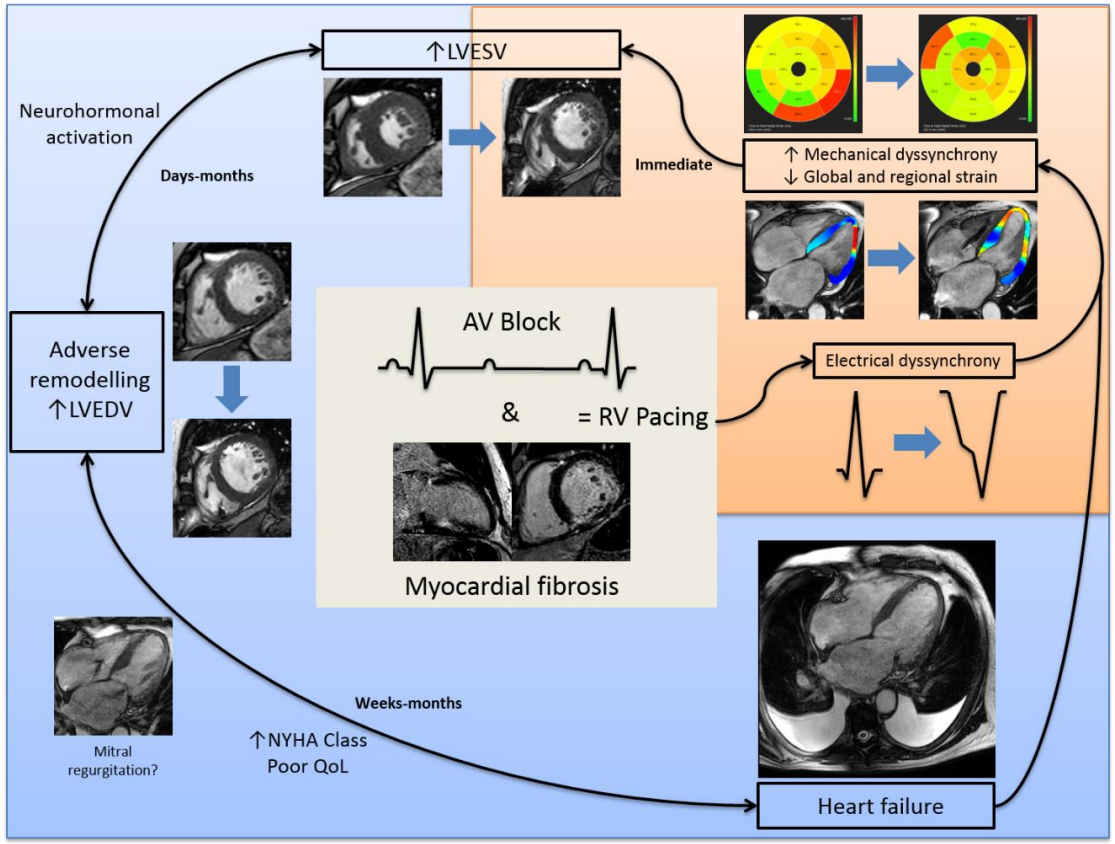


Figure 6-2: Proposed mechanism for the pathophysiology underpinning the development of heart failure in those with myocardial fibrosis.

Both the acute (orange box) and chronic (blue box) changes after initiation of RV pacing are shown.

Abbreviations: AV: atrioventricular, LVEDV: left ventricular end-diastolic volume, LVESV, left ventricular end-systolic volume, NYHA: New York heart association, QoL: quality of life, RV: right ventricle

6.2 Comparison to clinical trials evaluating RV pacing

Direct comparison to clinical trials is challenging because of the different study populations, lack of reporting of all echocardiographic measures of ventricular volumes and function and different outcome measures. Furthermore, most of the robust data is from clinical trials comparing RV apical pacing with either alternate RV pacing sites or biventricular pacing. A summary of the changes in ventricular volumes in patients assigned to RV apical pacing in large clinical trials (defined as >100 total recruited patients) compared to our total cohort and those with late gadolinium enhancement is shown in Table 6-1.

Trial	n	Inclusion criteria	Follow up (months)	Baseline TTE	Baseline LVEF (%)	Baseline HR (bpm)	LVEDV	LVESV	LVEF
PACE (2009) (159)	86	LVEF>45% SND & AV block	12	Before implant	61.5	59	↑ 3.4ml	↑ 7.1ml	↓ 6.7%
PREVENT-HF (2011) (161)	46	Pacing indication & VP>80%	12	Prior to hospital discharge	54.9	55	↑ 3.4ml	↑ 3.2ml	↓ 0.4%
Block-HF (2013) (127, 156)	319	AV block NYHA I-III LVEF ≤50%	6	At randomisation (after 30-60 days of RV pacing)	39.6	69	↓ 0.3ml/m^2	↓ 0.4ml/m^2	↓ 0.3%
Protect Pace (2015) (168)	76	AV block LVEF≥40%	24	Prior to hospital discharge	57	NR	↑ 2ml/m^2	↑ 2ml/m^2	↓ 3%
BLOCK MR (All patients)	50	AV block LVEF>35%	6	Before implant	57.3	54	↓ 10ml/m^2	↑ 4.7ml/m^2	↓ 10%
BLOCK MR (LGE+)	31	AV block LVEF>35%	6	Before implant	55.5	56	↓ 7.1ml/m^2	↑ 8.0ml/m^2	↓ 12.3%

Table 6-1: Changes in LV volumes and function in patients assigned to a right ventricular apical pacing in large clinical trials (>100 patients) and our study.

Significant (green arrows) and non-significant (orange arrows) at follow up are shown.

Abbreviations: AV: atrioventricular, HR: heart rate, LGE: late gadolinium enhancement, LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV, left ventricular end-systolic volume, NYHA: New York heart association, RV: right ventricle, SND: sinus node disease, TTE: transthoracic echocardiogram, VP: ventricular pacing

6.2.1 Left Ventricular End-Systolic Volume

LVESV in our study increased significantly after pacing and certainly to a greater degree than in the majority of previous studies (Table 6-1). This is presumably related to the timing of imaging in respect to pacemaker implantation: most studies performed baseline echocardiography after pacemaker implantation. This is important as we have shown that RV pacing can induce acute LV dyssynchrony, leading to immediate increases in LVESV, which may explain the greater change in LVESV seen in our study. When compared to the PACE trial, where baseline imaging was performed prior to pacemaker implantation, the increases in LVESV observed were of a similar magnitude to our cohort (159). The remaining studies did detect an increase in LVESV over the follow up period but this was only significant in the Protect-Pace study, which reported an increase of 2ml/m^2 (168). Interestingly this change was similar to the difference in LVESVi we observed between acute (5ml/m^2) and chronic (8ml/m^2) right ventricular pacing, albeit in different cohorts. The additional 3ml/m^2 increase in LVESVi may reflect LV remodelling rather than just dyssynchrony. Furthermore detecting dyssynchrony may also be important as its presence may be directly linked to longer term remodelling (83, 142). The failure to detect a difference in the PREVENT-HF trial may reflect the smaller sample size and lower interstudy reproducibility of echocardiography in ventricular volume assessment (161). Comparisons to the BLOCK-HF trial are particularly difficult as it evaluated a very different cohort of patients with a significantly lower LVEF at baseline, but it did demonstrate that a significantly greater proportion of patients assigned to right ventricular pacing had a ≥15% increase in LVESVi compared to those assigned to CRT (127).

6.2.2 Left Ventricular End-Diastolic Volume

We observed marked reductions in LVEDV from baseline to follow up in our study in both those with and without myocardial fibrosis. The most likely explanation for this is differences in diastolic filling time and preload between the baseline and follow up scans. In Chapter 5 baseline imaging was performed prior to pacemaker implantation when a significant proportion of patients were in AV block with profound bradycardia. The average baseline heart rate in our study was lower than in any other major trial. For example, in BLOCK-HF the mean heart rate at baseline was 68 bpm compared with 54 bpm in our study. Furthermore, follow up imaging in our study was performed primarily in a DOO pacing mode at 80bpm which meant there was a substantial difference in heart rate and filling time between baseline and follow up. DOO at a rate of 80 bpm was chosen to avoid competing rhythms but also because of manufacturers restrictions on

programming in the MRI environment which meant this was usually the safest mode to maintain AV synchrony. The heart rate differential between baseline and follow up was not reported in earlier studies and this may account for the absence of a significant fall in LVEDV. There was a trend to increased LVEDV in the majority of trials but it was predominantly a non-significant change and could just represent alterations in preload rather than remodelling.

6.2.3 Left Ventricular Ejection Fraction

Left ventricular ejection fell in patients with and without LGE in our study and was predominantly mediated by a reduction in LVEDVi between baseline and follow up. The extent of decline in LVEF was much greater in our study than any previous trial. These discrepant findings are probably a result of performing CMR prior to pacemaker implantation and the subsequent differences in heart rates and LV filling time between baseline and follow up. It is also possible that quantification was more accurate in our study given that we used CMR rather than echocardiographic parameters in contrast to previous literature. However, those with myocardial fibrosis had a much greater decline in LVEF (~5%) despite matched heart rates at baseline and follow up to those without myocardial fibrosis. Changes in heart rate alone cannot explain these differential findings and therefore it is highly likely that greater electromechanical dyssynchrony and remodelling mediate additional changes in LVESV and LVEF in patients with fibrosis.

6.3 Impact of Research Findings

Overall the findings of this research project are comparable with the published literature when timing of the baseline scan and differences in diastolic filling time are taken into account. Furthermore we have found that myocardial fibrosis is prevalent in patients with AV block and these patients experienced an increase in LVESV and lower LVEF at 6 months than those without fibrosis. These findings are novel and demonstrate the potential deleterious interaction between RV pacing and the presence of myocardial fibrosis.

We have demonstrated that in patients with pacemakers assessment of transvalvular flow is feasible and reproducible across a range of device manufacturers. CMR imaging in patients with profound bradycardia and AV block is feasible and provides diagnostic image quality. Furthermore advanced CMR techniques such as 4D flow and feature

tracking can be performed in patients with CIEDs to assess dyssynchrony and may even provide future novel imaging biomarkers to further our understanding of pacing-induced cardiomyopathy.

6.3.1 Limitations

Firstly, the findings of our study are not applicable to all pacemaker recipients as we excluded patients who were too unstable to undergo MRI, such as those with temporary pacing wires, and those with significant LV impairment. We also wanted to recruit patients with a high RV pacing burden, as this has previously been implicated as a risk factor for development of heart failure, and therefore did not include patients with sinus node disease who represent a significant proportion of patients who may experience RV pacing. Furthermore, as the standard practice in our study centre is to implant the RV lead in the RV apex, the results are not applicable to those with alternate RV pacing sites.

Secondly, we did not perform CMR immediately after pacemaker implantation as this is contraindicated in the majority of MRI conditional pacemakers. This makes it challenging to know whether the long term changes in LVESVi that we observed are due to pacing-induced dyssynchrony or reflect true LV remodelling. However, the differential results in LVESV between the cohorts undergoing CMR with acute and chronic RV pacing suggest the possibility of a degree of remodelling that occurs over the long term. Furthermore, the presence of significant LV dyssynchrony has been shown to be associated with future remodelling and heart failure risk, so this theoretical concern may not have major implications on our ability to draw conclusions from this study. As our study was not powered for clinical events and the period of follow-up was relatively short it is difficult to know the clinical impact of our observed changes in LVESV. We did identify a signal towards increased clinical events downstream in the fibrosis group, which is an interesting observation and an area that could be given more emphasis in future work.

Finally, although we found that patients with fibrosis, particularly those with an infarct pattern, have greater changes in LV volumes and function at 6 months the numbers in each group were small. On an individual level the response to RV pacing in any particular patient varied significantly. This suggests that there may be a complex relationship between the underlying fibrosis and pacing factors, such as pacing burden and paced QRS duration, in determining adverse LV remodelling. Indeed Aalen *et al.* have shown

in animal models of dyssynchrony that circumflex and left anterior descending artery occlusion have very different effects on regional septal work (326). The sample size in our study was too small to interrogate fully all the aforementioned factors either individually or together. Given the low number of patients without any LGE we cannot definitively conclude that these patients are not at risk of remodelling and heart failure, and equally, we cannot say with certainty that the changes we did observe were fully related to pacing given that we did not have a comparator arm of patients who did not undergo RV pacing. A matched control arm would have enabled evaluation of the natural temporal changes in volumes and QRS duration in the absence of RV pacing. However the study was predicated on people who had a pacing indication and were likely to have unavoidable RV pacing. Finally confounders such as the presence of atrial fibrillation, which was significantly different between the groups and found on multi-variate analysis to be predictive of the change in LVESVi, could well influence long-term changes in LV haemodynamics and these would need consideration in further work with larger sample sizes.

6.3.2 Clinical Impact

Despite the limitations to our study it paves the way for further CMR studies to increase our understanding of the pathophysiology underlying pacing-induced cardiomyopathy and heart failure.

We have shown that CMR scanning in patients with advanced AV block and profound bradycardia is feasible particularly with a flexible protocol to optimise image quality. Importantly no significant clinical events occurred either in patients with advanced AV block or in patients with MRI conditional cardiac devices. Minor changes in lead parameters did occur but no clinical intervention was required in these patients. Demonstrating the feasibility of CMR in this cohort of patients is important as it means that future studies utilising CMR can have significantly reduced sample sizes for detecting longitudinal changes than those previously performed with echocardiography (203, 204). The increased inter-observer agreement seen in CMR may also have implications for the accuracy of data going forward in this field. We also propose that LVESVi may be the optimal parameter for monitoring changes attributable to right ventricular pacing over the long term. Serial measurement of LVESV allows the assessment of acute dyssynchrony and long term remodelling that may occur after RV pacing. This is particularly important in patients with AV block where diastolic filling

period and preload have the capacity to alter LVEDV, and subsequently LVEF, significantly.

Finally, by using LGE imaging, we have potentially identified a particularly high risk group that is more susceptible to the deleterious effects of right ventricular pacing. If this observation is replicated in larger studies, there may be a role for greater vigilance in screening patients for myocardial fibrosis before pacemaker implantation or early monitoring in those with significant fibrotic burden.

6.3.3 Future implications

The multi-parametric nature of CMR means both scanning and subsequent analysis can be time consuming sometimes limiting its clinical applicability. There are some inherent risks to scanning patients in AV block in the MRI environment, such as the length of the scan and immediate access to resuscitation equipment, which can be circumvented with imaging modalities such as echocardiography. Furthermore the presence of AV block may increase scan time through longer breath holds. However several technological advances in CMR can be used to shorten both scan and post processing times as well as reducing or even negating the need for breath holding. Compressed sensing techniques allow acquisition of a full LV cine SA stack in a single breath hold with good reproducibility by utilising incoherent undersampling and non-linear reconstruction (334, 342). Application of post-acquisition motion correction has also been demonstrated for both real time cines and single shot LGE imaging with comparable image quality to standard segmented techniques with single shot acquisitions having been shown to reduce scan times (335, 337). Recently the use of machine learning and artificial intelligence has been shown to allow the accurate and reproducible quantification of ventricular volumes in a significantly shorter time (343, 344). Utilisation of these techniques has the potential to reduce scan time as well as ensure high image quality, both of which are integral to detecting serial changes in ventricular volumes and myocardial fibrosis.

Most patients tolerate RV pacing with no adverse haemodynamic consequences however, there is a cohort of patients who develop heart failure after pacemaker implantation. Our data suggest that patients with focal myocardial fibrosis are particularly susceptible to developing mechanical dyssynchrony after RV pacing and experience a greater decline in LV function than those without fibrosis. The fact that CMR enables the

upfront identification of these patients is of paramount importance as many of the other factors associated with development of pacing induced cardiomyopathy and heart failure such as paced QRS duration or pacing burden cannot be predicted prior to implantation. Furthermore the mean LVEF in patients with myocardial fibrosis was normal which means they would not have been identified as high risk if using echocardiography as a tool to guide management. Upfront identification of high risk patients is needed to individualise therapy as to date randomised studies of physiological pacing in those with a normal LVEF have not demonstrated improved clinical endpoints and these devices come with a greater risk of complications. However upfront intervention to mitigate any iatrogenic insult caused by RV pacing, in susceptible individuals, and reduce the downstream burden of heart failure is vital. This is particularly important with the ever ageing population and growing number of pacemaker implantations.

A larger trial incorporating CMR to guide upfront treatment, identify individuals most at risk of heart failure and evaluate the long term clinical outcomes of pacing this population is needed. We propose a double blinded randomised controlled trial in which all patients with AV block and LGE are implanted with a CRT device and assigned to either biventricular or RV pacing with thought given to relevant outcome measures such as adverse remodelling, heart failure hospitalisation and cardiovascular death. Patients without fibrosis would be implanted with a standard pacemaker and followed up in a registry. An additional CMR could be performed of as soon as possible after implantation to assess the impact of acute dyssynchrony, although there is limited evidence on the safety of scanning recently implanted devices and our data hint towards long term remodelling being the more relevant mechanism (43).

6.4 Conclusion

Multi-parametric CMR allows a comprehensive assessment of many of the factors implicated in LV remodelling after pacemaker implantation. CMR offers high reproducibility of ventricular volumetric assessment and detection of myocardial fibrosis without the need for ionising radiation. These factors mean it is an ideal test for assessment of myocardial fibrosis and its effect in long term LV remodelling in patients undergoing pacemaker implantation.

We have shown CMR to be feasible in detection of myocardial fibrosis in patients with AV block and in those with intracardiac devices. We demonstrate that volumetric, 4D and

tissue characterisation analyses can be carried out safely and accurately in patients with devices, using flexible CMR protocols. Right ventricular pacing in patients with myocardial fibrosis, compared to those without, leads to greater deterioration in cardiac function both immediately and after 6 months. This finding has enhanced our understanding of the mechanisms underlying pacing-induced cardiomyopathy and heart failure and paves the way for future observational and trial research. It is our hope that this foundation can be built upon to identify patients at higher risk of PICM and, perhaps, eventually find ways to individualise the manner and mode of pacing upfront to try and prevent it.

References

1. British Heart Rhytm Society. National Audit of Cardiac Rhythm Management Device and Ablation 2016/2017: Summary Report. [Online]. [Accessed 24 March 2020]. Available from: https://www.nicor.org.uk/wp-content/uploads/2019/07/CRM-Report-2016-2017.pdf
2. Kalin, R. and Stanton, M.S. Current clinical issues for MRI scanning of pacemaker and defibrillator patients. *Pacing Clin Electrophysiol.* 2005, 28(4), pp.326-328.
3. Gimbel, J.R., Bailey, S.M., Tchou, P.J., Ruggieri, P.M. and Wilkoff, B.L. Strategies for the safe magnetic resonance imaging of pacemaker-dependent patients. *Pacing Clin Electrophysiol.* 2005, 28(10), pp.1041-1046.
4. Sabzevari, K., Oldman, J., Herrey, A.S. et al. Provision of magnetic resonance imaging for patients with 'MR-conditional' cardiac implantable electronic devices: an unmet clinical need. *Europace.* 2017, 19(3), pp.425-431.
5. Hundley, W.G., Bluemke, D.A., Finn, J.P. et al. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *J Am Coll Cardiol.* 2010, 55(23), pp.2614-2662.
6. Greenwood, J.P., Maredia, N., Younger, J.F. et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. *Lancet.* 2012, 379(9814), pp.453-460.
7. Nagel, E., Greenwood, J.P., McCann, G.P. et al. Magnetic Resonance Perfusion or Fractional Flow Reserve in Coronary Disease. *N Engl J Med.* 2019, 380(25), pp.2418-2428.
8. Bruder, O., Wagner, A., Lombardi, M. et al. European Cardiovascular Magnetic Resonance (EuroCMR) registry--multi national results from 57 centers in 15 countries. *J Cardiovasc Magn Reson.* 2013, 15, p.9.
9. von Knobelsdorff-Brenkenhoff, F. and Schulz-Menger, J. Role of cardiovascular magnetic resonance in the guidelines of the European Society of Cardiology. *J Cardiovasc Magn Reson.* 2016, 18, p.6.
10. Tayal, B., Fruelund, P., Sogaard, P. et al. Incidence of heart failure after pacemaker implantation: a nationwide Danish Registry-based follow-up study. *Eur Heart J.* 2019.
11. Ebert, M., Jander, N., Minners, J. et al. Long-Term Impact of Right Ventricular Pacing on Left Ventricular Systolic Function in Pacemaker Recipients With Preserved Ejection Fraction: Results From a Large Single-Center Registry. *J Am Heart Assoc.* 2016, 5(7).
12. Shellock, F.G., Tkach, J.A., Ruggieri, P.M. and Masaryk, T.J. Cardiac pacemakers, ICDs, and loop recorder: evaluation of translational attraction using conventional ("long-bore") and "short-bore" 1.5- and 3.0-Tesla MR systems. *J Cardiovasc Magn Reson.* 2003, 5(2), pp.387-397.
13. Luechinger, R., Duru, F., Scheidegger, M.B., Boesiger, P. and Candinas, R. Force and torque effects of a 1.5-Tesla MRI scanner on cardiac pacemakers and ICDs. *Pacing Clin Electrophysiol.* 2001, 24(2), pp.199-205.
14. Irnich, W. Risks to pacemaker patients undergoing magnetic resonance imaging examinations. *Europace.* 2010, 12(7), pp.918-920.
15. Nordbeck, P., Fidler, F., Weiss, I. et al. Spatial distribution of RF-induced E-fields and implant heating in MRI. *Magn Reson Med.* 2008, 60(2), pp.312-319.
16. Nordbeck, P., Fidler, F., Friedrich, M.T. et al. Reducing RF-related heating of cardiac pacemaker leads in MRI: implementation and experimental verification of practical design changes. *Magn Reson Med.* 2012, 68(6), pp.1963-1972.

17. Luechinger, R., Zeijlemaker, V.A., Pedersen, E.M. et al. In vivo heating of pacemaker leads during magnetic resonance imaging. *Eur Heart J.* 2005, 26(4), pp.376-383; discussion 325-377.
18. Nordbeck, P., Weiss, I., Ehses, P. et al. Measuring RF-induced currents inside implants: Impact of device configuration on MRI safety of cardiac pacemaker leads. *Magn Reson Med.* 2009, 61(3), pp.570-578.
19. Langman, D.A., Goldberg, I.B., Finn, J.P. and Ennis, D.B. Pacemaker lead tip heating in abandoned and pacemaker-attached leads at 1.5 Tesla MRI. *J Magn Reson Imaging.* 2011, 33(2), pp.426-431.
20. Sommer, T., Naehle, C.P., Yang, A. et al. Strategy for safe performance of extrathoracic magnetic resonance imaging at 1.5 tesla in the presence of cardiac pacemakers in non-pacemaker-dependent patients: a prospective study with 115 examinations. *Circulation.* 2006, 114(12), pp.1285-1292.
21. Luechinger, R., Duru, F., Zeijlemaker, V.A. et al. Pacemaker reed switch behavior in 0.5, 1.5, and 3.0 Tesla magnetic resonance imaging units: are reed switches always closed in strong magnetic fields? *Pacing Clin Electrophysiol.* 2002, 25(10), pp.1419-1423.
22. Indik, J.H., Gimbel, J.R., Abe, H. et al. 2017 HRS expert consensus statement on magnetic resonance imaging and radiation exposure in patients with cardiovascular implantable electronic devices. *Heart Rhythm.* 2017, 14(7), pp.e97-e153.
23. Russo, R.J., Costa, H.S., Silva, P.D. et al. Assessing the Risks Associated with MRI in Patients with a Pacemaker or Defibrillator. *N Engl J Med.* 2017, 376(8), pp.755-764.
24. Gimbel, J.R. Unexpected asystole during 3T magnetic resonance imaging of a pacemaker-dependent patient with a 'modern' pacemaker. *Europace.* 2009, 11(9), pp.1241-1242.
25. Mollerus, M., Albin, G., Lipinski, M. and Lucca, J. Ectopy in patients with permanent pacemakers and implantable cardioverter-defibrillators undergoing an MRI scan. *Pacing Clin Electrophysiol.* 2009, 32(6), pp.772-778.
26. Babouri, A. and Hedjeidj, A. In vitro investigation of eddy current effect on pacemaker operation generated by low frequency magnetic field. *Conf Proc IEEE Eng Med Biol Soc.* 2007, 2007, pp.5684-5687.
27. American Society for Testing and Materials. *ASTM F2503–05. Standard practice for marking medical devices and other items for safety in the magnetic resonance environment.* West Conshohocken, PA: 2005.
28. Loewy, J., Loewy, A. and Kendall, E.J. Reconsideration of pacemakers and MR imaging. *Radiographics.* 2004, 24(5), pp.1257-1267; discussion 1267-1258.
29. Wilkoff, B.L., Bello, D., Taborsky, M. et al. Magnetic resonance imaging in patients with a pacemaker system designed for the magnetic resonance environment. *Heart Rhythm.* 2011, 8(1), pp.65-73.
30. Brignole, M., Auricchio, A., Baron-Esquivias, G. et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J.* 2013, 34(29), pp.2281-2329.
31. Gimbel, J.R., Bello, D., Schmitt, M. et al. Randomized trial of pacemaker and lead system for safe scanning at 1.5 Tesla. *Heart Rhythm.* 2013, 10(5), pp.685-691.
32. Gold, M.R., Sommer, T., Schwitter, J. et al. Full-Body MRI in Patients With an Implantable Cardioverter-Defibrillator: Primary Results of a Randomized Study. *J Am Coll Cardiol.* 2015, 65(24), pp.2581-2588.
33. Bailey, W.M., Rosenthal, L., Fananapazir, L. et al. Clinical safety of the ProMRI pacemaker system in patients subjected to head and lower lumbar 1.5-T magnetic resonance imaging scanning conditions. *Heart Rhythm.* 2015, 12(6), pp.1183-1191.

34. Awad, K., Griffin, J., Crawford, T.C. et al. Clinical safety of the Iforia implantable cardioverter-defibrillator system in patients subjected to thoracic spine and cardiac 1.5-T magnetic resonance imaging scanning conditions. *Heart Rhythm.* 2015, 12(10), pp.2155-2161.
35. Shenthar, J., Milasinovic, G., Al Fagih, A. et al. MRI scanning in patients with new and existing CapSureFix Novus 5076 pacemaker leads: randomized trial results. *Heart Rhythm.* 2015, 12(4), pp.759-765.
36. Bailey, W.M., Mazur, A., McCotter, C. et al. Clinical safety of the ProMRI pacemaker system in patients subjected to thoracic spine and cardiac 1.5-T magnetic resonance imaging scanning conditions. *Heart Rhythm.* 2016, 13(2), pp.464-471.
37. Ching, C.K., Chakraborty, R.N., Kler, T.S. et al. Clinical safety and performance of a MRI conditional pacing system in patients undergoing cardiac MRI. *Pacing Clin Electrophysiol.* 2017, 40(12), pp.1389-1395.
38. Williamson, B.D., Gohn, D.C., Ramza, B.M. et al. Real-World Evaluation of Magnetic Resonance Imaging in Patients With a Magnetic Resonance Imaging Conditional Pacemaker System: Results of 4-Year Prospective Follow-Up in 2,629 Patients. *JACC Clin Electrophysiol.* 2017, 3(11), pp.1231-1239.
39. Strach, K., Naehle, C.P., Muhlsteffen, A. et al. Low-field magnetic resonance imaging: increased safety for pacemaker patients? *Europace.* 2010, 12(7), pp.952-960.
40. Mollerus, M., Albin, G., Lipinski, M. and Lucca, J. Magnetic resonance imaging of pacemakers and implantable cardioverter-defibrillators without specific absorption rate restrictions. *Europace.* 2010, 12(7), pp.947-951.
41. Nazarian, S., Hansford, R., Roguin, A. et al. A prospective evaluation of a protocol for magnetic resonance imaging of patients with implanted cardiac devices. *Ann Intern Med.* 2011, 155(7), pp.415-424.
42. Cohen, J.D., Costa, H.S. and Russo, R.J. Determining the risks of magnetic resonance imaging at 1.5 tesla for patients with pacemakers and implantable cardioverter defibrillators. *Am J Cardiol.* 2012, 110(11), pp.1631-1636.
43. Friedman, H.L., Acker, N., Dalzell, C. et al. Magnetic resonance imaging in patients with recently implanted pacemakers. *Pacing Clin Electrophysiol.* 2013, 36(9), pp.1090-1095.
44. Muehling, O.M., Wakili, R., Greif, M. et al. Immediate and 12 months follow up of function and lead integrity after cranial MRI in 356 patients with conventional cardiac pacemakers. *J Cardiovasc Magn Reson.* 2014, 16, p.39.
45. Higgins, J.V., Sheldon, S.H., Watson, R.E., Jr. et al. "Power-on resets" in cardiac implantable electronic devices during magnetic resonance imaging. *Heart Rhythm.* 2015, 12(3), pp.540-544.
46. Nazarian, S., Hansford, R., Rahsepar, A.A. et al. Safety of Magnetic Resonance Imaging in Patients with Cardiac Devices. *N Engl J Med.* 2017, 377(26), pp.2555-2564.
47. Mason, S., Osborn, J.S., Dhar, R. et al. Real world MRI experience with nonconditional and conditional cardiac rhythm devices after MagnaSafe. *J Cardiovasc Electrophysiol.* 2017, 28(12), pp.1468-1474.
48. Lupo, P., Cappato, R., Di Leo, G. et al. An eight-year prospective controlled study about the safety and diagnostic value of cardiac and non-cardiac 1.5-T MRI in patients with a conventional pacemaker or a conventional implantable cardioverter defibrillator. *Eur Radiol.* 2018, 28(6), pp.2406-2416.
49. Sasaki, T., Hansford, R., Zviman, M.M. et al. Quantitative assessment of artifacts on cardiac magnetic resonance imaging of patients with pacemakers and implantable cardioverter-defibrillators. *Circ Cardiovasc Imaging.* 2011, 4(6), pp.662-670.
50. Delgado, V., Tops, L.F., Trines, S.A. et al. Acute effects of right ventricular apical pacing on left ventricular synchrony and mechanics. *Circ Arrhythm Electrophysiol.* 2009, 2(2), pp.135-145.

51. Lanzer, P., Barta, C., Botvinick, E.H. et al. ECG-synchronized cardiac MR imaging: method and evaluation. *Radiology.* 1985, 155(3), pp.681-686.
52. van der Graaf, A.W., Bhagirath, P., Ghoerbien, S. and Gotte, M.J. Cardiac magnetic resonance imaging: artefacts for clinicians. *Neth Heart J.* 2014, 22(12), pp.542-549.
53. Kaasalainen, T., Kivisto, S., Holmstrom, M. et al. Cardiac MRI in patients with cardiac pacemakers: practical methods for reducing susceptibility artifacts and optimizing image quality. *Acta Radiol.* 2016, 57(2), pp.178-187.
54. Hilbert, S., Jahnke, C., Loebe, S. et al. Cardiovascular magnetic resonance imaging in patients with cardiac implantable electronic devices: a device-dependent imaging strategy for improved image quality. *Eur Heart J Cardiovasc Imaging.* 2018, 19(9), pp.1051-1061.
55. Thiele, H., Paetsch, I., Schnackenburg, B. et al. Improved accuracy of quantitative assessment of left ventricular volume and ejection fraction by geometric models with steady-state free precession. *J Cardiovasc Magn Reson.* 2002, 4(3), pp.327-339.
56. Schwitter, J., Gold, M.R., Al Fagih, A. et al. Image Quality of Cardiac Magnetic Resonance Imaging in Patients With an Implantable Cardioverter Defibrillator System Designed for the Magnetic Resonance Imaging Environment. *Circ Cardiovasc Imaging.* 2016, 9(5).
57. Klein-Wiele, O., Garmer, M., Busch, M. et al. Cardiovascular magnetic resonance in patients with magnetic resonance conditional pacemaker systems at 1.5 T: influence of pacemaker related artifacts on image quality including first pass perfusion, aortic and mitral valve assessment, flow measurement, short tau inversion recovery and T1-weighted imaging. *Int J Cardiovasc Imaging.* 2017, 33(3), pp.383-394.
58. Raphael, C.E., Vassiliou, V., Alpendurada, F. et al. Clinical value of cardiovascular magnetic resonance in patients with MR-conditional pacemakers. *Eur Heart J Cardiovasc Imaging.* 2016, 17(10), pp.1178-1185.
59. Schwitter, J., Kanal, E., Schmitt, M. et al. Impact of the Advisa MRI pacing system on the diagnostic quality of cardiac MR images and contraction patterns of cardiac muscle during scans: Advisa MRI randomized clinical multicenter study results. *Heart Rhythm.* 2013, 10(6), pp.864-872.
60. Toff, W.D., Camm, A.J., Skehan, J.D., United Kingdom, P. and Cardiovascular Events Trial, I. Single-chamber versus dual-chamber pacing for high-grade atrioventricular block. *N Engl J Med.* 2005, 353(2), pp.145-155.
61. Klein-Wiele, O., Garmer, M., Urbien, R. et al. Feasibility and safety of adenosine cardiovascular magnetic resonance in patients with MR conditional pacemaker systems at 1.5 Tesla. *J Cardiovasc Magn Reson.* 2015, 17, p.112.
62. Messroghli, D.R., Moon, J.C., Ferreira, V.M. et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). *J Cardiovasc Magn Reson.* 2017, 19(1), p.75.
63. Hong, K., Jeong, E.K., Wall, T.S., Drakos, S.G. and Kim, D. Wideband arrhythmia-Insensitive-rapid (AIR) pulse sequence for cardiac T1 mapping without image artifacts induced by an implantable-cardioverter-defibrillator. *Magn Reson Med.* 2015, 74(2), pp.336-345.
64. Shao, J., Rashid, S., Renella, P., Nguyen, K.L. and Hu, P. Myocardial T1 mapping for patients with implanted cardiac devices using wideband inversion recovery spoiled gradient echo readout. *Magn Reson Med.* 2017, 77(4), pp.1495-1504.
65. Weng, Z., Yao, J., Chan, R.H. et al. Prognostic Value of LGE-CMR in HCM: A Meta-Analysis. *JACC Cardiovasc Imaging.* 2016, 9(12), pp.1392-1402.
66. Hulten, E., Agarwal, V., Cahill, M. et al. Presence of Late Gadolinium Enhancement by Cardiac Magnetic Resonance Among Patients With Suspected Cardiac Sarcoidosis Is Associated With Adverse Cardiovascular

Prognosis: A Systematic Review and Meta-Analysis. *Circ Cardiovasc Imaging.* 2016, 9(9), p.e005001.

67. Becker, M.A.J., Cornel, J.H., van de Ven, P.M. et al. The Prognostic Value of Late Gadolinium-Enhanced Cardiac Magnetic Resonance Imaging in Nonischemic Dilated Cardiomyopathy: A Review and Meta-Analysis. *JACC Cardiovasc Imaging.* 2018, 11(9), pp.1274-1284.
68. Ganesan, A.N., Gunton, J., Nucifora, G., McGavigan, A.D. and Selvanayagam, J.B. Impact of Late Gadolinium Enhancement on mortality, sudden death and major adverse cardiovascular events in ischemic and nonischemic cardiomyopathy: A systematic review and meta-analysis. *Int J Cardiol.* 2018, 254, pp.230-237.
69. Raina, S., Lensing, S.Y., Nairooz, R.S. et al. Prognostic Value of Late Gadolinium Enhancement CMR in Systemic Amyloidosis. *JACC Cardiovasc Imaging.* 2016, 9(11), pp.1267-1277.
70. Bhuva, A.N., Kellman, P., Graham, A. et al. Clinical impact of cardiovascular magnetic resonance with optimized myocardial scar detection in patients with cardiac implantable devices. *Int J Cardiol.* 2019, 279, pp.72-78.
71. Hilbert, S., Weber, A., Nehrke, K. et al. Artefact-free late gadolinium enhancement imaging in patients with implanted cardiac devices using a modified broadband sequence: current strategies and results from a real-world patient cohort. *Europace.* 2018, 20(5), pp.801-807.
72. Kim, R.J., Wu, E., Rafael, A. et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med.* 2000, 343(20), pp.1445-1453.
73. Rashid, S., Rapacchi, S., Vaseghi, M. et al. Improved late gadolinium enhancement MR imaging for patients with implanted cardiac devices. *Radiology.* 2014, 270(1), pp.269-274.
74. Elmqvist R and A., S. An implantable pacemaker for the heart. *In: Smyth CN, editor. Proceedings of the Second International Conference on Medical Electronics. London: Iliffe; 1959. p.253.* 1959.
75. van Hemel, N.M. and van der Wall, E.E. 8 October 1958, D Day for the implantable pacemaker. *Neth Heart J.* 2008, 16(Suppl 1), pp.S3-4.
76. Wiggers C. The muscular reactions of the mammalian ventricles to artificial surface stimuli. *American Journal of Physiology.* 1925, 37C, pp.275-282.
77. Prinzen, F.W., Hunter, W.C., Wyman, B.T. and McVeigh, E.R. Mapping of regional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. *J Am Coll Cardiol.* 1999, 33(6), pp.1735-1742.
78. Nielsen, J.C., Andersen, H.R., Thomsen, P.E. et al. Heart failure and echocardiographic changes during long-term follow-up of patients with sick sinus syndrome randomized to single-chamber atrial or ventricular pacing. *Circulation.* 1998, 97(10), pp.987-995.
79. Lamas, G.A., Lee, K.L., Sweeney, M.O. et al. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. *N Engl J Med.* 2002, 346(24), pp.1854-1862.
80. Wilkoff, B.L., Cook, J.R., Epstein, A.E. et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA.* 2002, 288(24), pp.3115-3123.
81. Durrer, D., van Dam, R.T., Freud, G.E. et al. Total excitation of the isolated human heart. *Circulation.* 1970, 41(6), pp.899-912.
82. Ramanathan, C., Ghanem, R.N., Jia, P., Ryu, K. and Rudy, Y. Noninvasive electrocardiographic imaging for cardiac electrophysiology and arrhythmia. *Nat Med.* 2004, 10(4), pp.422-428.
83. Tops, L.F., Schalij, M.J., Holman, E.R. et al. Right ventricular pacing can induce ventricular dyssynchrony in patients with atrial fibrillation after atrioventricular node ablation. *J Am Coll Cardiol.* 2006, 48(8), pp.1642-1648.

84. Vassallo, J.A., Cassidy, D.M., Miller, J.M. et al. Left ventricular endocardial activation during right ventricular pacing: effect of underlying heart disease. *J Am Coll Cardiol.* 1986, 7(6), pp.1228-1233.
85. Servier Medical ART. [Online]. 2020. [Accessed 19 June 2019]. Available from: https://smart.servier.com/
86. Prinzen, F.W. and Peschar, M. Relation between the pacing induced sequence of activation and left ventricular pump function in animals. *Pacing Clin Electrophysiol.* 2002, 25(4 Pt 1), pp.484-498.
87. Baller, D., Wolpers, H.G., Zipfel, J., Bretschneider, H.J. and Hellige, G. Comparison of the effects of right atrial, right ventricular apex and atrioventricular sequential pacing on myocardial oxygen consumption and cardiac efficiency: a laboratory investigation. *Pacing Clin Electrophysiol.* 1988, 11(4), pp.394-403.
88. Delhaas, T., Arts, T., Prinzen, F.W. and Reneman, R.S. Regional fibre stress-fibre strain area as an estimate of regional blood flow and oxygen demand in the canine heart. *J Physiol.* 1994, 477 (Pt 3), pp.481-496.
89. Prinzen, F.W., Augustijn, C.H., Arts, T., Allessie, M.A. and Reneman, R.S. Redistribution of myocardial fiber strain and blood flow by asynchronous activation. *Am J Physiol.* 1990, 259(2 Pt 2), pp.H300-308.
90. Kleber, A.G., Janse, M.J., Wilms-Schopmann, F.J., Wilde, A.A. and Coronel, R. Changes in conduction velocity during acute ischemia in ventricular myocardium of the isolated porcine heart. *Circulation.* 1986, 73(1), pp.189-198.
91. Zile, M.R., Blaustein, A.S., Shimizu, G. and Gaasch, W.H. Right ventricular pacing reduces the rate of left ventricular relaxation and filling. *J Am Coll Cardiol.* 1987, 10(3), pp.702-709.
92. Maurer, G., Torres, M.A., Corday, E., Haendchen, R.V. and Meerbaum, S. Two-dimensional echocardiographic contrast assessment of pacing-induced mitral regurgitation: relation to altered regional left ventricular function. *J Am Coll Cardiol.* 1984, 3(4), pp.986-991.
93. van Oosterhout, M.F., Prinzen, F.W., Arts, T. et al. Asynchronous electrical activation induces asymmetrical hypertrophy of the left ventricular wall. *Circulation.* 1998, 98(6), pp.588-595.
94. Prinzen, F.W., Cheriex, E.C., Delhaas, T. et al. Asymmetric thickness of the left ventricular wall resulting from asynchronous electric activation: a study in dogs with ventricular pacing and in patients with left bundle branch block. *Am Heart J.* 1995, 130(5), pp.1045-1053.
95. Lee, M.A., Dae, M.W., Langberg, J.J. et al. Effects of long-term right ventricular apical pacing on left ventricular perfusion, innervation, function and histology. *J Am Coll Cardiol.* 1994, 24(1), pp.225-232.
96. Karpawich, P.P., Justice, C.D., Cavitt, D.L. and Chang, C.H. Developmental sequelae of fixed-rate ventricular pacing in the immature canine heart: an electrophysiologic, hemodynamic, and histopathologic evaluation. *Am Heart J.* 1990, 119(5), pp.1077-1083.
97. Spragg, D.D., Leclercq, C., Loghmani, M. et al. Regional alterations in protein expression in the dyssynchronous failing heart. *Circulation.* 2003, 108(8), pp.929-932.
98. Klug, D., Boule, S., Wissocque, L. et al. Right ventricular pacing with mechanical dyssynchrony causes apoptosis interruptus and calcium mishandling. *Can J Cardiol.* 2013, 29(4), pp.510-518.
99. Liu, W.H., Chen, M.C., Chen, Y.L. et al. Right ventricular apical pacing acutely impairs left ventricular function and induces mechanical dyssynchrony in patients with sick sinus syndrome: a real-time three-dimensional echocardiographic study. *J Am Soc Echocardiogr.* 2008, 21(3), pp.224-229.
100. Matsuoka, K., Nishino, M., Kato, H. et al. Right ventricular apical pacing impairs left ventricular twist as well as synchrony: acute effects of right ventricular apical pacing. *J Am Soc Echocardiogr.* 2009, 22(8), pp.914-919; quiz 970-911.

101. Fang, F., Chan, J.Y., Yip, G.W. et al. Prevalence and determinants of left ventricular systolic dyssynchrony in patients with normal ejection fraction received right ventricular apical pacing: a real-time three-dimensional echocardiographic study. *Eur J Echocardiogr.* 2010, 11(2), pp.109-118.
102. Bank, A.J., Schwartzman, D.S., Burns, K.V. et al. Intramural dyssynchrony from acute right ventricular apical pacing in human subjects with normal left ventricular function. *J Cardiovasc Transl Res.* 2010, 3(4), pp.321-329.
103. Sato-Iino, T., Watanabe, H., Koyama, T. et al. The prevalence of apical wall motion abnormalities in patients with long-term right ventricular apical pacing. *J Am Soc Echocardiogr.* 2011, 24(5), pp.556-564 e551.
104. Saito, M., Kaye, G., Negishi, K. et al. Dyssynchrony, contraction efficiency and regional function with apical and non-apical RV pacing. *Heart.* 2015, 101(8), pp.600-608.
105. Al-Hesayen, A. and Parker, J.D. Adverse effects of atrioventricular synchronous right ventricular pacing on left ventricular sympathetic activity, efficiency, and hemodynamic status. *Am J Physiol Heart Circ Physiol.* 2006, 291(5), pp.H2377-2379.
106. Thambo, J.B., Bordachar, P., Garrigue, S. et al. Detrimental ventricular remodeling in patients with congenital complete heart block and chronic right ventricular apical pacing. *Circulation.* 2004, 110(25), pp.3766-3772.
107. Karpawich, P.P., Rabah, R. and Haas, J.E. Altered cardiac histology following apical right ventricular pacing in patients with congenital atrioventricular block. *Pacing Clin Electrophysiol.* 1999, 22(9), pp.1372-1377.
108. Tse, H.F. and Lau, C.P. Long-term effect of right ventricular pacing on myocardial perfusion and function. *J Am Coll Cardiol.* 1997, 29(4), pp.744-749.
109. Lakkis, N.M., He, Z.X. and Verani, M.S. Diagnosis of coronary artery disease by exercise thallium-201 tomography in patients with a right ventricular pacemaker. *J Am Coll Cardiol.* 1997, 29(6), pp.1221-1225.
110. Tse, H.F., Yu, C., Wong, K.K. et al. Functional abnormalities in patients with permanent right ventricular pacing: the effect of sites of electrical stimulation. *J Am Coll Cardiol.* 2002, 40(8), pp.1451-1458.
111. Nielsen, J.C., Bottcher, M., Nielsen, T.T., Pedersen, A.K. and Andersen, H.R. Regional myocardial blood flow in patients with sick sinus syndrome randomized to long-term single chamber atrial or dual chamber pacing--effect of pacing mode and rate. *J Am Coll Cardiol.* 2000, 35(6), pp.1453-1461.
112. Barold, S.S. and Ovsyshcher, I.E. Pacemaker-induced mitral regurgitation. *Pacing Clin Electrophysiol.* 2005, 28(5), pp.357-360.
113. Preumont, N., Jansens, J.L., Berkenboom, G. et al. Effects of right ventricular pacing on regional myocardial glucose metabolism. *Europace.* 2005, 7(6), pp.584-591.
114. Choy, A.M., Su, H.H., Elder, D.H. et al. Right ventricular pacing impairs endothelial function in man. *Europace.* 2011, 13(6), pp.853-858.
115. Khurshid, S., Epstein, A.E., Verdino, R.J. et al. Incidence and predictors of right ventricular pacing-induced cardiomyopathy. *Heart Rhythm.* 2014, 11(9), pp.1619-1625.
116. Kim, J.H., Kang, K.W., Chin, J.Y. et al. Major determinant of the occurrence of pacing-induced cardiomyopathy in complete atrioventricular block: a multicentre, retrospective analysis over a 15-year period in South Korea. *BMJ Open.* 2018, 8(2), p.e019048.
117. Kiehl, E.L., Makki, T., Kumar, R. et al. Incidence and predictors of right ventricular pacing-induced cardiomyopathy in patients with complete atrioventricular block and preserved left ventricular systolic function. *Heart Rhythm.* 2016, 13(12), pp.2272-2278.
118. Kaye, G., Ng, J.Y., Ahmed, S. et al. The Prevalence of Pacing-Induced Cardiomyopathy (PICM) in Patients With Long Term Right Ventricular Pacing - Is it a Matter Of Definition? *Heart Lung Circ.* 2018.

119. Ahmed, F.Z., Motwani, M., Cunnington, C. et al. One-Month Global Longitudinal Strain Identifies Patients Who Will Develop Pacing-Induced Left Ventricular Dysfunction over Time: The Pacing and Ventricular Dysfunction (PAVD) Study. *PLoS One.* 2017, 12(1), p.e0162072.
120. Kachboura, S., Ben Halima, A., Fersi, I. et al. Assessment of heart failure and left ventricular systolic dysfunction after cardiac pacing in patients with preserved left ventricular systolic function. *Ann Cardiol Angeiol (Paris).* 2008, 57(1), pp.29-36.
121. Dreger, H., Maethner, K., Bondke, H., Baumann, G. and Melzer, C. Pacing-induced cardiomyopathy in patients with right ventricular stimulation for >15 years. *Europace.* 2012, 14(2), pp.238-242.
122. Khurshid, S., Liang, J.J., Owens, A. et al. Longer Paced QRS Duration is Associated With Increased Prevalence of Right Ventricular Pacing-Induced Cardiomyopathy. *J Cardiovasc Electrophysiol.* 2016, 27(10), pp.1174-1179.
123. Cho, S.W., Gwag, H.B., Hwang, J.K. et al. Clinical features, predictors, and long-term prognosis of pacing-induced cardiomyopathy. *Eur J Heart Fail.* 2019.
124. Lee, W.C., Fang, H.Y., Chen, H.C. et al. Post-pacemaker implant QRS duration and heart failure admission in patients with sick sinus syndrome and complete atrioventricular block. *ESC Heart Fail.* 2019.
125. Safak, E., Ince, H., Gkouvatsou, L. et al. Pacing-induced cardiomyopathy in chronic right ventricular apical pacing: a midterm follow-up study. *Eur J Med Res.* 2019, 24(1), p.23.
126. Sweeney, M.O., Hellkamp, A.S., Ellenbogen, K.A. et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation.* 2003, 107(23), pp.2932-2937.
127. Curtis, A.B., Worley, S.J., Adamson, P.B. et al. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med.* 2013, 368(17), pp.1585-1593.
128. Merchant, F.M., Hoskins, M.H., Musat, D.L. et al. Incidence and Time Course for Developing Heart Failure With High-Burden Right Ventricular Pacing. *Circ Cardiovasc Qual Outcomes.* 2017, 10(6).
129. White, H.D., Norris, R.M., Brown, M.A. et al. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation.* 1987, 76(1), pp.44-51.
130. Yu, C.M., Bleeker, G.B., Fung, J.W. et al. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. *Circulation.* 2005, 112(11), pp.1580-1586.
131. Yu, C.M., Fung, W.H., Lin, H. et al. Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. *Am J Cardiol.* 2003, 91(6), pp.684-688.
132. Lee, S.A., Cha, M.J., Cho, Y. et al. Paced QRS duration and myocardial scar amount: predictors of long-term outcome of right ventricular apical pacing. *Heart Vessels.* 2016, 31(7), pp.1131-1139.
133. Mazza, A., Bendini, M.G., Leggio, M. et al. Incidence and predictors of heart failure hospitalization and death in permanent pacemaker patients: a single-centre experience over medium-term follow-up. *Europace.* 2013, 15(9), pp.1267-1272.
134. Sweeney, M.O. and Hellkamp, A.S. Heart failure during cardiac pacing. *Circulation.* 2006, 113(17), pp.2082-2088.
135. Antoni, M.L., Boden, H., Hoogslag, G.E. et al. Prevalence of dyssynchrony and relation with long-term outcome in patients after acute myocardial infarction. *Am J Cardiol.* 2011, 108(12), pp.1689-1696.
136. Schietinger, B.J., Brammer, G.M., Wang, H. et al. Patterns of late gadolinium enhancement in chronic hemodialysis patients. *JACC Cardiovasc Imaging.* 2008, 1(4), pp.450-456.

137. Sharma, A.D., Rizo-Patron, C., Hallstrom, A.P. et al. Percent right ventricular pacing predicts outcomes in the DAVID trial. *Heart Rhythm.* 2005, 2(8), pp.830-834.
138. Sohn, J., Lee, Y.S., Park, H.S., Han, S. and Kim, Y.N. Predictors of an adverse clinical outcome in patients with long-term right ventricular apical pacing. *J Cardiol.* 2017, 70(5), pp.420-424.
139. Xu, H., Li, J., Bao, Z. et al. Early Change in Global Longitudinal Strain is an Independent Predictor of Left Ventricular Adverse Remodelling in Patients With Right Ventricular Apical Pacing. *Heart Lung Circ.* 2018.
140. Fent, G.J., Garg, P., Foley, J.R.J. et al. The utility of global longitudinal strain in the identification of prior myocardial infarction in patients with preserved left ventricular ejection fraction. *Int J Cardiovasc Imaging.* 2017, 33(10), pp.1561-1569.
141. Udo, E.O., van Hemel, N.M., Zuithoff, N.P., Doevendans, P.A. and Moons, K.G. Risk of heart failure- and cardiac death gradually increases with more right ventricular pacing. *Int J Cardiol.* 2015, 185, pp.95-100.
142. Auger, D., Hoke, U., Marsan, N.A. et al. Effect of induced LV dyssynchrony by right ventricular apical pacing on all-cause mortality and heart failure hospitalization rates at long-term follow-up. *J Cardiovasc Electrophysiol.* 2014, 25(6), pp.631-637.
143. Zhang, X.H., Chen, H., Siu, C.W. et al. New-onset heart failure after permanent right ventricular apical pacing in patients with acquired high-grade atrioventricular block and normal left ventricular function. *J Cardiovasc Electrophysiol.* 2008, 19(2), pp.136-141.
144. Moss, A.J., Hall, W.J., Cannom, D.S. et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med.* 2009, 361(14), pp.1329-1338.
145. Cleland, J.G., Daubert, J.C., Erdmann, E. et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med.* 2005, 352(15), pp.1539-1549.
146. Bristow, M.R., Saxon, L.A., Boehmer, J. et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med.* 2004, 350(21), pp.2140-2150.
147. Vatankulu, M.A., Goktekin, O., Kaya, M.G. et al. Effect of long-term resynchronization therapy on left ventricular remodeling in pacemaker patients upgraded to biventricular devices. *Am J Cardiol.* 2009, 103(9), pp.1280-1284.
148. Sideris, S., Poulidakis, E., Aggeli, C. et al. Upgrading pacemaker to cardiac resynchronization therapy: an option for patients with chronic right ventricular pacing and heart failure. *Hellenic J Cardiol.* 2014, 55(1), pp.17-23.
149. Foley, P.W., Muhyaldeen, S.A., Chalil, S. et al. Long-term effects of upgrading from right ventricular pacing to cardiac resynchronization therapy in patients with heart failure. *Europace.* 2009, 11(4), pp.495-501.
150. Kosztin, A., Vamos, M., Aradi, D. et al. De novo implantation vs. upgrade cardiac resynchronization therapy: a systematic review and meta-analysis. *Heart Fail Rev.* 2018, 23(1), pp.15-26.
151. van Geldorp, I.E., Vernooy, K., Delhaas, T. et al. Beneficial effects of biventricular pacing in chronically right ventricular paced patients with mild cardiomyopathy. *Europace.* 2010, 12(2), pp.223-229.
152. Gierula, J., Cubbon, R.M., Jamil, H.A. et al. Cardiac resynchronization therapy in pacemaker-dependent patients with left ventricular dysfunction. *Europace.* 2013, 15(11), pp.1609-1614.
153. Kindermann, M., Hennen, B., Jung, J. et al. Biventricular versus conventional right ventricular stimulation for patients with standard pacing indication and left ventricular dysfunction: the Homburg Biventricular Pacing Evaluation (HOBIPACE). *J Am Coll Cardiol.* 2006, 47(10), pp.1927-1937.

154. Martinelli Filho, M., de Siqueira, S.F., Costa, R. et al. Conventional versus biventricular pacing in heart failure and bradyarrhythmia: the COMBAT study. *J Card Fail.* 2010, 16(4), pp.293-300.
155. Curtis, A.B., Worley, S.J., Chung, E.S. et al. Improvement in Clinical Outcomes With Biventricular Versus Right Ventricular Pacing: The BLOCK HF Study. *J Am Coll Cardiol.* 2016, 67(18), pp.2148-2157.
156. St John Sutton, M., Plappert, T., Adamson, P.B. et al. Left Ventricular Reverse Remodeling With Biventricular Versus Right Ventricular Pacing in Patients With Atrioventricular Block and Heart Failure in the BLOCK HF Trial. *Circ Heart Fail.* 2015, 8(3), pp.510-518.
157. Albertsen, A.E., Nielsen, J.C., Poulsen, S.H. et al. Biventricular pacing preserves left ventricular performance in patients with high-grade atrio-ventricular block: a randomized comparison with DDD(R) pacing in 50 consecutive patients. *Europace.* 2008, 10(3), pp.314-320.
158. Albertsen, A.E., Mortensen, P.T., Jensen, H.K. et al. Adverse effect of right ventricular pacing prevented by biventricular pacing during long-term follow-up: a randomized comparison. *Eur J Echocardiogr.* 2011, 12(10), pp.767-772.
159. Yu, C.M., Chan, J.Y., Zhang, Q. et al. Biventricular pacing in patients with bradycardia and normal ejection fraction. *N Engl J Med.* 2009, 361(22), pp.2123-2134.
160. Yu, C.M., Fang, F., Luo, X.X. et al. Long-term follow-up results of the pacing to avoid cardiac enlargement (PACE) trial. *Eur J Heart Fail.* 2014, 16(9), pp.1016-1025.
161. Stockburger, M., Gomez-Doblas, J.J., Lamas, G. et al. Preventing ventricular dysfunction in pacemaker patients without advanced heart failure: results from a multicentre international randomized trial (PREVENT-HF). *Eur J Heart Fail.* 2011, 13(6), pp.633-641.
162. Blanc JJ, F.R., Lunati M et al. *Biopace Trial Premliminary Results:* Biventricular Pacing for Atrio-ventricular Block to Prevent Cardiac Desynchronization. [Online] 2014. [Accessed 24 March 2020]. Available from: http://clinicaltrialresults.org/Slides/TCT%202014/Blanc_Biopace.pdf
163. Funck, R.C., Mueller, H.H., Lunati, M. et al. Characteristics of a large sample of candidates for permanent ventricular pacing included in the Biventricular Pacing for Atrio-ventricular Block to Prevent Cardiac Desynchronization Study (BioPace). *Europace.* 2014, 16(3), pp.354-362.
164. Slotwiner, D.J., Raitt, M.H., Del-Carpio Munoz, F. et al. Impact of Physiologic Pacing Versus Right Ventricular Pacing Among Patients With Left Ventricular Ejection Fraction Greater Than 35%: A Systematic Review for the 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay. *J Am Coll Cardiol.* 2018.
165. Lu, D., Zhang, H. and Zhang, H. Cardiac resynchronization therapy improves left ventricular remodeling and function compared with right ventricular pacing in patients with atrioventricular block. *Heart Fail Rev.* 2018, 23(6), pp.919-926.
166. Lu, D., Zhang, H., Chen, C., Wang, K. and Shan, Q. Clinical outcomes with biventricular versus right ventricular pacing in patients with atrioventricular conduction defects. *Heart Fail Rev.* 2018, 23(6), pp.897-906.
167. Zhuang, L., Mao, Y., Wu, L., Niu, W. and Chen, K. Effects of right ventricular septum or His-bundle pacing versus right ventricular apical pacing on cardiac function: A systematic review and meta-analysis of randomized controlled trials. *J Int Med Res.* 2018, p.300060518781415.
168. Kaye, G.C., Linker, N.J., Marwick, T.H. et al. Effect of right ventricular pacing lead site on left ventricular function in patients with high-grade atrioventricular block: results of the Protect-Pace study. *Eur Heart J.* 2015, 36(14), pp.856-862.
169. Muto, C., Calvi, V., Botto, G.L. et al. Chronic Apical and Nonapical Right Ventricular Pacing in Patients with High-Grade Atrioventricular Block: Results of the Right Pace Study. *Biomed Res Int.* 2018, p.1404659.

170. El-Sherif, N., Amay, Y.L.F., Schonfield, C. et al. Normalization of bundle branch block patterns by distal His bundle pacing. Clinical and experimental evidence of longitudinal dissociation in the pathologic his bundle. *Circulation.* 1978, 57(3), pp.473-483.
171. Occhetta, E., Bortnik, M., Magnani, A. et al. Prevention of ventricular desynchronization by permanent para-Hisian pacing after atrioventricular node ablation in chronic atrial fibrillation: a crossover, blinded, randomized study versus apical right ventricular pacing. *J Am Coll Cardiol.* 2006, 47(10), pp.1938-1945.
172. Pastore, G., Zanon, F., Baracca, E. et al. The risk of atrial fibrillation during right ventricular pacing. *Europace.* 2016, 18(3), pp.353-358.
173. Kronborg, M.B., Mortensen, P.T., Poulsen, S.H. et al. His or para-His pacing preserves left ventricular function in atrioventricular block: a double-blind, randomized, crossover study. *Europace.* 2014, 16(8), pp.1189-1196.
174. Yu, Z., Chen, R., Su, Y. et al. Integrative and quantitive evaluation of the efficacy of his bundle related pacing in comparison with conventional right ventricular pacing: a meta-analysis. *BMC Cardiovasc Disord.* 2017, 17(1), p.221.
175. Vijayaraman, P., Naperkowski, A., Subzposh, F.A. et al. Permanent His-bundle pacing: Long-term lead performance and clinical outcomes. *Heart Rhythm.* 2018, 15(5), pp.696-702.
176. Abdelrahman, M., Subzposh, F.A., Beer, D. et al. Clinical Outcomes of His Bundle Pacing Compared to Right Ventricular Pacing. *J Am Coll Cardiol.* 2018, 71(20), pp.2319-2330.
177. Keene, D., Arnold, A., Shun-Shin, M.J. et al. Rationale and design of the randomized multicentre His Optimized Pacing Evaluated for Heart Failure (HOPE-HF) trial. *ESC Heart Fail.* 2018, 5(5), pp965-976.
178. Shan, P., Su, L., Zhou, X. et al. Beneficial effects of upgrading to His bundle pacing in chronically paced patients with left ventricular ejection fraction <50. *Heart Rhythm.* 2018, 15(3), pp.405-412.
179. Sweeney, M.O., Bank, A.J., Nsah, E. et al. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. *N Engl J Med.* 2007, 357(10), pp.1000-1008.
180. Stockburger, M., Boveda, S., Moreno, J. et al. Long-term clinical effects of ventricular pacing reduction with a changeover mode to minimize ventricular pacing in a general pacemaker population. *Eur Heart J.* 2015, 36(3), pp.151-157.
181. Stockburger, M., Defaye, P., Boveda, S. et al. Safety and efficiency of ventricular pacing prevention with an AAI-DDD changeover mode in patients with sinus node disease or atrioventricular block: impact on battery longevity-a sub-study of the ANSWER trial. *Europace.* 2016, 18(5), pp.739-746.
182. Shurrab, M., Healey, J.S., Haj-Yahia, S. et al. Reduction in unnecessary ventricular pacing fails to affect hard clinical outcomes in patients with preserved left ventricular function: a meta-analysis. *Europace.* 2017, 19(2), pp.282-288.
183. Gierula, J., Jamil, H.A., Byrom, R. et al. Pacing-associated left ventricular dysfunction? Think reprogramming first! *Heart.* 2014, 100(10), pp.765-769.
184. Vijayaraman, P., Bordachar, P. and Ellenbogen, K.A. The Continued Search for Physiological Pacing: Where Are We Now? *J Am Coll Cardiol.* 2017, 69(25), pp.3099-3114.
185. Sweeney, M.O., Ellenbogen, K.A., Tang, A.S. et al. Atrial pacing or ventricular backup-only pacing in implantable cardioverter-defibrillator patients. *Heart Rhythm.* 2010, 7(11), pp.1552-1560.
186. Ponikowski, P., Voors, A.A., Anker, S.D. et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the

Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2016, 18(8), pp.891-975.
187. Schwerg, M., Dreger, H., Poller, W.C., Dust, B. and Melzer, C. Efficacy of optimal medical therapy and cardiac resynchronization therapy upgrade in patients with pacemaker-induced cardiomyopathy. *J Interv Card Electrophysiol.* 2015, 44(3), pp.289-296.
188. Doshi, R.N., Daoud, E.G., Fellows, C. et al. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). *J Cardiovasc Electrophysiol.* 2005, 16(11), pp.1160-1165.
189. Brignole, M., Botto, G., Mont, L. et al. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. *Eur Heart J.* 2011, 32(19), pp.2420-2429.
190. Ezekowitz, J.A., O'Meara, E., McDonald, M.A. et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. *Can J Cardiol.* 2017, 33(11), pp.1342-1433.
191. Kusumoto, F.M., Schoenfeld, M.H., Barrett, C. et al. 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. *J Am Coll Cardiol.* 2018.
192. Writing Committee, M., Yancy, C.W., Jessup, M. et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation.* 2013, 128(16), pp.e240-327.
193. Taylor, C.J., Ordonez-Mena, J.M., Roalfe, A.K. et al. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study. *BMJ.* 2019, 364, p.l223.
194. Poole, J.E., Gleva, M.J., Mela, T. et al. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: results from the REPLACE registry. *Circulation.* 2010, 122(16), pp.1553-1561.
195. Ooka, J., Tanaka, H., Hatani, Y. et al. Risk Stratification of Future Left Ventricular Dysfunction for Patients with Indications for Right Ventricular Pacing due to Bradycardia. *Int Heart J.* 2017, 58(5), pp.724-730.
196. Babu, N.M.S., Srinath, S.C., Lahiri, A. et al. Three-dimensional echocardiography with left ventricular strain analyses helps earlier prediction of right ventricular pacing-induced cardiomyopathy. *J Saudi Heart Assoc.* 2018, 30(2), pp.102-107.
197. Bank, A.J., Gage, R.M. and Burns, K.V. Right ventricular pacing, mechanical dyssynchrony, and heart failure. *J Cardiovasc Transl Res.* 2012, 5(2), pp.219-231.
198. Papadopoulou, E., Kaladaridou, A., Mattheou, J. et al. Effect of pacing mode and pacing site on torsional and strain parameters and on coronary flow. *J Am Soc Echocardiogr.* 2015, 28(3), pp.347-354.
199. Pastore, G., Noventa, F., Piovesana, P. et al. Left ventricular dyssynchrony resulting from right ventricular apical pacing: relevance of baseline assessment. *Pacing Clin Electrophysiol.* 2008, 31(11), pp.1456-1462.
200. Albertsen, A.E., Nielsen, J.C., Poulsen, S.H. et al. DDD(R)-pacing, but not AAI(R)-pacing induces left ventricular desynchronization in patients with sick sinus syndrome: tissue-Doppler and 3D echocardiographic evaluation in a randomized controlled comparison. *Europace.* 2008, 10(2), pp.127-133.
201. Fang, F., Luo, X.X., Zhang, Q. et al. Deterioration of left ventricular systolic function in extended Pacing to Avoid Cardiac Enlargement (PACE) trial: the predictive value of early systolic dyssynchrony. *Europace.* 2015, 17 Suppl 2, pp.ii47-53.

202. Nordbeck, P., Ertl, G. and Ritter, O. Magnetic resonance imaging safety in pacemaker and implantable cardioverter defibrillator patients: how far have we come? *Eur Heart J.* 2015, 36(24), pp.1505-1511.
203. Grothues, F., Moon, J.C., Bellenger, N.G. et al. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. *Am Heart J.* 2004, 147(2), pp.218-223.
204. Grothues, F., Smith, G.C., Moon, J.C. et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol.* 2002, 90(1), pp.29-34.
205. Rutz, A.K., Manka, R., Kozerke, S. et al. Left ventricular dyssynchrony in patients with left bundle branch block and patients after myocardial infarction: integration of mechanics and viability by cardiac magnetic resonance. *Eur Heart J.* 2009, 30(17), pp.2117-2127.
206. Garot, J., Bluemke, D.A., Osman, N.F. et al. Fast determination of regional myocardial strain fields from tagged cardiac images using harmonic phase MRI. *Circulation.* 2000, 101(9), pp.981-988.
207. Kowallick, J.T., Lamata, P., Hussain, S.T. et al. Quantification of left ventricular torsion and diastolic recoil using cardiovascular magnetic resonance myocardial feature tracking. *PLoS One.* 2014, 9(10), p.e109164.
208. Jiang, K. and Yu, X. Quantification of regional myocardial wall motion by cardiovascular magnetic resonance. *Quant Imaging Med Surg.* 2014, 4(5), pp.345-357.
209. van der Graaf, A.W., Bhagirath, P., Scheffer, M.G., de Medina, R.R. and Gotte, M.J. MR feature tracking in patients with MRI-conditional pacing systems: The impact of pacing. *J Magn Reson Imaging.* 2016, 44(4), pp.964-971.
210. Mahrholdt, H., Wagner, A., Judd, R.M., Sechtem, U. and Kim, R.J. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. *Eur Heart J.* 2005, 26(15), pp.1461-1474.
211. Axelsson, J., Wieslander, B., Jablonowski, R. et al. Ejection fraction in left bundle branch block is disproportionately reduced in relation to amount of myocardial scar. *J Electrocardiol.* 2018, 51(6), pp.1071-1076.
212. Chalil, S., Foley, P.W., Muyhaldeen, S.A. et al. Late gadolinium enhancement-cardiovascular magnetic resonance as a predictor of response to cardiac resynchronization therapy in patients with ischaemic cardiomyopathy. *Europace.* 2007, 9(11), pp.1031-1037.
213. Chalil, S., Stegemann, B., Muhyaldeen, S.A. et al. Effect of posterolateral left ventricular scar on mortality and morbidity following cardiac resynchronization therapy. *Pacing Clin Electrophysiol.* 2007, 30(10), pp.1201-1209.
214. Petryka, J., Misko, J., Przybylski, A. et al. Magnetic resonance imaging assessment of intraventricular dyssynchrony and delayed enhancement as predictors of response to cardiac resynchronization therapy in patients with heart failure of ischaemic and non-ischaemic etiologies. *Eur J Radiol.* 2012, 81(10), pp.2639-2647.
215. Chen, Z., Sohal, M., Sammut, E. et al. Focal But Not Diffuse Myocardial Fibrosis Burden Quantification Using Cardiac Magnetic Resonance Imaging Predicts Left Ventricular Reverse Modeling Following Cardiac Resynchronization Therapy. *J Cardiovasc Electrophysiol.* 2016, 27(2), pp.203-209.
216. Leyva, F., Foley, P.W., Chalil, S. et al. Cardiac resynchronization therapy guided by late gadolinium-enhancement cardiovascular magnetic resonance. *J Cardiovasc Magn Reson.* 2011, 13, p.29.
217. Taylor, R.J., Umar, F., Panting, J.R., Stegemann, B. and Leyva, F. Left ventricular lead position, mechanical activation, and myocardial scar in relation to left ventricular reverse remodeling and clinical outcomes after cardiac resynchronization therapy: A feature-tracking and contrast-enhanced

cardiovascular magnetic resonance study. *Heart Rhythm.* 2016, 13(2), pp.481-489.
218. Puntmann, V.O., Peker, E., Chandrashekhar, Y. and Nagel, E. T1 Mapping in Characterizing Myocardial Disease: A Comprehensive Review. *Circ Res.* 2016, 119(2), pp.277-299.
219. Schelbert, E.B., Piehler, K.M., Zareba, K.M. et al. Myocardial Fibrosis Quantified by Extracellular Volume Is Associated With Subsequent Hospitalization for Heart Failure, Death, or Both Across the Spectrum of Ejection Fraction and Heart Failure Stage. *J Am Heart Assoc.* 2015, 4(12).
220. Puntmann, V.O., Carr-White, G., Jabbour, A. et al. T1-Mapping and Outcome in Nonischemic Cardiomyopathy: All-Cause Mortality and Heart Failure. *JACC Cardiovasc Imaging.* 2016, 9(1), pp.40-50.
221. Dass, S., Suttie, J.J., Piechnik, S.K. et al. Myocardial tissue characterization using magnetic resonance noncontrast t1 mapping in hypertrophic and dilated cardiomyopathy. *Circ Cardiovasc Imaging.* 2012, 5(6), pp.726-733.
222. Ugander, M., Oki, A.J., Hsu, L.Y. et al. Extracellular volume imaging by magnetic resonance imaging provides insights into overt and sub-clinical myocardial pathology. *Eur Heart J.* 2012, 33(10), pp.1268-1278.
223. Puntmann, V.O., Voigt, T., Chen, Z. et al. Native T1 mapping in differentiation of normal myocardium from diffuse disease in hypertrophic and dilated cardiomyopathy. *JACC Cardiovasc Imaging.* 2013, 6(4), pp.475-484.
224. Lin, L.Y., Wu, C.K., Juang, J.M. et al. Myocardial Regional Interstitial Fibrosis is Associated With Left Intra-Ventricular Dyssynchrony in Patients With Heart Failure: A Cardiovascular Magnetic Resonance Study. *Sci Rep.* 2016, 6, p.20711.
225. Engblom, H., Xue, H., Akil, S. et al. Fully quantitative cardiovascular magnetic resonance myocardial perfusion ready for clinical use: a comparison between cardiovascular magnetic resonance imaging and positron emission tomography. *J Cardiovasc Magn Reson.* 2017, 19(1), p.78.
226. Hsu, L.Y., Jacobs, M., Benovoy, M. et al. Diagnostic Performance of Fully Automated Pixel-Wise Quantitative Myocardial Perfusion Imaging by Cardiovascular Magnetic Resonance. *JACC Cardiovasc Imaging.* 2018, 11(5), pp.697-707.
227. van der Geest, R.J. and Garg, P. Advanced Analysis Techniques for Intra-cardiac Flow Evaluation from 4D Flow MRI. *Curr Radiol Rep.* 2016, 4, p.38.
228. Dyverfeldt, P., Bissell, M., Barker, A.J. et al. 4D flow cardiovascular magnetic resonance consensus statement. *J Cardiovasc Magn Reson.* 2015, 17, p.72.
229. Zhang, J.M., Tan, R.S., Zhang, S. et al. Comparison of Image Acquisition Techniques in Four-Dimensional Flow Cardiovascular MR on 3 Tesla in Volunteers and Tetralogy of Fallot Patients. *Conf Proc IEEE Eng Med Biol Soc.* 2018, 2018, pp.1115-1118.
230. Crandon, S., Elbaz, M.S.M., Westenberg, J.J.M. et al. Clinical applications of intra-cardiac four-dimensional flow cardiovascular magnetic resonance: A systematic review. *Int J Cardiol.* 2017, 249, pp.486-493.
231. Garg, P., Westenberg, J.J.M., van den Boogaard, P.J. et al. Comparison of fast acquisition strategies in whole-heart four-dimensional flow cardiac MR: Two-center, 1.5 Tesla, phantom and in vivo validation study. *J Magn Reson Imaging.* 2017.
232. Westenberg, J.J., Roes, S.D., Ajmone Marsan, N. et al. Mitral valve and tricuspid valve blood flow: accurate quantification with 3D velocity-encoded MR imaging with retrospective valve tracking. *Radiology.* 2008, 249(3), pp.792-800.
233. Kanski, M., Arvidsson, P.M., Toger, J. et al. Left ventricular fluid kinetic energy time curves in heart failure from cardiovascular magnetic resonance 4D flow data. *J Cardiovasc Magn Reson.* 2015, 17, p.111.
234. Eriksson, J., Bolger, A.F., Ebbers, T. and Carlhall, C.J. Four-dimensional blood flow-specific markers of LV dysfunction in dilated cardiomyopathy. *Eur Heart J Cardiovasc Imaging.* 2013, 14(5), pp.417-424.

235. Eriksson, J., Zajac, J., Alehagen, U. et al. Left ventricular hemodynamic forces as a marker of mechanical dyssynchrony in heart failure patients with left bundle branch block. *Sci Rep.* 2017, 7(1), p.2971.
236. Cicchitti, V., Radico, F., Bianco, F. et al. Heart failure due to right ventricular apical pacing: the importance of flow patterns. *Europace.* 2016, 18(11), pp.1679-1688.
237. Sengupta, P.P., Khandheria, B.K., Korinek, J. et al. Left ventricular isovolumic flow sequence during sinus and paced rhythms: new insights from use of high-resolution Doppler and ultrasonic digital particle imaging velocimetry. *J Am Coll Cardiol.* 2007, 49(8), pp.899-908.
238. Suwa, K., Saitoh, T., Takehara, Y. et al. Intra-left ventricular flow dynamics in patients with preserved and impaired left ventricular function: Analysis with 3D cine phase contrast MRI (4D-Flow). *J Magn Reson Imaging.* 2016, 44(6), pp.1493-1503.
239. Raatikainen, M.J.P., Arnar, D.O., Merkely, B. et al. A Decade of Information on the Use of Cardiac Implantable Electronic Devices and Interventional Electrophysiological Procedures in the European Society of Cardiology Countries: 2017 Report from the European Heart Rhythm Association. *Europace.* 2017, 19(suppl_2), pp.ii1-ii90.
240. Naehle, C.P., Kreuz, J., Strach, K. et al. Safety, feasibility, and diagnostic value of cardiac magnetic resonance imaging in patients with cardiac pacemakers and implantable cardioverters/defibrillators at 1.5 T. *Am Heart J.* 2011, 161(6), pp.1096-1105.
241. Feneis, J.F., Kyubwa, E., Atianzar, K. et al. 4D flow MRI quantification of mitral and tricuspid regurgitation: Reproducibility and consistency relative to conventional MRI. *J Magn Reson Imaging.* 2018, 48(4), pp.1147-1158.
242. Zhong, L., Schrauben, E.M., Garcia, J. et al. Intracardiac 4D Flow MRI in Congenital Heart Disease: Recommendations on Behalf of the ISMRM Flow & Motion Study Group. *J Magn Reson Imaging.* 2019, 50(3), pp.677-681.
243. Barker, N., Fidock, B., Johns, C.S. et al. A Systematic Review of Right Ventricular Diastolic Assessment by 4D Flow CMR. *Biomed Res Int.* 2019, 2019, p.6074984.
244. Fidock, B., Barker, N., Balasubramanian, N. et al. A Systematic Review of 4D-Flow MRI Derived Mitral Regurgitation Quantification Methods. *Front Cardiovasc Med.* 2019, 6, p.103.
245. Roes, S.D., Hammer, S., van der Geest, R.J. et al. Flow assessment through four heart valves simultaneously using 3-dimensional 3-directional velocity-encoded magnetic resonance imaging with retrospective valve tracking in healthy volunteers and patients with valvular regurgitation. *Invest Radiol.* 2009, 44(10), pp.669-675.
246. Lotz, J., Meier, C., Leppert, A. and Galanski, M. Cardiovascular flow measurement with phase-contrast MR imaging: basic facts and implementation. *Radiographics.* 2002, 22(3), pp.651-671.
247. Galderisi, M., Henein, M.Y., D'Hooge, J. et al. Recommendations of the European Association of Echocardiography: how to use echo-Doppler in clinical trials: different modalities for different purposes. *Eur J Echocardiogr.* 2011, 12(5), pp.339-353.
248. Lancellotti, P., Tribouilloy, C., Hagendorff, A. et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2013, 14(7), pp.611-644.
249. Biner, S., Rafique, A., Rafii, F. et al. Reproducibility of proximal isovelocity surface area, vena contracta, and regurgitant jet area for assessment of mitral regurgitation severity. *JACC Cardiovasc Imaging.* 2010, 3(3), pp.235-243.
250. Kamphuis, V.P., Roest, A.A.W., Ajmone Marsan, N. et al. Automated Cardiac Valve Tracking for Flow Quantification with Four-dimensional Flow MRI. *Radiology.* 2019, 290(1), pp.70-78.

251. Kamphuis, V.P., van der Palen, R.L.F., de Koning, P.J.H. et al. In-scan and scan-rescan assessment of LV in- and outflow volumes by 4D flow MRI versus 2D planimetry. *J Magn Reson Imaging.* 2018, 47(2), pp.511-522.
252. Chelu, R.G., Horowitz, M., Sucha, D. et al. Evaluation of atrial septal defects with 4D flow MRI-multilevel and inter-reader reproducibility for quantification of shunt severity. *MAGMA.* 2019, 32(2), pp.269-279.
253. Hsiao, A., Tariq, U., Alley, M.T., Lustig, M. and Vasanawala, S.S. Inlet and outlet valve flow and regurgitant volume may be directly and reliably quantified with accelerated, volumetric phase-contrast MRI. *J Magn Reson Imaging.* 2015, 41(2), pp.376-385.
254. Tops, L.F., Schalij, M.J. and Bax, J.J. The effects of right ventricular apical pacing on ventricular function and dyssynchrony implications for therapy. *J Am Coll Cardiol.* 2009, 54(9), pp.764-776.
255. Garg, P., Crandon, S., Swoboda, P.P. et al. Left ventricular blood flow kinetic energy after myocardial infarction - insights from 4D flow cardiovascular magnetic resonance. *J Cardiovasc Magn Reson.* 2018, 20(1), p.61.
256. Svalbring, E., Fredriksson, A., Eriksson, J. et al. Altered Diastolic Flow Patterns and Kinetic Energy in Subtle Left Ventricular Remodeling and Dysfunction Detected by 4D Flow MRI. *PLoS One.* 2016, 11(8), p.e0161391.
257. Zajac, J., Eriksson, J., Alehagen, U. et al. Mechanical dyssynchrony alters left ventricular flow energetics in failing hearts with LBBB: a 4D flow CMR pilot study. *Int J Cardiovasc Imaging.* 2018, 34(4), pp.587-596.
258. Bianco, F., Cicchitti, V., Bucciarelli, V. et al. Intraventricular flow patterns during right ventricular apical pacing. *Open Heart.* 2019, 6(1), p.e001057.
259. Brix, L., Ringgaard, S., Rasmusson, A., Sorensen, T.S. and Kim, W.Y. Three dimensional three component whole heart cardiovascular magnetic resonance velocity mapping: comparison of flow measurements from 3D and 2D acquisitions. *J Cardiovasc Magn Reson.* 2009, 11, p.3.
260. Nordmeyer, S., Riesenkampff, E., Crelier, G. et al. Flow-sensitive four-dimensional cine magnetic resonance imaging for offline blood flow quantification in multiple vessels: a validation study. *J Magn Reson Imaging.* 2010, 32(3), pp.677-683.
261. Kanski, M., Toger, J., Steding-Ehrenborg, K. et al. Whole-heart four-dimensional flow can be acquired with preserved quality without respiratory gating, facilitating clinical use: a head-to-head comparison. *BMC Med Imaging.* 2015, 15, p.20.
262. Udo, E.O., van Hemel, N.M., Zuithoff, N.P. et al. Long-term outcome of cardiac pacing in octogenarians and nonagenarians. *Europace.* 2012, 14(4), pp.502-508.
263. Udo, E.O., van Hemel, N.M., Zuithoff, N.P. et al. Long term quality-of-life in patients with bradycardia pacemaker implantation. *Int J Cardiol.* 2013, 168(3), pp.2159-2163.
264. Bongiorni, M.G., Proclemer, A., Dobreanu, D. et al. Preferred tools and techniques for implantation of cardiac electronic devices in Europe: results of the European Heart Rhythm Association survey. *Europace.* 2013, 15(11), pp.1664-1668.
265. Wolber, T., Haegeli, L., Huerlimann, D. et al. Altered left ventricular contraction pattern during right ventricular pacing: assessment using real-time three-dimensional echocardiography. *Pacing Clin Electrophysiol.* 2011, 34(1), pp.76-81.
266. Puntmann, V.O., Valbuena, S., Hinojar, R. et al. Society for Cardiovascular Magnetic Resonance (SCMR) expert consensus for CMR imaging endpoints in clinical research: part I - analytical validation and clinical qualification. *J Cardiovasc Magn Reson.* 2018, 20(1), p.67.
267. Almutairi, H.M., Boubertakh, R., Miquel, M.E. and Petersen, S.E. Myocardial deformation assessment using cardiovascular magnetic resonance-feature tracking technique. *Br J Radiol.* 2017, 90(1080), p.20170072.

268. Messroghli, D.R., Bainbridge, G.J., Alfakih, K. et al. Assessment of regional left ventricular function: accuracy and reproducibility of positioning standard short-axis sections in cardiac MR imaging. *Radiology.* 2005, 235(1), pp.229-236.
269. Mosteller, R.D. Simplified calculation of body-surface area. *N Engl J Med.* 1987, 317(17), p.1098.
270. Flett, A.S., Hasleton, J., Cook, C. et al. Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. *JACC Cardiovasc Imaging.* 2011, 4(2), pp.150-156.
271. Pedrizzetti, G., Claus, P., Kilner, P.J. and Nagel, E. Principles of cardiovascular magnetic resonance feature tracking and echocardiographic speckle tracking for informed clinical use. *J Cardiovasc Magn Reson.* 2016, 18(1), p.51.
272. Taylor, R.J., Moody, W.E., Umar, F. et al. Myocardial strain measurement with feature-tracking cardiovascular magnetic resonance: normal values. *Eur Heart J Cardiovasc Imaging.* 2015, 16(8), pp.871-881.
273. Kowallick, J.T., Morton, G., Lamata, P. et al. Inter-study reproducibility of left ventricular torsion and torsion rate quantification using MR myocardial feature tracking. *J Magn Reson Imaging.* 2016, 43(1), pp.128-137.
274. Cerqueira, M.D., Weissman, N.J., Dilsizian, V. et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation.* 2002, 105(4), pp.539-542.
275. Onishi, T., Saha, S.K., Ludwig, D.R. et al. Feature tracking measurement of dyssynchrony from cardiovascular magnetic resonance cine acquisitions: comparison with echocardiographic speckle tracking. *J Cardiovasc Magn Reson.* 2013, 15, p.95.
276. Bombardini, T., Agrusta, M., Natsvlishvili, N. et al. Noninvasive assessment of left ventricular contractility by pacemaker stress echocardiography. *Eur J Heart Fail.* 2005, 7(2), pp.173-181.
277. Colonna, P., Montisci, R., Galiuto, L., Meloni, L. and Iliceto, S. Effects of acute myocardial ischemia on intramyocardial contraction heterogeneity: A study performed with ultrasound integrated backscatter during transesophageal atrial pacing. *Circulation.* 1999, 100(17), pp.1770-1776.
278. Elbaz, M.S., van der Geest, R.J., Calkoen, E.E. et al. Assessment of viscous energy loss and the association with three-dimensional vortex ring formation in left ventricular inflow: In vivo evaluation using four-dimensional flow MRI. *Magn Reson Med.* 2017, 77(2), pp.794-805.
279. Garg, P., van der Geest, R.J., Swoboda, P.P. et al. Left ventricular thrombus formation in myocardial infarction is associated with altered left ventricular blood flow energetics. *Eur Heart J Cardiovasc Imaging.* 2019, 20(1), pp.108-117.
280. Xie, J.M., Fang, F., Zhang, Q. et al. Acute effects of right ventricular apical pacing on left atrial remodeling and function. *Pacing Clin Electrophysiol.* 2012, 35(7), pp.856-862.
281. Lieberman, R., Padeletti, L., Schreuder, J. et al. Ventricular pacing lead location alters systemic hemodynamics and left ventricular function in patients with and without reduced ejection fraction. *J Am Coll Cardiol.* 2006, 48(8), pp.1634-1641.
282. Dai, M., Lu, J., Qian, D.J. et al. Assessment of left ventricular dyssynchrony and cardiac function in patients with different pacing modes using real-time three-dimensional echocardiography: Comparison with tissue Doppler imaging. *Exp Ther Med.* 2013, 6(5), pp.1213-1219.
283. Musa, T.A., Treibel, T.A., Vassiliou, V.S. et al. Myocardial Scar and Mortality in Severe Aortic Stenosis. *Circulation.* 2018, 138(18), pp.1935-1947.
284. Alter, P., Rupp, H., Adams, P. et al. Occurrence of late gadolinium enhancement is associated with increased left ventricular wall stress and mass in patients with non-ischaemic dilated cardiomyopathy. *Eur J Heart Fail.* 2011, 13(9), pp.937-944.

285. Gulati, A., Jabbour, A., Ismail, T.F. et al. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. *JAMA.* 2013, 309(9), pp.896-908.
286. Fang, F., Zhang, Q., Chan, J.Y. et al. Early pacing-induced systolic dyssynchrony is a strong predictor of left ventricular adverse remodeling: analysis from the Pacing to Avoid Cardiac Enlargement (PACE) trial. *Int J Cardiol.* 2013, 168(2), pp.723-728.
287. Friedberg, M.K., Dubin, A.M., Van Hare, G.F. et al. Pacing-induced electromechanical ventricular dyssynchrony does not acutely influence right ventricular function and global hemodynamics in children with normal hearts. *J Cardiovasc Electrophysiol.* 2009, 20(5), pp.539-544.
288. Nunes, M.C., Abreu, C.D., Ribeiro, A.L. et al. Effect of pacing-induced ventricular dyssynchrony on right ventricular function. *Pacing Clin Electrophysiol.* 2011, 34(2), pp.155-162.
289. Vaturi, M., Kusniec, J., Shapira, Y. et al. Right ventricular pacing increases tricuspid regurgitation grade regardless of the mechanical interference to the valve by the electrode. *Eur J Echocardiogr.* 2010, 11(6), pp.550-553.
290. Saito, M., Iannaccone, A., Kaye, G. et al. Effect of Right Ventricular Pacing on Right Ventricular Mechanics and Tricuspid Regurgitation in Patients With High-Grade Atrioventricular Block and Sinus Rhythm (from the Protection of Left Ventricular Function During Right Ventricular Pacing Study). *Am J Cardiol.* 2015, 116(12), pp.1875-1882.
291. Chen, J.Y., Tsai, W.C., Liu, Y.W. et al. Long-term effect of septal or apical pacing on left and right ventricular function after permanent pacemaker implantation. *Echocardiography.* 2013, 30(7), pp.812-819.
292. Sugeng, L., Mor-Avi, V., Weinert, L. et al. Multimodality comparison of quantitative volumetric analysis of the right ventricle. *JACC Cardiovasc Imaging.* 2010, 3(1), pp.10-18.
293. Varma, N. Left ventricular conduction delays induced by right ventricular apical pacing: effect of left ventricular dysfunction and bundle branch block. *J Cardiovasc Electrophysiol.* 2008, 19(2), pp.114-122.
294. De Pooter, J., El Haddad, M., Kamoen, V. et al. Relation between electrical and mechanical dyssynchrony in patients with left bundle branch block: An electro- and vectorcardiographic study. *Ann Noninvasive Electrocardiol.* 2018, 23(4), p.e12525.
295. Yu, C.M., Lin, H., Zhang, Q. and Sanderson, J.E. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. *Heart.* 2003, 89(1), pp.54-60.
296. Crandon, S., Westenberg, J.J.M., Swoboda, P.P. et al. Impact of Age and Diastolic Function on Novel, 4D flow CMR Biomarkers of Left Ventricular Blood Flow Kinetic Energy. *Sci Rep.* 2018, 8(1), p.14436.
297. Poller, W.C., Dreger, H., Schwerg, M. and Melzer, C. Prevalence of E/A wave fusion and A wave truncation in DDD pacemaker patients with complete AV block under nominal AV intervals. *PLoS One.* 2015, 10(2), p.e0116075.
298. Pedrizzetti, G., La Canna, G., Alfieri, O. and Tonti, G. The vortex--an early predictor of cardiovascular outcome? *Nat Rev Cardiol.* 2014, 11(9), pp.545-553.
299. Antonini, L., Auriti, A., Pasceri, V. et al. Optimization of the atrioventricular delay in sequential and biventricular pacing: physiological bases, critical review, and new purposes. *Europace.* 2012, 14(7), pp.929-938.
300. Leonelli, F.M., Wang, K., Youssef, M., Hall, R. and Brown, D. Systolic and diastolic effects of variable atrioventricular delay in patients with complete heart block and normal ventricular function. *Am J Cardiol.* 1997, 80(3), pp.294-298.
301. Styliadis, I.H., Gouzoumas, N.I., Karvounis, H.I. et al. Effects of variation of atrioventricular interval on left ventricular diastolic filling dynamics and atrial natriuretic peptide levels in patients with DDD pacing for complete heart block. *Europace.* 2005, 7(6), pp.576-583.

302. Panou, F.K., Kafkas, N.V., Michelakakis, N.A. et al. Effect of different AV delays on left ventricular diastolic function and ANF levels in DDD paced hypertensive patients during daily activity and exercise. *Pacing Clin Electrophysiol.* 1999, 22(4 Pt 1), pp.635-642.
303. Occhetta, E., Piccinino, C., Francalacci, G. et al. Lack of influence of atrioventricular delay on stroke volume at rest in patients with complete atrioventricular block and dual chamber pacing. *Pacing Clin Electrophysiol.* 1990, 13(7), pp.916-926.
304. Kindermann, M., Frohlig, G., Doerr, T. and Schieffer, H. Optimizing the AV delay in DDD pacemaker patients with high degree AV block: mitral valve Doppler versus impedance cardiography. *Pacing Clin Electrophysiol.* 1997, 20(10 Pt 1), pp.2453-2462.
305. Statescu, C., Sascau, R.A., Maciuc, V. and Arsenescu Georgescu, C. Programming an optimal atrioventricular interval in a dual chamber pacemaker regional population. *Maedica (Buchar).* 2011, 6(4), pp.272-276.
306. Steinberg, J.S., Fischer, A., Wang, P. et al. The clinical implications of cumulative right ventricular pacing in the multicenter automatic defibrillator trial II. *J Cardiovasc Electrophysiol.* 2005, 16(4), pp.359-365.
307. Hamer, A.W., Takayama, M., Abraham, K.A. et al. End-systolic volume and long-term survival after coronary artery bypass graft surgery in patients with impaired left ventricular function. *Circulation.* 1994, 90(6), pp.2899-2904.
308. St John Sutton, M., Pfeffer, M.A., Plappert, T. et al. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril. *Circulation.* 1994, 89(1), pp.68-75.
309. Schelbert, E.B., Cao, J.J., Sigurdsson, S. et al. Prevalence and prognosis of unrecognized myocardial infarction determined by cardiac magnetic resonance in older adults. *JAMA.* 2012, 308(9), pp.890-896.
310. Brooks, R. EuroQol: the current state of play. *Health Policy.* 1996, 37(1), pp.53-72.
311. Dolan, P. Modeling valuations for EuroQol health states. *Med Care.* 1997, 35(11), pp.1095-1108.
312. Wong, T.C., Piehler, K.M., Kang, I.A. et al. Myocardial extracellular volume fraction quantified by cardiovascular magnetic resonance is increased in diabetes and associated with mortality and incident heart failure admission. *Eur Heart J.* 2014, 35(10), pp.657-664.
313. Flett, A.S., Hayward, M.P., Ashworth, M.T. et al. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: preliminary validation in humans. *Circulation.* 2010, 122(2), pp.138-144.
314. Szende, A., Janssen, B. and Cabases, J. *Self-Reported Population Health: An International Perspective based on EQ-5D.* Dordrecht: Springer, 2014.
315. Hung, J., Kelly, D.T., Hutton, B.F., Uther, J.B. and Baird, D.K. Influence of heart rate and atrial transport on left ventricular volume and function: relation to hemodynamic changes produced by supraventricular arrhythmia. *Am J Cardiol.* 1981, 48(4), pp.632-638.
316. Starzl, T.E., Gaertner, R.A. and Baker, R.R. Acute complete heart block in dogs. *Circulation.* 1955, 12(1), pp.82-89.
317. Peschar, M., Vernooy, K., Cornelussen, R.N. et al. Structural, electrical and mechanical remodeling of the canine heart in AV-block and LBBB. *Eur Heart J Supplements.* 2004, 6, pp.D61-D65.
318. Brockman, S.K. Cardiodynamics of Complete Heart Block. *Am J Cardiol.* 1965, 16, pp.72-83.
319. Gobel, F.L., Jorgensen, C.R., Kitamura, K. and Wang, Y. Acute changes in left ventricular volume and contractility during ventricular pacing in patients with complete heart block. *Circulation.* 1971, 44(5), pp.771-781.

320. Suga, H., Sagawa, K. and Shoukas, A.A. Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects of epinephrine and heart rate on the ratio. *Circ Res.* 1973, 32(3), pp.314-322.
321. Sagawa, K., Suga, H., Shoukas, A.A. and Bakalar, K.M. End-systolic pressure/volume ratio: a new index of ventricular contractility. *Am J Cardiol.* 1977, 40(5), pp.748-753.
322. Suga, H., Kitabatake, A. and Sagawa, K. End-systolic pressure determines stroke volume from fixed end-diastolic volume in the isolated canine left ventricle under a constant contractile state. *Circ Res.* 1979, 44(2), pp.238-249.
323. Park, R.C., Little, W.C. and O'Rourke, R.A. Effect of alteration of left ventricular activation sequence on the left ventricular end-systolic pressure-volume relation in closed-chest dogs. *Circ Res.* 1985, 57(5), pp.706-717.
324. Rosenquist, R., Gobel, F.L. and Wang, Y. Hemodynamic changes during ventricular pacing in patients with complete heart block and aortic and mitral valvular heart disease. *Am Heart J.* 1975, 89(2), pp.144-152.
325. Tops, L.F., Suffoletto, M.S., Bleeker, G.B. et al. Speckle-tracking radial strain reveals left ventricular dyssynchrony in patients with permanent right ventricular pacing. *J Am Coll Cardiol.* 2007, 50(12), pp.1180-1188.
326. Aalen, J.M., Remme, E.W., Larsen, C.K. et al. Mechanism of Abnormal Septal Motion in Left Bundle Branch Block: Role of Left Ventricular Wall Interactions and Myocardial Scar. *JACC Cardiovasc Imaging.* 2019.
327. Stofmeel, M.A., Post, M.W., Kelder, J.C., Grobbee, D.E. and van Hemel, N.M. Psychometric properties of Aquarel. a disease-specific quality of life questionnaire for pacemaker patients. *J Clin Epidemiol.* 2001, 54(2), pp.157-165.
328. van Eck, J.W., van Hemel, N.M., van den Bos, A. et al. Predictors of improved quality of life 1 year after pacemaker implantation. *Am Heart J.* 2008, 156(3), pp.491-497.
329. Wong, T.C., Piehler, K.M., Zareba, K.M. et al. Myocardial damage detected by late gadolinium enhancement cardiovascular magnetic resonance is associated with subsequent hospitalization for heart failure. *J Am Heart Assoc.* 2013, 2(6), p.e000416.
330. Shanbhag, S.M., Greve, A.M., Aspelund, T. et al. Prevalence and prognosis of ischaemic and non-ischaemic myocardial fibrosis in older adults. *Eur Heart J.* 2019, 40(6), pp.529-538.
331. Boston Scientific. Clinical Summary: ImageReady (TM) MR Conditional Pacing System Clinical Study *(SAMURAI).* 2019.
332. Kellman, P. and Arai, A.E. Cardiac imaging techniques for physicians: late enhancement. *J Magn Reson Imaging.* 2012, 36(3), pp.529-542.
333. Zoghbi, W.A., Adams, D., Bonow, R.O. et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr.* 2017, 30(4), pp.303-371.
334. Kido, T., Kido, T., Nakamura, M. et al. Compressed sensing real-time cine cardiovascular magnetic resonance: accurate assessment of left ventricular function in a single-breath-hold. *J Cardiovasc Magn Reson.* 2016, 18(1), p.50.
335. Xue, H., Kellman, P., Larocca, G., Arai, A.E. and Hansen, M.S. High spatial and temporal resolution retrospective cine cardiovascular magnetic resonance from shortened free breathing real-time acquisitions. *J Cardiovasc Magn Reson.* 2013, 15, p.102.
336. Captur, G., Lobascio, I., Ye, Y. et al. Motion-corrected free-breathing LGE delivers high quality imaging and reduces scan time by half: an independent validation study. *Int J Cardiovasc Imaging.* 2019, 35(10), pp.1893-1901.
337. Piehler, K.M., Wong, T.C., Puntil, K.S. et al. Free-breathing, motion-corrected late gadolinium enhancement is robust and extends risk stratification to vulnerable patients. *Circ Cardiovasc Imaging.* 2013, 6(3), pp.423-432.

338. Sharma, P.S., Dandamudi, G., Naperkowski, A. et al. Permanent His-bundle pacing is feasible, safe, and superior to right ventricular pacing in routine clinical practice. *Heart Rhythm.* 2015, 12(2), pp.305-312.
339. Akita, K., Kohno, T., Kohsaka, S. et al. Prognostic Impact of Previous Hospitalization in Acute Heart Failure Patients. *Circ J.* 2019, 83(6), pp.1261-1268.
340. Braunschweig, F., Cowie, M.R. and Auricchio, A. What are the costs of heart failure? *Europace.* 2011, 13 Suppl 2, pp.ii13-17.
341. Bombardini, T. Myocardial contractility in the echo lab: molecular, cellular and pathophysiological basis. *Cardiovasc Ultrasound.* 2005, 3, p.27.
342. Vincenti, G., Monney, P., Chaptinel, J. et al. Compressed sensing single-breath-hold CMR for fast quantification of LV function, volumes, and mass. *JACC Cardiovasc Imaging.* 2014, 7(9), pp.882-892.
343. Bai, W., Sinclair, M., Tarroni, G. et al. Automated cardiovascular magnetic resonance image analysis with fully convolutional networks. *J Cardiovasc Magn Reson.* 2018, 20(1), p.65.
344. Bhuva, A.N., Bai, W., Lau, C. et al. A Multicenter, Scan-Rescan, Human and Machine Learning CMR Study to Test Generalizability and Precision in Imaging Biomarker Analysis. *Circ Cardiovasc Imaging.* 2019, 12(10), p.e009214.

Appendix

Ethical approval, Patient information sheets and consent form for Chapters 3 and 4

NHS
Health Research Authority
NRES Committee Yorkshire & The Humber - Leeds West
First Floor
Millside
Mill Pond Lane
Leeds
LS6 4RA

Telephone: 0113 3050122
Facsimile: 0113 8556191

24 January 2013

Dr John P Greenwood
Consultant Cardiologist, Senior Lecturer
University of Leeds
Academic Unit of Cardiovascular Medicine
G floor, Jubilee Wing
Leeds General Infirmary
LS1 3EX

Dear Dr Greenwood

Study title:	**CE-MARC 2: Optimization of Image Acquisition and Analysis Methods**
REC reference:	**12/YH/0551**
IRAS project ID:	**116093**

Thank you for your letter of 18 January 2013, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Mrs Elaine Hazell, nrescommittee.yorkandhumber-leedswest@nhs.uk.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Please insert spaces between paragraphs in the section 'What will happen to me if I take part' to improve readability.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*

Advertisement	1.1	
Covering Letter		23 November 2012
Evidence of insurance or indemnity		29 September 2012
Investigator CV		10 August 2012
Letter of invitation to participant		22 November 2012
Participant Consent Form: Healthy volunteers	1.1	18 January 2013
Participant Consent Form	1.1	18 January 2013
Participant Information Sheet: Volunteer	1.1	18 January 2013
Participant Information Sheet	1.1	18 January 2013
Protocol	1.0	05 November 2012
REC application	3.4	23 November 2012
Response to Request for Further Information		18 January 2013

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/YH/0551	**Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

pp
Dr Rhona Bratt
Chair

Email:nrescommittee.yorkandhumber-leedswest@nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Ms Clare E Skinner*
Ms Anne Gowing, Leeds Teaching Hospitals NHS Trust

NHS
Health Research Authority
Yorkshire & The Humber - Leeds West Research Ethics Committee
Jarrow Business Centre
Rolling Mill Road
Jarrow
NE32 3DT

Tel: 0207 104 8117

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

24 October 2017

Dr John Greenwood
University of Leeds
Academic Unit of Cardiovascular Medicine
G floor, Jubilee Wing
Leeds General Infirmary
Leeds
LS1 3EX

Dear Dr Greenwood

Study title:	**CE-MARC 2: Optimization of Image Acquisition and Analysis Methods**
REC reference:	**12/YH/0551**
Amendment number:	**SA5**
Amendment date:	**05 October 2017**
IRAS project ID:	**116093**

The above amendment was reviewed at the meeting of the Sub-Committee held in correspondence.

Summary of amendment

This substantial amendment was submitted to add an extra possible imaging sequence called Diffusion Weighted Imaging, due to this change the protocol was updated.

Ethical opinion

The Sub-Committee did not raise any ethical issues.

The members of the Committee taking part in the review gave a **favourable ethical opinion** of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP) [Substantial amendment form]	SA5	05 October 2017
Research protocol or project proposal [Protocol - tracked]	1.4	05 October 2017

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

12/YH/0551:	**Please quote this number on all correspondence**

Yours sincerely
pp

Dr Vera Neumann
Vice Chair

E-mail: nrescommittee.yorkandhumber-leedswest@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mrs Anne Gowing*

Yorkshire & The Humber - Leeds West Research Ethics Committee

Attendance at Sub-Committee of the REC meeting held in correspondence

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Martin Elliott	Consultant Paediatric Oncologist	Yes	
Dr Vera Neumann	Retired Consultant in Rehabilitation Medicine	Yes	Chair of the Sub-Committee

Also in attendance:

Name	*Position (or reason for attending)*
Miss Rheanneon Fuller	REC Assistant

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

PATIENT INFORMATION SHEET
Version 1.3 16 February 2017

CE-MARC 2: Optimization of acquisition and analysis methods (patients).

Chief Investigator: Dr John Greenwood

Dear Patient,

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Purpose of the study

Magnetic Resonance Imaging (MRI) is a test which produces detailed pictures of your internal organs by putting you within a strong magnetic field. With Cardiac MRI we are able to detect a number of important abnormalities that are caused by heart disease. Importantly, MRI is a safe test and does not use any radiation. MRI may become one of the most important tests in patients who suffer with different types of heart disease.
We have been doing MRI scans of the heart in Leeds since 1995. However, research into improving the images is a continuous process. We always work at developing and improving the scanning protocols, i.e. the computer programmes that produce the images of patients' hearts.

Why have I been chosen?

This study is looking at up to 300 people like you, who either have heart disease, are currently being investigated for heart disease, or have risk factors for heart disease. We are also recruiting 400 healthy volunteers.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care that you receive from the NHS. If there is a possibility that you might be pregnant, you should not take part in the study. Our research team will be happy to discuss any other questions that you may have concerning your suitability for the study, before you decide whether to take part.

What will happen to me if I take part?

Most patients will have a single MRI scan. A small group of participants in this study will be asked to undergo up to four MRI scans to allow comparisons between different ways of obtaining MRI pictures. It is entirely up to you how many scans you wish to volunteer for, and you will remain free to withdraw from the study at any time. All scans will be performed at the Leeds General Infirmary, and will be performed on separate days.
The MRI scan will take approximately 60 minutes to complete. You lie in a short 'tunnel', which holds a large magnet. Short bursts of radio waves from the MRI scanner allow images to

be created. You will hear periodical loud "banging" noises while we are acquiring the images of your heart, so we protect your ears with headphones through which you can listen to the radio or one of your own CDs. We will remain in communication with you throughout the scan. For most scans we will insert one or two cannulae (small plastic tubes) into veins in your arm. It is likely that we will inject a contrast dye during the scan. Usually people are not aware of the contrast dye injection. At one point we may also inject a medication (Adenosine) into a vein in your arm, which is a drug to increase the blood flow to your heart. This can cause a brief feeling of warmth, breathlessness or chest discomfort. However all of these feelings, if they occur, usually settle within one or two minutes. A doctor will stay in the room with you whilst you are having the medication. In some cases instead of using adenosine we may immerse your hands or feet in cold water for up to 2 minutes to achieve the same increased blood flow to the heart muscle, or we may ask you to use a cycle ergometer, a bicycle which can be used whilst lying down in the scanner.
If we wish to obtain specific images of your heart arteries we will wrap a belt around your abdomen to help improve the quality of the pictures. This is not painful and is a recognized method of doing this type of scan. You may be given a nitrate (GTN) spray under the tongue which helps us to obtaining good images. If your heart beat is quite fast we would give you a beta blocker to reduce your heart rate. Again, these methods are widely used in other centres worldwide and are used in normal clinical work too.
Some of the MRI methods used in the heart are also applicable to other body organs. In some patients we will, for example, take images of the blood vessels and/or muscles in the abdomen, or a leg or arm during the same scan. The only difference to the heart scans is that we will use a different receiver coil (the aerial used for reception of MRI signals) to obtain these images.
As this study is about improving our scan protocols on an ongoing basis for a period of five years the information we give you has to describe all the different techniques we wish to use in the study overall, but not all the techniques described above will be used during your scan(s). Before you sign the consent form we will discuss with you the specific scanning protocol that we are going to use.

We may ask you for a blood sample, which would be taken whilst we insert the cannula in your arm for the contrast, so there are no extra needles involved. Knowing your haematocrit (the volume percentage of red blood cells in the blood) helps us to create specific images which are applicable to clinical practice. We may also test your blood glucose and lipid levels. In the unlikely event of an abnormality we will, with your permission, inform your GP.

We may ask you to have an ECG, this is a heart tracing to measure the electrical impulses within the heart. It involves having 10 stickers applied to your chest for 5 minutes.

Risks and discomforts
Magnetic Resonance Imaging (MRI) is safe and no x-rays or radiation are used for this scan. There are no known risks from this technique. Some people may experience claustrophobia. Our MRI staff will do all that they can to make you feel comfortable during the scan, and will be monitoring you via a video camera and an audio link. If we are unable to make you feel comfortable in the scanner, we will not go ahead with scanning. The contrast medication which we use is very safe but, as with any injection, reactions may occur. These include a warm sensation at the injection site, nausea or vomiting and transient skin rash. These effects usually only last for a few minutes. People with a history of allergy are more likely to suffer a more severe reaction, but this is rare (less than 1 in 3000). The department is equipped to cope with allergic reactions if they happen. Adenosine, the medication we use to increase the blood flow to the heart, can cause flushing, breathlessness and chest discomfort. However, all of these feelings usually subside within one or two minutes or even more quickly if the medication is stopped. Immersing your hands or feet in cold water is unpleasant, but the effects wear off very quickly.

Nitrates and a beta blocker can cause temporary light headedness. For this reason if these drugs are used you will be kept under observation until the effects have worn off.

Benefits to you
This study does not form part of your normal clinical care and is done solely for research purposes. Your participation may however benefit future patients.

Expenses
We will provide reasonable travel expenses should this be necessary for you to attend the MRI scan. We are also happy to arrange transport to the hospital and return you home if needs be.

Will my taking part be kept confidential?
All information, which is collected about you during the course of the research will be kept strictly confidential. This information will be securely stored at the Cardiac MRI Unit at Leeds General Infirmary on paper and electronically, under the provisions of the 1998 Data Protection Act. You will not be identified in any publication that may result from this research.

We will inform your General Practitioner (GP) in the event of an unexpected abnormality on the scan.

With your permission, your data may also provide a resource for future studies. If any information from this study is used to develop new research, data protection regulations will be observed and strict confidentiality maintained. Ethical approval will be obtained for any future studies involving your data. You will not be identified in the results of any future studies.

What will happen to the results of the research study?
When the study is complete the results will be published in a medical journal, but no individual patients will be identified. If you would like a copy of the published results, please ask your doctor.

Indemnity/Compensation
If you are harmed as a direct result of taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds to a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

The research organisation
This is a research project of the Cardiac MRI department at Leeds General Infirmary.

For further information please contact:
Petra Bijsterveld
Research Nurse
CMR Clinical Research Group
X47, Sunshine Corridor
Leeds General Infirmary
Leeds
LS1 3EX
T 0113 392 5481

F 0113 392 5225
M 07922 512 887
Email p.bijsterveld@leeds.ac.uk

I am interested in hearing more about this study

(study code: CE-MARC 2 physics - patients)

I give permission for a researcher to contact me by telephone to discuss the study further.

My phone number is……

Name……

Address……

……

Please return this slip to Petra Bijsterveld in the stamped addressed envelope provided.

Thank you.

CONSENT FORM v 1.3 16 February 2017

CE-MARC 2: Optimization of acquisition and analysis methods (patients).
Chief Investigator: Dr John Greenwood

Patient Number: …….. Date of Birth: ……

Patient initials ……

Please initial boxes

1. I have read the Patient Information Sheet dated 16 February 2017 (Version 1.3) for the above study and I have had the opportunity to ask questions and discuss the research study and I am satisfied with the answers to my questions. ☐

2. I have received enough information about this study. ☐

3. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason. ☐

4. I give my consent for my General Practitioner to be informed in the event of any abnormality being discovered and that the cardiologist will be informed only if we find any abnormality over and above which is already known. ☐

5. I understand that images collected will be stored on a computer system, and, after my personal details have been removed, may be available to researchers at other institutions. ☐

6. I understand that some of the blood samples taken from me may be stored and may be analyzed in the future for markers related to heart disease ☐

7. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of Leeds, from regulatory authorities, or from the Leeds Teaching Hospitals NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

8. If I were to lose capacity, I understand that data already collected will be kept and used for the purposes of the study. ☐

9. I agree to take part in this research study and that the general results of the study will be made available to the medical community most likely through publication in a reputable medical journal. ☐

Signature.....

Name (block capitals)..... Date.....

Signature of researcher.....

Name (block capitals).....Date……

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Sven Plein
BHF Professor of Cardiology and Honorary Consultant Cardiologist
University of Leeds
LICAMM
LIGHT building
University of Leeds
LS2 9JT

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

15 June 2018

Dear Professor Plein

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Advanced Magnetic Resonance Imaging: Optimization of Image Acquisition and Analysis Methods (AMaRI)**
IRAS project ID:	**245109**
REC reference:	**18/YH/0168**
Sponsor	**University of Leeds**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

IRAS project ID	245109

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: NHS Research Ethics Officer
Email: governance-ethics@leeds.ac.uk

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **245109**. Please quote this on all correspondence.

IRAS project ID	245109

Yours sincerely

Thomas Fairman
HRA Assessor

Email: hra.approval@nhs.net

Copy to: *NHS Research Ethics Office, Leeds University, (Sponsor Contact)*
Ms Anne Gowing, Leeds Teaching Hospitals NHS Trust, (Lead NHS R&D Contact)

IRAS project ID	245109

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Copies of advertisement materials for research participants [AMaRI recruitment email]	1.0	27 March 2018
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Confirmation of Liability]		21 September 2017
HRA Schedule of Events	1.0	11 April 2018
HRA Statement of Activities	1.0	11 April 2018
IRAS Application Form [IRAS_Form_06042018]		06 April 2018
Laboratory Manual [Laboratory manual]	1.0	01 March 2018
Letter from funder [BHF Programme Grant]		24 May 2016
Letter from sponsor [confirmation of sponsorship]		27 March 2018
Letters of invitation to participant [AMaRI invitation letter]	1.0	27 March 2018
Participant consent form [AMaRI PIS Consent Patients (tracked changes)]	1.1	12 June 2018
Participant consent form [AMaRI PIS Consent Volunteers]	1.1	12 June 2018
Research protocol or project proposal [AMaRI Protocol]	1.1	12 June 2018
Response to Additional Conditions Met		
Summary CV for Chief Investigator (CI) [CV]		01 November 2017

IRAS project ID	245109

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	No comment
3.1	Protocol assessment	Yes	No comment
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	The sponsor has submitted the HRA Statement of Activities and intends for this to form the agreement between the sponsor and study sites. The sponsor is not requesting, and does not require any additional contracts with study sites.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this research study
4.3	Financial arrangements assessed	Yes	External study funding has been secured from the British Heart Foundation. Study funding will be provided to sites, as detailed at Schedule 1 of the Statement of Activities.

IRAS project ID	245109

Section	Assessment Criteria	Compliant with Standards	Comments
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comment
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England and Wales

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
All participating NHS organisations will undertake the same study activities. There is therefore only one study site 'type' involved in the research. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. Where applicable, the local LCRN contact should also be copied into this correspondence. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS, the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

IRAS project ID	245109

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and Wales, and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A Principal Investigator should be appointed at study sites. GCP training is not a generic training expectation, in line with the HRA/HCRW/MHRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
As a non-commercial study undertaken by local staff, it is unlikely that letters of access or honorary research contracts will be applicable, except where local network staff employed by another Trust (or University) are involved (and then it is likely that arrangements are already in place). Where arrangements are not already in place, network staff (or similar) undertaking any of the research activities listed in A18 or A19 of the IRAS form (except for administration of questionnaires or surveys), would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance. For research team members only administering questionnaires or surveys, a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.
The applicant has indicated that they do intend to apply for inclusion on the NIHR CRN Portfolio.

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

PARTICIPANT INFORMATION SHEET - PATIENTS
Version 1.2 –October 04 2018
AMaRI

Advanced Magnetic Resonance Imaging: Optimization of Image Acquisition and Analysis Methods

Chief Investigator: Professor Sven Plein

Dear Patient,

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Purpose of the study
Magnetic Resonance Imaging (MRI) is a test which produces detailed pictures of your internal organs by putting you within a strong magnetic field. MRI allows us to detect abnormalities in many organs in the human body with a very high sensitivity. Importantly, MRI is a safe test and does not use any harmful radiation. It is therefore an increasingly used test in many areas of medicine with over 100,000 MRI scans performed in the NHS every year.

In Leeds, we have an ongoing research programme that aims to continuously improve the way we acquire MRI pictures. This is mostly achieved by making scans shorter, increasing the detail in the image or finding out new information from within the acquired images. These developments are first tested in phantoms (bottles filled with a special liquid) and later need confirmation in volunteers and then in patients.

Why have I been chosen?
This study is looking at up to 300 people like you, who may have a range of conditions that are of interest to our research into improving imaging. We are also asking 400 healthy volunteers to participate in the study.

Do I have to take part?
No. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care that you receive from the NHS. If there is a possibility that you might be pregnant, you should not take part in the study. Our research team will be happy to discuss any other questions that you may have concerning your suitability for the study, before you decide whether to take part.

What will happen to me if I take part?
Most patients will have a single MRI scan. A small group of participants in this study will be asked to undergo up to four MRI scans to allow comparisons between different ways of obtaining MRI pictures. It is entirely up to you how many scans you wish to volunteer for, and

you will remain free to withdraw from the study at any time. All scans will be performed at the Leeds General Infirmary, and will be performed on separate days.
The MRI scan will take approximately 60 to 90 minutes to complete. You lie in a short 'tunnel', which holds a large magnet. Short bursts of radio waves from the MRI scanner allow images to be created. You will hear periodical loud "banging" noises while we are acquiring the images, so we protect your ears with headphones through which you can listen to the radio or one of your own CDs. We will remain in communication with you throughout the scan.

For most scans we will insert one or two cannulae (small plastic tubes) into veins in your arm. It is likely that we will inject a contrast dye during the scan. Usually people are not aware of the contrast dye injection. At one point we may also inject a medication (Adenosine, or occasionally Dobutamine) into a vein in your arm, which is a drug to increase the blood flow to your heart. This can cause a brief feeling of warmth, breathlessness or chest discomfort. However all of these feelings, if they occur, usually settle within one or two minutes of the medication being stopped. A doctor will stay in the room with you whilst you are having the medication. In some cases instead of using adenosine we may immerse your hands or feet in cold water for up to 2 minutes to achieve the same increased blood flow to the heart muscle, or we may ask you to use a cycle ergometer, a bicycle which can be used whilst lying down in the scanner.

If we wish to obtain specific images of your heart arteries we will wrap a belt around your abdomen to help improve the quality of the pictures. This is not painful and is a recognized method of doing this type of scan. You may be given a nitrate (GTN) spray under the tongue which helps us to obtaining good images. If your heart beat is quite fast we would give you a beta blocker tablet to reduce your heart rate. Again, these methods are widely used in other centres worldwide and are used in normal clinical work too.

As this study is about improving our scan protocols on an ongoing basis for a period of four years the information we give you has to describe all the different techniques we wish to use in the study overall, but not all the techniques described above will be used during your scan(s). Before you sign the consent form we will discuss with you the specific scanning protocol that we are going to use.

We may ask you for a blood sample (5 to 10 mls. or 1 to 2 teaspoons), which would be taken whilst we insert the cannula in your arm for the contrast, so there are no extra needles involved. Knowing your haematocrit (the volume percentage of red blood cells in the blood) helps us to create specific images which are applicable to clinical practice. We may also test your blood glucose and lipid levels. With your permission we may store serum samples and analyse them at the end of the study for markers of heart function.
We may ask you to come for the scan in a fasted state, or offer to scan you following a meal which we will provide you with, so that we can assess the influence of fed or fasted state on the heart scan assessments.

We may ask you to have an ECG, this is a heart tracing to measure the electrical impulses within the heart. It involves having 10 stickers applied to your chest for 5 minutes.

In the unlikely event of any abnormality we will, with your permission, inform your GP.

Risks and discomforts
Magnetic Resonance Imaging (MRI) is safe and no x-rays or radiation are used for this scan. There are no known risks from this technique. Some people may experience claustrophobia. Our MRI staff will do all that they can to make you feel comfortable during the scan, and will be monitoring you via a video camera and an audio link. If we are unable to make you

feel comfortable in the scanner, we will not go ahead with scanning. You may experience minor bruising or irritation at the site where we place the cannula in your arm. The contrast medication which we use is very safe but, as with any injection, reactions may occur. These include a warm sensation at the injection site, nausea or vomiting and transient skin rash. These effects usually only last for a few minutes. People with a history of allergy are more likely to suffer a more severe reaction, but this is rare (less than 1 in 3000). The department is equipped to cope with allergic reactions if they happen. Adenosine, the medication we use to increase the blood flow to the heart, can cause flushing, breathlessness and chest discomfort. However, all of these feelings usually subside within one or two minutes or even more quickly if the medication is stopped. Immersing your hands or feet in cold water is unpleasant, but the effects wear off very quickly. Nitrates and a beta blocker can cause temporary light headedness. For this reason if these drugs are used you will be kept under observation until the effects have worn off.

Benefits to you
This study does not form part of your normal clinical care and is done solely for research purposes. Your participation may however benefit future patients.

Expenses
We will provide reasonable travel expenses should this be necessary for you to attend the MRI scan. We are also happy to arrange transport to the hospital and return you home if needs be.

Will my taking part be kept confidential?
All information, which is collected about you during the course of the research will be kept strictly confidential. This information will be securely stored at the Cardiac MRI Unit at Leeds General Infirmary on paper and electronically, under the provisions of the 2018 Data Protection Act. The data collected will be coded and your personal details will be kept separately. If we keep any of your serum samples these will be stored in -80°C freezers in a secure environment, in University of Leeds or Leeds Teaching Hospitals NHS Trust Research laboratories. Stored serum samples will be anonymized and identified only by sample IDs. You will not be identified in any publication that may result from this research.

We will inform your General Practitioner (GP) in the event of an unexpected abnormality being found.

With your permission, your data may also provide a resource for future studies. If any information from this study is used to develop new research, data protection regulations will be observed and strict confidentiality maintained. Your anonymized data and or images may be sent to institutions in the UK, the European Economic Area or outside the EEA. Ethical approval will be obtained for any future studies involving your data. You will not be identified in the results of any future studies.

The University of Leeds is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Leeds and the Leeds Teaching Hospitals NHS Trust (on behalf of the University of Leeds), will keep identifiable information about you for the purpose of the study for a maximum of 15 years after the study has finished. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about

you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.
You can find out more about how we use your information at http://www.leeds.ac.uk/secretariat/data_protection.html

The University of Leeds will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the University of Leeds and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Leeds Teaching Hospitals NHS Trust will pass these details to the University of Leeds along with the information collected from you and your medical records. The only people in the University of Leeds who will have access to information that identifies you will be people who need to contact you to organize the research or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number and contact details.

What will happen to the results of the research study?
When the study is complete the results will be published in a medical journal, but no individual participants will be identified. If you would like a copy of the published results, please ask your doctor.

Indemnity/Compensation
If you are harmed as a direct result of taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds to a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

The research organisation
This is a research project of the Department of Biomedical Imaging Science at the Leeds Institute of Cardiovascular and Metabolic Medicine (LICAMM).

For further information please contact:
Research Nurses
CMR Clinical Research Group
X47, Sunshine Corridor
Leeds General Infirmary
Leeds
LS1 3EX
T 0113 392 5481 or 392 5504
cmrresearch@leeds.ac.uk

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

CONSENT FORM v 1.2 October 04 2018

AMaRI

Advanced Magnetic Resonance Imaging: Optimization of Image Acquisition and Analysis Methods

Chief Investigator: Professor Sven Plein

Patient Number: …….. Date of Birth: ……

Patient initials ……

Please initial boxes

1. I have read the Patient Information Sheet dated October 042018 (Version 1.2) for the above study and I have had the opportunity to ask questions and discuss the research study and I am satisfied with the answers to my questions. ☐

2. I have received enough information about this study. ☐

3. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason. ☐

4. I give my consent for my General Practitioner to be informed in the event of any abnormality being discovered and that the cardiologist will be informed only if we find any abnormality over and above which is already known. ☐

5. I understand that images collected will be stored on an NHS computer system, and, after my personal details have been removed, may be available to researchers at other institutions in the UK, the EEA, and countries outside the EEA. ☐

6. I understand that some of the blood samples taken from me may be stored and may be analyzed in the future for markers related to heart disease ☐

7. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of Leeds, from regulatory authorities, or from the Leeds Teaching Hospitals NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

8. If I were to lose capacity, I understand that data already collected will be kept and used for the purposes of the study. ☐

9. I agree to take part in this research study and that the general results of the study will be made available to the medical community most likely through publication in a reputable medical journal. ☐

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

	Yes	No
10. I am willing to be contacted again in the future to receive information about the publication of this study.	☐	☐
11. I am willing to be contacted again in the future with regard to potentially taking part (without any obligation) in further related research studies, or attending for further MRI scans.	☐	☐

12. I would like to receive a summary of the final results when they are available ☐

Signature.....

Name (block capitals)..... Date.....

Signature of researcher.....

Name (block capitals).....Date……

1 copy to be given to the patient

1 copy to be filed in notes

1 copy to be retained researcher

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

.....

I am interested in hearing more about this study

(study code: AMaRI - patients)

I give permission for a researcher to contact me by telephone to discuss the study further.

My phone number is.....

Name.....

Address.....

.....

Please return this slip to the research nurse office in the stamped addressed envelope provided.

Thank you.

Clinical and CMR parameters of patients excluded from analysis in Chapter 4

Baseline Characteristics	n=4		
Male Sex – n (%)	4 (100%)		
Age – yr	74.1 ± 12.2		
Indication for device – no (%) Sinus node disease No pacing indication/ICD	 3 (75%) 1 (25%)		
BMI	26.9 ± 2.4		
Intrinsic QRS duration (ms)	123 ± 28.6		
Paced QRS duration (ms)	160 ± 6.7		
Imaging parameters			
	AOO	DOO	P value
LV end-diastolic volume index – mL/m^2	119.8 ± 18.5	119 ± 15.1	0.80
LV end-systolic volume index – mL/m^2	82 ± 23.2	85.6 ± 16.2	0.46
LV ejection fraction - %	32.5 ± 8.4	28.4 ± 6.0	0.20
LV mass index – g/m^2	61.5 ± 20.6	65.7 ± 20.9	0.40
RV end-diastolic volume index – mL/m^2	69.7 ± 10.1	70.3 ± 9.8	0.85
RV end-systolic volume index – mL/m^2	33.0 ± 8.1	35.3 ± 7.3	0.51
RV ejection fraction - %	55.2 ± 6.4	50.0 ± 5.3	0.63
Presence of LGE (n)	4 (100%)		

Ethical approval, Patient information sheets and consent form for Chapter 5

NHS
Health Research Authority

Dr Peter Swoboda
Lecturer in Cardiology
University of Leeds
Leeds
LS2 9JT

Email: hra.approval@nhs.net

12 January 2018

Dear Dr Swoboda

Letter of HRA Approval

Study title:	**Effect of right ventricular pacing in atrioventricular block by cardiovascular magnetic resonance: BLOCK-MR**
IRAS project ID:	**236042**
REC reference:	**17/EM/0475**
Sponsor	**University of Leeds**

I am pleased to confirm that HRA Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

IRAS project ID	236042

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from the HRA website.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found through IRAS.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

IRAS project ID	236042

procedure. If you wish to make your views known please use the feedback form available on the HRA website.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details on the HRA website.

Your IRAS project ID is **236042**. Please quote this on all correspondence.

Yours sincerely

Joanna Ho
Assessor

Email: hra.approval@nhs.net

Copy to: *NHS Research Ethics Officer, Sponsor Representative, University of Leeds*
Petra Bijsterveld, Sponsor's Delegated Point of Contact, University of Leeds
Anne Gowing, Lead NHS R&D Contact, Leeds Teaching Hospitals NHS Trust
Dr Christopher Saunderson, Student, University of Leeds
Professor Sven Plein, Academic Supervisor, University of Leeds

IRAS project ID	236042

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		21 September 2017
GP/consultant information sheets or letters	1.0	21 November 2017
HRA Schedule of Events		
HRA Statement of Activities		
IRAS Application Form [IRAS_Form_30112017]		30 November 2017
IRAS Application Form XML file [IRAS_Form_30112017]		30 November 2017
IRAS Checklist XML [Checklist_05012018]		05 January 2018
Letters of invitation to participant	1.0	21 November 2017
Other [Invitation Letter]	1.1	03 January 2018
Other [Protocol - Tracked Changes]	1.1	03 January 2018
Other [Response to REC]		05 January 2018
Other [Consent Form -TC]	1.1	03 January 2018
Other [CRF - BLOCK -MR]	1.0	03 January 2018
Participant information sheet (PIS)	1.1	03 January 2018
Summary CV for Chief Investigator (CI)		11 August 2017
Summary CV for student		
Summary CV for supervisor (student research)		30 November 2017
Validated questionnaire [EQ-5D]		

IRAS project ID	236042

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations, capacity and capability* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Name: Petra Bijsterveld
Tel: 0113 392 5481
Email: p.bijsterveld@leeds.ac.uk

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	The Statement of Activities will act as agreement of an NHS organisation to participate. No other agreement is expected.
4.2	Insurance/indemnity arrangements assessed	Yes	Sponsor indemnity arrangements are in place for the management and design of the study. NHS indemnity applies to the conduct of the study. Where applicable, independent

IRAS project ID	236042

Section	HRA Assessment Criteria	Compliant with Standards	Comments
			contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this research study
4.3	Financial arrangements assessed	Yes	No application for external funding was made for this study. Participating NHS organisations will be provided with funding as detailed in the Statement of Activities.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	REC provisional opinion issued 02 January 2018; REC favourable opinion issued 11 January 2018
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

IRAS project ID	236042

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
This is a non-commercial single centre study where the participating NHS organisation will be undertaking all research activities. There is therefore only one site type in this study. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.
Participating NHS organisations in England **will be expected to formally confirm their capacity and capability to host this research**. • Following issue of this letter, participating NHS organisations in England may now confirm to the sponsor their capacity and capability to host this research, when ready to do so. How capacity and capacity will be confirmed is detailed in the *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* section of this appendix. • The Assessing, Arranging, and Confirming document on the HRA website provides further information for the sponsor and NHS organisations on assessing, arranging and confirming capacity and capability.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A Principal Investigator should be in place at each participating NHS organisation. GCP training is not a generic training expectation, in line with the HRA/MHRA statement on training expectations.

IRAS project ID	236042

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
Local staff substantively employed by the participating NHS organisation will be undertaking research activities as described in the IRAS application. No HR access arrangements are therefore expected for this study. Where arrangements are not already in place, network staff employed by another Trust or University (or similar) undertaking any of the research activities listed in A18 or A19 of the IRAS form (except for administration of questionnaires or surveys), would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance. For research team members only administering questionnaires or surveys, a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

Effect of right ventricular pacing in atrioventricular block by cardiovascular magnetic resonance: BLOCK-MR

PARTICIPANT INFORMATION SHEET

Chief Investigator: Dr Peter Swoboda, Clinical Lecturer in Cardiology, University of Leeds

Version 1.2 November 8 2018

1. Invitation

You are being invited to take part in a research study. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully, and discuss it with others if you wish. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part.

2. What is the purpose of the study?

Slow heart rates (bradycardia) cause symptoms such as shortness of breath and blackouts. The diagnosis is made by performing a heart tracing (electrocardiogram) and is treated by giving you a pacemaker. The leads of the pacemaker that regulate the heart rate are positioned in the right side of the heart and attached to a generator which is inserted underneath the skin. We know from previous studies using heart ultrasound that measureable changes in the pumping function of the left side of the heart can occur in the longer term with pacemakers. In a small subgroup of patients this can lead to abnormalities in the heart muscle and a condition known as heart failure. This mainly leads to shortness of breath which in turn can lead to being admitted to hospital or a worse quality of life.

At present there are no good ways of identifying patients at risk of heart failure prior to pacemaker insertion. Current pacemakers are now deemed 'magnetic resonance imaging (MRI) conditional' and studies have shown they are safe to scan under the right conditions. Therefore this allows the opportunity to perform more detailed scans of the heart with cardiac MRI.

We plan to recruit patients when they present to hospital with symptomatic slow heart rates that require implantation of a pacemaker. By carrying out comprehensive heart scans before and after the pacemaker is implanted we will be able to see which features on the scan predict who is at risk of developing heart failure. Identifying patients at risk of heart failure will hopefully allow us to tailor therapies to prevent heart failure and the associated symptoms in the future.

3. Why have I been chosen?

You have been chosen because you have a slow heart rate that requires treatment with a cardiac pacemaker.

4. Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care that you receive from the NHS. If there is a possibility that you might be pregnant, you should not take part in the study. Our research team will be happy to discuss any other questions that you may have concerning your suitability for the study, before you decide whether to take part.

5. What will happen to me if I take part?

If you want to take part you will have the initial tests during your admission and will have to return to the LGI on one separate occasion. On both visits you will have a cardiac MRI scan, a blood sample taken and an ECG (heart tracing) performed. During your admission you will also have an ECHO (heart ultrasound) performed. This whole process should take around an hour and a half (although you should allow 120 minutes in the department including time to get changed and look at your scan).

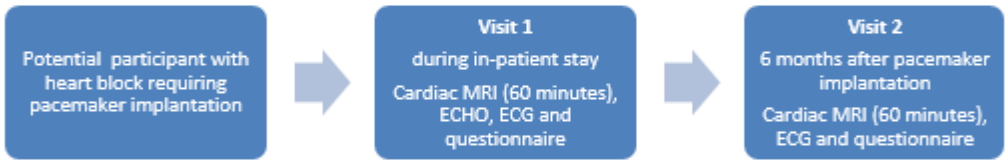
MRI scan: This will last approximately 60 minutes during which you will lie flat in the scanner and be asked to hold your breath several times for up to 10 seconds. We will give you a contrast dye that allows us to learn more about your heart and is used commonly in this type of scan.

ECG: This is a heart tracing to measure the electrical impulses within the heart. It involves having 10 stickers applied to your chest for 5 minutes.

ECHO: This is an ultrasound of the heart that allows measurements of the structure and function of the heart. It involves applying an ultrasound probe to your chest and takes about 30 minutes.

Blood Tests: During the MRI scan we put a small plastic tube in a vein in your arm to allow administration of the contrast dye. During this procedure we will take a small blood sample (10mls which is 2 teaspoons).

Questionnaire: You will be asked to complete a short questionnaire to assess how you feel and how this impacts on your day-to-day living .A member of the research team can help you with this if you need assistance. We will ask you to complete these again at the second visit.



Follow up: We will follow your progress by checking your medical records in both paper and electronic form for up to five years. If we cannot find the information we need we may briefly contact you or your GP by telephone.

6. What do I have to do?

Your only commitment is to attend for the two appointments. We can be flexible with the timing of these to fit in with you and your pacemaker implantation, and we are able to reimburse your travel expenses.

7. What are other possible disadvantages and risks of taking part?

MRI scan: Magnetic Resonance Imaging (MRI) is safe and no radiation is used for this scan. There are no known risks from the technique.
Some people may experience claustrophobia (fear of confined spaces). Our MRI staff will do all that they can to make you feel comfortable during the scan, and will be monitoring you via a video camera and an audio link. If we are unable to make you feel comfortable in the scanner, we will not go ahead with scanning.
We will need to insert a small tube (cannula) into your arm for the contrast dye. The dye we use during the scan is very safe but, as with any injection, reactions may occur. These include a warm sensation at the injection site, nausea or vomiting and transient skin rash.
People with a history of allergy are more likely to suffer a more severe reaction to the medication used, but this is rare (less than 1 in 3000). The department is equipped to cope with allergic reactions if they happen.

MRI with pacemakers:
MRI scans can now be performed safely in patients with pacemakers and your device will be checked before and after your scan. We have performed over 100 MRI scans on patients with pacemakers over the last 2 years with no adverse events. If the pacemaker you have implanted is not MRI conditional then you will not be able to attend for the second MRI scan.

For Women:

If there is any possibility that you might be pregnant you will be asked to have a pregnancy test (urine or blood) before taking part.

8. What are the possible benefits of taking part?

We cannot promise the study will help you but the information we get might help to identify patients at risk of heart muscle deterioration after pacemaker implantation.

If you are interested a doctor can show you the results of your scan.

There is also a small chance that an abnormality may be detected on your scan. If this is the case we will provide a full report to your medical team so that appropriate action can be taken.

9. What happens when the research study stops?

After your second visit your direct involvement with the study will cease but your normal care will continue, under your clinical team, uninterrupted.

10. What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your question. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. This can be done via the Patient Advice and Liaison Service (PALS) at Leeds Teaching Hospitals NHS Trust (0113 2066261).

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements, however in certain circumstances arrangements may differ. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

11. What if new information becomes available?

Sometimes during the course of a study, new information becomes available on the condition being studied. If this happens, we will tell you about it and discuss with you whether you want to or should continue in the study. If you decide to withdraw, we will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

On receiving new information, we might consider it to be in your best interests to withdraw you from the study. If so, we will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

12. What will happen if I don't want to carry on with the study?

If you withdraw consent or lose the capacity to consent, unless you object, your data and samples will remain on file and will be included in the final study analysis.
If you decide to withdraw from the study the rest of your medical care will not be affected.

13. Will my part in this study be kept confidential?

All information collected about you during the course of the study will be kept strictly confidential. This information will be securely stored, electronically on the Leeds Teaching Hospitals NHS Trust secure server, and on paper, under the provisions of the 2018 Data Protection Act. The data collected will be coded and your personal details will be kept separately. You will not be identified in any publication that may result from this research. With your permission, we will inform your GP of your participation in the study. If any unexpected abnormality or condition were found we would inform your GP. If you withdraw consent from further study follow-up, or if you were to become incapacitated, any data collected about you up to that point will remain on file and will be included in the final study analysis.

The University of Leeds is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Leeds Teaching Hospitals NHS Trust and the University of Leeds will keep identifiable information about you for the purpose of the study for 20 years after the study

has finished. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your information at http://www.leeds.ac.uk/secretariat/data_protection.html

Leeds Teaching Hospitals NHS Trust and the University of Leeds will use your name, NHS number, and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the University of Leeds and regulatory organizations may look at your medical and research records to check the accuracy of the research study. The Leeds Teaching Hospitals NHS Trust will pass these details to the University of Leeds along with the information collected from you and/or your medical records. The only people in the University of Leeds who will have access to information that identifies you will be people who need to contact you to or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details
When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.
This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

With your permission we will retain the link to your personal details so that we can contact you about any publications arising from this study, and with regard to potentially taking part in further related studies.

14. Informing your General Practitioner (GP)

We will inform your GP that you are taking part, but the study will not have an impact on your care.

15. What will happen to any samples I give?

Blood samples will be analysed to determine your haematocrit, which is a measure of the 'thickness' of your blood. We require this to be able to read the MRI scan correctly. Blood samples will be stored in an access-controlled location within the laboratories of the Leeds General Infirmary to allow for specialist tests to be performed in one batch. With your permission your stored sample may be used in future heart related research studies, this can only happen if a research ethics committee allows it.

16. Will any Genetic testing be done?

No

17. What will happen to the results of this medical study?

The results of the study will be available after it finishes and will usually be published in a medical journal or be presented at a scientific conference. The data will be anonymous and none of the patients involved in the trial will be identified in any report or publication.

Should you wish to see the results, or the publication, please ask your study doctor.

18. Who is organising this study?

This study is being organised by Leeds Institute of Cardiovascular and Metabolic Medicine (LICAMM) within the University of Leeds.

19. Who has reviewed the study?

This study was given favourable ethical opinion for conduct in the NHS by 17/EM/0475 Research Ethics Committee.

20. Contact for further information

You are encouraged to ask any questions you wish, before, during or after your research investigations. If you have any questions about the study, please speak to your study nurse or doctor, who will be able to provide you with up to date information about the drug(s)/procedure(s) involved. If you wish to read the research on which this study is based, please ask your study nurse or doctor. If you require any further information or have any concerns while taking part in the study please contact one of the following people:

Dr Christopher Saunderson
Clinical Research Fellow in Cardiology
Cardiac MRI department,
Clarendon wing,
Leeds General Infirmary
01133925909
c.saunderson@leeds.ac.uk

Research Nurses
Cardiovascular Research
Sunshine Corridor
Leeds General Infirmary
Tel: 0113 392 5481 or 392 6286
cmrresearch@leeds.ac.uk

If you decide you would like to take part then please read and sign the consent form. You will be given a copy of this information sheet and the consent form to keep. A copy of the consent form will be filed in your patient notes, one will be filed with the study records and one may be sent to the Research Sponsor.

You can have more time to think this over if you are at all unsure.

Thank you for taking the time to read this information sheet and to consider this study.

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

CONSENT FORM v 1.2 November 08 2018

Effect of right ventricular pacing in atrioventricular block by cardiovascular magnetic resonance: BLOCK-MR

Chief Investigator: Dr Peter Swoboda, Clinical Lecturer in Cardiology, University of Leeds

Subject Study Number: ..... Subject Initials.....

Please initial boxes

1. I have read the Patient Information Sheet dated November 8th 2018 (version 1.2) for the above study and I have had the opportunity to ask questions and discuss the research study and I am satisfied with the answers to my questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason. ☐

3. I give my consent for my General Practitioner and other doctors looking after me to be informed. ☐

4. I understand that data and images collected will be stored on a computer system, and, after my personal details have been removed, may be sent to participating study centres or to an independent laboratory, and may be available to researchers at other institutions in the UK, the EEA, and countries outside the EEA. ☐

5. I understand that relevant sections of my medical notes and data collected during the study (including personal data) may be looked at by individuals from the University of Leeds, from regulatory authorities, or from the Leeds Teaching Hospitals NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

6. If I were to lose capacity or withdraw consent for further follow-up I understand that identifiable data already collected will be kept and used for the purposes of the study. ☐

7. I agree to take part in this research study and that the general results of the study will be made available to the medical community most likely through publication in a reputable medical journal. ☐

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

		Yes	No
8.	I am willing to be contacted again in the future to receive information about the publication of this study.	☐	☐
9.	I am willing to be contacted again in the future with regard to potentially taking part (without any obligation) in further related research studies.	☐	☐
10.	I agree to my blood samples being stored and used in future heart related research.	☐	☐

Optional

11. I would like to receive a summary of the final results when they are available ☐

Signature.....

Name (block capitals)..... Date.....

Signature of researcher.....

Name (block capitals).....Date.....

1 copy for patient, 1 copy for medical records and 1 copy for Investigator Site File