# THE EFFECT OF CARDIAC RESYNCHRONISATION THERAPY ON CARDIAC FUNCTION AS ASSESSED USING MRI

Aaron Ommen Koshy

Submitted in accordance with the requirements for the degree of

Doctor of Philosophy

University of Leeds

Faculty of Medicine and Health

January 2021

The candidate confirms that the work submitted is his/her own and that appropriate credit has been given 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. The right of Aaron Ommen Koshy to be identified as Author of this work has been asserted by Aaron Ommen Koshy in accordance with the Copyright, Designs and Patents Act 1988.

**Manuscripts arising from this thesis:**

Koshy AO, Swoboda PPP, Gierula J, Witte KK. Cardiac magnetic resonance in patients with cardiac resynchronization therapy: Is it time to scan with resynchronization on? Europace. 2019;21(4):554-62.

Koshy A, Witte K. Uses and potential for cardiac magnetic resonance imaging in patients with cardiac resynchronisation pacemakers. Expert Review of Medical Devices. 2019;16(6):445-50.

Koshy AO, Gallivan ER, McGinlay M, Straw S, Drozd M, Toms AG, et al. Prioritizing symptom management in the treatment of chronic heart failure. ESC Heart Failure. 2020;7(5):2193-207.

**Abstracts arising from this thesis:**

Cardiac response to CRT and heart rate augmentation: The first assessment with CMR. A Koshy. Oral presentation at the Heart Rhythm Congress in 2019

Revealing cardiac mechanics with CMR whilst CRT is active: the first step. A Koshy, J Gierula, M Paton, P Swoboda, A Toms C Saunderson, D Shelley, D Plein, R Cubbon, M Kearney, K Witte. Moderated presentation at ESC 2019

Partial normalisation of cardiac mechanics through CRT in patients with chronic heart failure demonstrated by 3.0T CMR. A Koshy, J Gierula, M Paton, P Swoboda, A Toms C Saunderson, D Shelley, D Plein, R Cubbon, M Kearney, K Witte. Moderated presentation at ESC 2020

This research has been carried out by a team which has included the candidate, Dr Aaron Ommen Koshy (AK), Dr Klaus Witte (KW), Dr Peter Swoboda (PS), Professor Jurgen Schneider (JS), Dr John Gierula (JG), Mr David Shelley (DS), Dr David Broadbent (DB) and Dr Nadira Yuldasheva (NY).

My own contributions, fully and explicitly indicated in the thesis, have been:

- Design of the thesis
- Ethics submissions
- Design & conduct of the Research
- Drafting all manuscripts - First author of all published research.

The other members of the group and their contributions have been as follows:

- Design of the thesis (KW, PS, JS)
- Ethics submissions (KW)
- Design of the study protocols (KW, PS, JS, JG, DS, NY)
- Conduct of the study protocols (JG, DS, DB)
- Analysis of results (KW, JS, DB)
- Review of submitted manuscripts (KW, JG)

# Acknowledgements

I want to express my gratitude to a number of individuals. Firstly, I would like to thank Dr Klaus Witte for the many supervisory sessions that we have had to formulate, conduct, analyse and write up this PhD. It has been under continual review, the evolution of which has been formed from aiming higher to deliver a significant impact to clinical practice.
Professor Jurgen Schneider has helped me understand the complex world of physics that little bit more. His guidance with the multiple porcine phantom models was critical to finally confirming viability of novel scanning techniques in the context of heart failure devices.
Dr Peter Swoboda has been the font of knowledge for the practical application of cardiac magnetic resonance in patients with heart failure. It was Peter's experience of cardiac magnetic resonance that helped me to develop a working scanning protocol for the clinical aspects of this project.
Dr John Gierula has been pivotal in conducting the clinical trial aspect of this study. His experience in cardiac pacing and programming has allowed this study to push the boundaries of programming potential.
Mr David Shelley has been incredibly helpful in his approach to scanning patients using the 3.0T MRI scanner. His knowledge of the practical aspects of MRI scanning and attention to detail has been a repeated source of reassurance.
I am grateful to Dr David Broadbent and Professor Sven Plein for their continued guidance and encouragement. Their knowledge of MRI, safety and logistics gave confidence to all involved in my research.
Dr Nadira Yuldasheva was invaluable in her guidance and support in the practical aspects of creating the phantom model using porcine organs. Her experience in tissue sterilisation, extraction and preservation are second to none.
I must thank my wife Anet, my family and friends for their patience during this long period of work. It was only near the end of the journey that I realised the importance their support which made the experience not only manageable but of value.
Lastly, but perhaps most importantly, I greatly appreciate the participants of my research. None of this work would have been possible without their enthusiasm and dedication to our shared ambition; improving care for patients with heart failure.

# Abbreviations

ACEI - Angiotensin converting enzyme inhibitors

AF - Atrial fibrillation

ARB - Angiotensin receptor blockers

AV – Atrioventricular

AU – Arbitrary units

BB - Beta-blockers

BiV – Biventricular

BMI - Body mass index

BP – Blood pressure

cAMP- Cyclic adenosine monophosphate

CHF - Chronic heart failure

CHR – Critical heart rate

CIED – Cardiac implantable electronic device

CMR - Cardiac magnetic resonance

CO – Cardiac output

CRT - Cardiac resynchronisation therapy

CS – Circumferential strain

CSI – Chemical shift imaging

DBP - Diastolic blood pressure

DCM – Dilated cardiomyopathy

ECG - Electrocardiogram

FFR – Force frequency relationship

FOV – Field of view

FT – Feature tracking

$^{1}$H-MRS – Hydrogen magnetic resonance spectroscopy

HF – Heart failure

HFpEF - Heart failure with a preserved ejection fraction

HFrEF - Heart failure with reduced ejection fraction

HTN – Hypertension

ICD - Implantable cardioverter defibrillator

IHD – Ischaemic heart disease

LGE - Late gadolinium enhancement imaging

LS – Longitudinal strain

LV – Left ventricle

LVAD - Left ventricular assist device

LVCO – Left ventricular cardiac output

LVEDV - Left ventricular end diastolic volume

LVEF - Left ventricular ejection fraction

LVESV - Left ventricular end systolic volume

LVSD - Left ventricular systolic dysfunction

LVSV – Left ventricular stroke volume

MI - Myocardial infarction

MR – Magnetic resonance

MRA - Mineralocorticoid receptor antagonists

MRI – Magnetic resonance imaging

MRSI - Magnetic resonance spectroscopic imaging

mRNA – Messenger RNA

NCX - Na/Ca exchanger

NE – Norepinephrine

NMR - Nuclear magnetic resonance

NYHA - New York Heart Association functional class

$^{31}$P-MRS – Phosphorus magnetic resonance spectroscopy

PET – Positron emission tomography

PPM - Permanent pacemakers

RA – Right atrium

RAS - Renin angiotensin system

RF - Radiofrequency

RS – Radial strain

RV – Right ventricle

RVEDV – Right ventricular end diastolic volume

RVESV – Right ventricular end systolic volume

RVF – Right ventricular failure

SAR - Specific absorption rate

SBP - Systolic blood pressure

SERCA - Sarco/endoplasmic reticulum Ca2+-ATPase

SPECT - Single-photon emission computed tomography

SR – Sarcoplasmic reticulum

SV – Stroke volume

TE – Echo time

TR – Repetition time

# Abstract

Heart failure with reduced ejection fraction (HFrEF) is a common condition in the UK that is increasingly managed with devices including cardiac resynchronisation therapy (CRT). Modern CRT devices are largely compatible with magnetic resonance imaging (MRI) but are reverted to right ventricular pacing settings with CRT switched off during an MRI scan. MRI itself is becoming more commonplace in the clinical setting and is considered the gold standard imaging modality for assessing cardiac dimensions and function. I have shown that scanning patients with compatible CRT devices in a MRI scanner with CRT active is not only safe but potentially valuable in the cardiac assessment, especially in considering the impact CRT has for the patient. By utilising the capability of pacemakers to alter the heart rate and pacing mode and combining this with the fidelity of MRI, I investigated the mechanism by which CRT augments function in patients with HFrEF. I focus on the Force-Frequency Relationship (FFR) which highlights the increase in contractility observed in healthy individuals in higher heart rates as found in healthy tissue. The FFR has been shown to be abnormal in patients with HFrEF. Investigating the FFR in the context of CRT also allows exploration of how CRT may be improving cardiac mechanics in HFrEF patients. This thesis will describe the abnormal FFR found in patients with HFrEF characterised by a lower contractility response to heart rate rise, an earlier plateau at a lower heart rate and an excessive and rapid drop in contractility at heart rates beyond this. My data also show that although CRT does not normalise the FFR, it contributes to an improvement in this adaptive mechanism which is lost when CRT is deactivated. This thesis will describe potential mechanisms underlying the abnormal FFR, effects of CRT and explore how, despite progress, existing MRI techniques such as spectroscopy to explore cardiac metabolism remain challenging in the context of CRT. This work has a number of clinical implications ranging from greater awareness of a heart range in heart failure and control patients after which cardiac response is non-beneficial and the apparent viability of high-fidelity MRI to evaluate cardiac mechanisms and energetics.

# Contents

# List of Tables

# List of Figures

# Chapter 1 - Introduction to Heart failure

## 1.1 Introduction

Chronic heart failure (CHF) is a syndrome characterised by shortness of breath, fatigue and reduced exercise capacity due to functional or structural heart disease. CHF has a prevalence of approximately 1-2% of the adult population in developed countries which increases further in older cohorts [1]. This condition is a leading cause of morbidity and mortality with patients experiencing reduced quality of life and recurrent hospitalisations. Recent data indicates that the survival rate for patients with CHF is 87%, 57% and 35% at 1, 5 and 10 years respectively [2].

The classification of CHF includes objective evidence of cardiac dysfunction and can be split into three categories based upon the degree of left ventricular (LV) function measured by the left ventricular ejection fraction (LVEF):

1. Heart failure with a reduced ejection fraction (HFrEF) in which the LVEF is ≤40% and otherwise termed as left ventricular systolic dysfunction (LVSD).
2. Heart failure with a mid-range ejection fraction between 41-49% (HFmrEF). This relatively new category is reflective of the lack of effective treatment for patients with mild LVSD [3].
3. Heart failure with preserved ejection fraction (HFpEF) in which the LVEF ≥50% and otherwise termed left ventricular diastolic dysfunction.

This thesis will focus on patients with LVSD and my use of the term CHF will imply that patients have HFrEF or HFmrEF. Where relevant, I will use the term HFpEF to categorise patients with symptoms of heart failure but without LVSD (LVEF>50%).

## 1.2 Pathogenesis of CHF

CHF usually occurs after exposure to risk factors such as: myocardial infarction (MI), hypercholesterolaemia, diabetes mellitus, hypertension or obesity [3, 4]. CHF is generally a progressive condition manifesting through myocyte loss and increased myocardial strain [5]. This combination leads to detrimental hypertrophy both directly

and through compensatory mechanisms secondary to reduced cardiac output (CO) and organ perfusion (figure 1). Neurohormonal activation results in increased catecholamines, endothelin, natriuretic peptides and up regulation of the renin-angiotensin-aldosterone system (RAS) [6]. These changes alter the LV from an elliptical shape to a spherical structure, termed LV remodelling. The consequence is less efficient myocardial contraction with increased myocardial oxygen consumption [7, 8]. Interestingly despite the multiple aetiologies of CHF, the pathways seem to partially merge leaving relatively similar mechanisms resulting in heart failure (HF).

Overall, ischaemic heart disease (IHD) is the main cause of CHF in developed countries [9]. A MI can cause cardiac myocytes to be replaced by scar tissue with variable levels of myocardial contraction loss. Small vessel occlusion rarely leads to LVSD, however repeat ischaemic episodes can lead to a “stunning” phenomenon in which there is repeated transient loss of muscle contractility. “Hibernating” myocardium is used to describe the chronic dysfunction of cardiac contractility as a result of ischaemia [10]. This usually occurs when reduced coronary blood flow results in an ischaemic myocardium that causes lower levels of contractility despite myocytes remaining viable. Recent large trials highlight the impact of reducing cardiovascular ischaemia on increasing survival [11]. The role of revascularisation and contemporary treatment in improving LVEF remains mixed with up to 47% of patients not showing an increased LVEF post MI [12]. Hypertension may be the most significant risk factor worldwide through increases in afterload as found in IHD [13]. Other risk factors include idiopathic dilated cardiomyopathy (DCM), valvular heart disease, viral infections, infiltrative diseases (amyloidosis) and tachycardia induced myopathy.

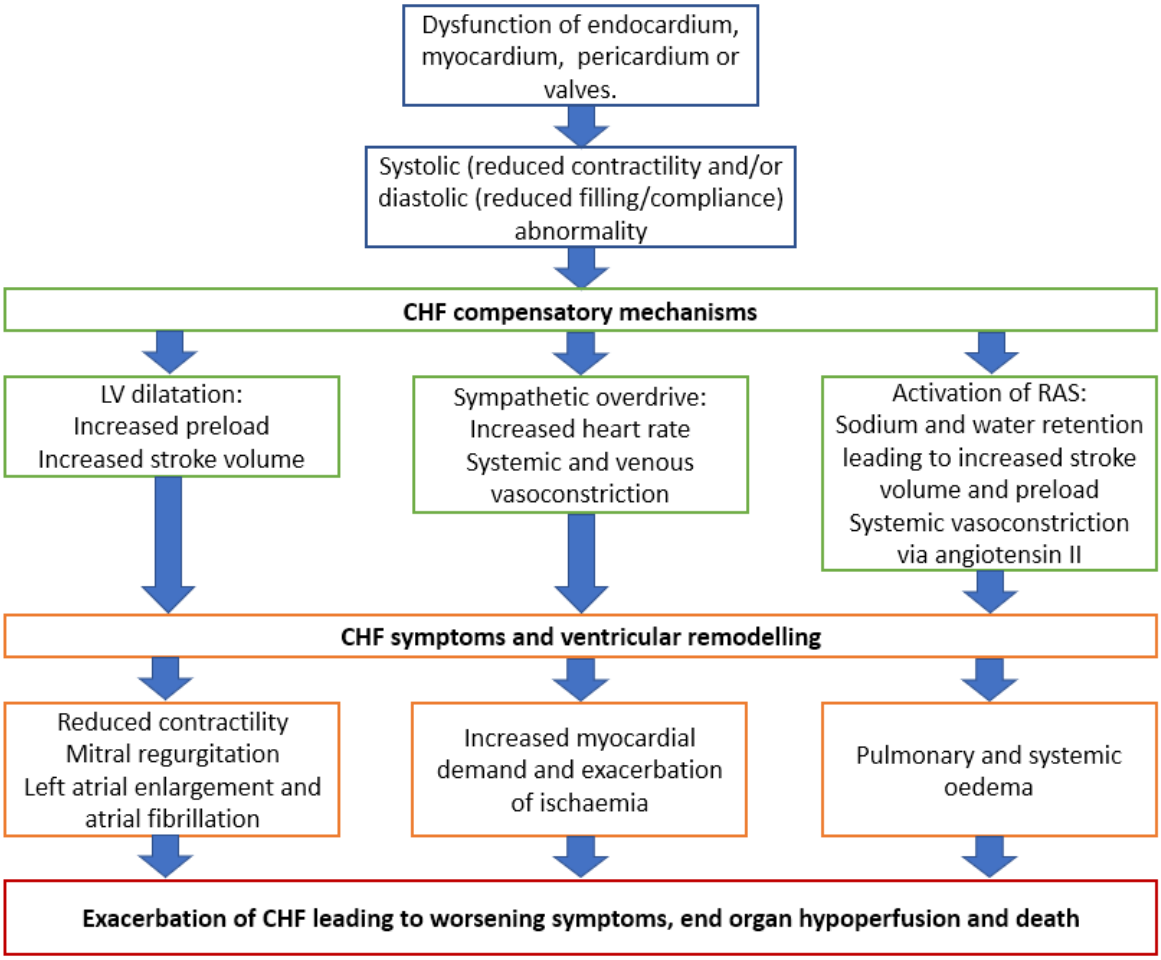



Figure 1 - Development and progression of CHF [14, 15].

## 1.3 Epidemiology of CHF

HF is a common condition in developed countries with an estimated 900,000 people in the UK with CHF [16]. The disease is associated with older age and the average age of first diagnosis is 76 years [17]. However from the age of 55, the lifetime risk of CHF is 33% in men and 29% in women [18].

CHF patients often have a poor quality of life not only because of symptoms and a reduced exercise capacity affecting daily living but also due to high hospital readmission rates [19, 20]. CHF patients remain with a poor prognosis despite advances in therapeutic options. In the primary care setting they have a reported survival rate of 81.3%, 51.5% and 29.5% at 1, 5 and 10 years respectively following diagnosis [21]. Indeed CHF is responsible for approximately 5% of all emergency

medical hospital admissions and 2% of all NHS hospital inpatient bed-days [22]. CHF associated hospital admissions are expected to increase dramatically due to the general ageing population [23].

## 1.4 Diagnosis of CHF

CHF is often defined by exercise intolerance with dyspnoea and fatigue. However, these symptoms neither constitute the diagnosis nor exclude it in its absence with other symptoms such as peripheral oedema which can suggest the syndrome. Making a diagnosis of CHF requires an accurate history complimented by clinical examination. Investigations including blood tests, an ECG, chest x-ray, exercise tests and imaging are valuable in confirming the presence, aetiology and severity of cardiac dysfunction [3]. In most cases the diagnosis is based on a patient's history and symptoms, signs on clinical examination and echocardiographic findings of CHF. Classic indicators of CHF on echocardiography are a reduced LVEF with a dilated LV [24]. Making a diagnosis can be complicated by non-specific symptoms or insignificant abnormal values on echocardiography [25]. Measuring B-type natriuretic peptide (BNP or NT-proBNP) is an effective screening tool for CHF and remains a useful biomarker for assessing response to interventions [3, 26]. UK national guidelines indicate that patients suspected of CHF with a NT-proBNP level >2000 pg/ml need an urgent cardiology review and echocardiogram within 2 weeks [22]. Symptomatic patients with a NT-proBNP level between 400-2000 pg/ml should have an echocardiogram and specialist review within 6 weeks [22].

Cardiovascular magnetic resonance (CMR) whilst becoming more accessible with a class 1C recommendation for diagnosis in ambulatory patients, predominately has a complimentary rather than diagnostic role in the work up of CHF [3]. CMR is particularly useful when echocardiographic images are inconclusive and is the gold standard method of assessing LVEF and volume [27]. CMR is becoming increasingly utilised in CHF patients due to its high reproducibility, accuracy and ability to characterise tissue. It is also used in patients suspected of rarer aetiologies of CHF such as amyloidosis [28].

## 1.5 Imaging Options for CHF

There are multiple options for imaging patients with suspected or established HF. These techniques are improving and expanding at a rapid pace, enabling not only improved diagnosis but also monitoring progression of CHF via LVEF and newer concepts such as myocardial deformation via strain imaging [29].

### *Chest X-ray*

A chest x-ray was commonly utilised historically for diagnosing CHF through the signs of fluid overload consistent with decompensated CHF. In modern times it is primarily used to identify a pulmonary aetiology for symptoms and occasionally in the acute setting to confirm pulmonary oedema or congestion in decompensated CHF [3].

### *Echocardiography*

Echocardiography is the first line diagnostic imaging option for CHF patients. This technology uses ultrasound to obtain two and three-dimensional imaging of the heart. There are two common methods of obtaining an echocardiogram; one is transthoracic and the other is transoesophageal which is more invasive and used in specific circumstances such as imaging of the posterior heart or valves in higher detail. A number of additional techniques and technologies can be integrated to obtain further measurements including deformation imaging and Doppler (pulsed, continuous and colour flow) [3]. Echocardiography is being increasingly used for measuring inducible ischaemia and myocardial viability via exercise or pharmacological stress with particular utility in certain valve disease, exertional dyspnoea and HFpEF patients [30]. Notably the LVEF can be obtained from a number of techniques with three-dimensional echocardiography, further improving volume quantification and estimation of ejection fraction. Use of Doppler enables haemodynamics to be measured including cardiac output (CO) and the stroke volume (SV) index [3]. More recently, deformation imaging has become available via strain and strain rate which is likely to be useful at the preclinical stage despite reference values varying amongst devices [31]. Echocardiography has a number of limitations. For example, when obtaining LVEF or cardiac dimensions, measurements are reliant on image quality with geometric assumptions made and a

relatively high intra and inter-observer variability rate. Using Doppler technology is reliant on good angle alignment, appreciation of tethering artefact and can also be heart rate (HR) dependent when focusing on diastolic function [32].

### *Nuclear imaging*

This modality is effective in assessing the level of sympathetic innervation and blood flow through the myocardium. Nuclear imaging involves a small amount of radioactive material (tracer) that is either swallowed or injected into the body. The material gives off gamma radiation that is picked up by sensors. The tracer travels via the chosen route to the area being examined which then allows images to be formed by computer-based analysis. There are largely two methods of nuclear imaging employed in HF. Single-photon emission computed tomography (SPECT) is useful in analysing myocardial perfusion in relative terms. It may be helpful in assessing the myocardial viability, general ischaemia and evaluation for cardiac amyloidosis. It must be noted however that SPECT exposes the patient to ionising radiation [3]. Positron emission tomography (PET) enables accurate quantification of blood flow through the myocardium [33]. It has improved temporal and spatial resolution compared to SPECT with greater ability to assess dynamic images [34]. This combination makes PET effective in evaluating cardiac sympathetic innervation which is achieved through radiolabelled catecholamines and analogues.

It is becoming increasingly common for CT systems to be combined with SPECT or PET, creating hybrid scans. This has had a significant impact towards molecular-targeted imaging and personalised cardiovascular medicine [34]. Both SPECT and PET are options for imaging in European guidelines in relatively specific situations due to the high cost, radiation exposure and limited general availability of these imaging modalities [3].

### *Cardiac computed tomography (Cardiac CT)*

Cardiac CT is largely used as a non-invasive method of identifying plaque or coronary artery disease risk in CHF patients and is comparable to invasive angiography. Cardiac CT is extremely cost effective and recommended by the National Institute for Health and Care Excellence (NICE) as first-line investigation in

patients who have new-onset chest pain possibly caused by coronary artery disease [35].

***Cardiac magnetic resonance (CMR)***

CMR is the gold standard imaging modality for assessing cardiac ventricular volumes, mass and ejection fraction. It is the recommended imaging option for patients with inconclusive echocardiograms and first choice in patients with complex congenital heart disease. CMR is also preferred in the measurement of myocardial fibrosis and can be useful in confirming HF aetiology especially in less common conditions such as myocarditis, sarcoidosis, Chagas disease and haemochromotosis [3]. There is also utility in using CMR for assessing ischaemia and myocardial viability in the work up for CHF.

The limitations around CMR largely surface with the capital cost and expertise required in image acquisition and interpretation. Although MRI is becoming increasingly accessible to hospitals, it remains at a higher cost than echocardiography. Due to the size of the 'bore hole' (area that the patient slides into for scanning), claustrophobic or morbidly obese patients may be declined imaging. Finally, this modality has unclear risks to patients with metallic implants and devices [3]. CMR will be discussed in further detail at Chapter 3.

| **Recommendation** | **Class** | **Level** |
|---|---|---|
| Transthoracic Echocardiogram (TTE) is recommended for the assessment of myocardial structure and function in patients to establish a diagnosis of HFrEF or HFpEF. | I | C |
| TTE is recommended to assess LVEF in order to identify patients who could be suitable for evidence-based pharmacological and device (ICT, CRT) treatment recommended for HFrEF. | I | C |
| Other techniques (including Doppler and deformation indices) should be considered in the TTE protocol for subjects at risk of developing HF in order to identify | IIa | C |

| | | |
|---|---|---|
| myocardial dysfunction at the preclinical stage. | | |
| CMR is recommended for the assessment of myocardial structure and function in subjects with poor acoustic window or complex congenital heart diseases. | I | C |
| CMR with late gadolinium enhancement should be considered in patients with dilated cardiomyopathy in order to distinguish between ischaemic and non-ischaemic myocardial damage in case of equivocal clinical and other imaging data. | IIa | C |
| CMR is recommended for the characterisation of myocardial tissue in cases of suspected myocarditis, amyloidosis, sarcoidosis, Chagas disease, Fabry disease non-compaction cardiomyopathy and haemochromatosis. | I | C |
| Non-invasive stress imaging (CMR, stress echocardiography, SPECT, PET) may be considered for the assessment myocardial ischaemia and viability in patients with HF and coronary artery disease (CAD). | IIb | C |
| Cardiac CT may be considered in patients with HF and low to intermediate pre-test probability of coronary artery disease. | IIa | C |
| Reassessment of myocardial structure and function is recommended using non-invasive imaging:<br>• In patients presenting with worsening HF symptoms.<br>• In patients with HF who have received evidence-based pharmacotherapy in maximal tolerated doses, before the decision on device implantation (ICD, CRT). | I | C |

Table 1 - Recommendations for cardiac imaging in CHF by the European Society of Cardiology [3].

# Chapter 2 – Management of CHF

## 2.1 Evolution of CHF management

The management of CHF is largely evidence based and the European Society of Cardiology working group on HF have published international guidance [3]. More recently we have published a review article that focuses on the relevance of identifying and monitoring symptoms of patients with CHF [36]. Patient related outcomes could enable tailoring of management to focus on the symptomology of the patient and likely improve quality of life [36]. The focus of management in CHF is to increase survival, improve functional capacity and relieve symptoms. The management options have gone through a number of changes with one of the most dramatic being the reversal of betablockers (BB) from being contraindicated in CHF patients (due to its negative inotropic properties) to becoming a mainstay treatment in this syndrome. Indeed the first clinical trial in BB that showed an improvement in survival took place only in 2009 [37]. Other medications such as angiotensin-converting enzyme inhibitors (ACEI) had proven efficacy as early as 1987 with mineralocorticoid receptor antagonists (MRA) following suit shortly after in 1999 [38, 39]. There have also been some newer drug mechanisms uncovered and novel drugs entering the market such as angiotensin receptor neprilysin inhibitors which have improved survival further. Additionally, device therapy may provide significant improvements when pharmacological therapies have already been explored. Notably, many patients (44%) with HFrEF that improve with pharmacological therapy (a normal LVEF, minor or normal biomarkers and absence of symptoms) relapse back into CHF within 6 months when medical management is stopped [40]. This suggests that current markers such as LVEF are likely to not be sufficient for monitoring disease or to appreciate CHF as a syndrome that causes changes beyond the heart. The management of CHF can be split into pharmacological and non-pharmacological options.

## 2.2 Pharmacological management of CHF

### *Angiotensin-converting enzyme inhibitors (ACEI)*

Angiotensin converting enzymes convert angiotensin I to angiotensin II. Angiotensin II is a peptide hormone that causes systemic vasoconstriction and sodium retention via kidneys and the adrenal gland, thereby increasing SV, afterload and systemic blood pressure (BP). Inhibition of this enzyme through ACEI thereby leads to vasorelaxation, reduced afterload, and less renal salt and water retention. Since ACEI also block the activity of the kininase enzyme, ACEI enhance the vasodilating properties of bradykinin through inhibition of its breakdown [41].

Guidelines recommend that ACEI are initiated at a low dose with regular dose increments to the highest level tolerated to maximise renin-angiotensin-aldosterone system (RAS) inhibition [42]. This has beneficial effects on cardiovascular remodelling through arterial and venous dilatation, reduced systemic volume and afterload resulting in lower systemic BP. Optimal dosing of ACEI is associated with significant improvements to mortality and morbidity in patients with symptomatic CHF and acute LVSD following MI [42, 43].

### *Angiotensin II type I receptor blockers (ARB)*

Patients with CHF usually receive an ARB when they are not able to tolerate ACEI. ARB independently reduce cardiovascular mortality and are also associated with lower hospitalisation rates when combined with standard medical therapy including ACEI [44, 45]. Despite this, ARB should only be combined with ACEI under strict supervision, often in patients that are intolerant to standard treatment. In general, ARB are not used in combination with ACEI due to the increased side effect profile, particularly to renal dysfunction (and the associated serious electrolyte imbalances) which usually outweigh the benefits to CHF hospitalisation rates [46].

### *Angiotensin receptor neprilysin inhibitor (ARNI)*

This is a newer class of RAS blocking drugs. It is a combination of an ARB and a neprilysin inhibitor. Neprilysin inhibitors augment (slows) the breakdown of peptides, most relevantly, natriuretic peptide levels (A & B-type natriuretic peptides) and bradykinin. Maintaining natriuretic peptides promotes diuresis, sodium loss, myocardial relaxation and inhibits aldosterone and renin whilst slowing LV remodelling. The PARADIGM-HF trial compared ambulatory patients with symptomatic CHF and found ARNIs superior to ACEI in terms of a reduced cardiovascular mortality, all-cause mortality and CHF related hospitalisations [47]. The only commercial option is Sacubitril/valsartan and on release represented the end of a 10 year gap in novel medication approval for patients with CHF [48].

### *β-adrenoreceptor antagonists (Beta-blockers)*

BB reduce the effect of adrenaline on β-receptors, impeding sympathetic nervous system activation. Patients with CHF have altered neurohormonal activation with profound increases in sympathetic activity as a compensatory positive inotropic mechanism to improve SV alongside peripheral vasoconstriction [49]. Inhibiting sympathetic over-activation is associated with improved ventricular remodelling and survival [50]. In the last decade, drugs that block beta-1 receptors (predominately expressed in cardiac muscle) have been utilised in HF although BB that are non-selective may be more beneficial [51]. Guidelines suggest starting BB following a diagnosis of HF even in acute circumstances due to the associated improvements in mortality and morbidity, albeit cautiously [52]. The dosing should be gradually increased to the maximum dose that is tolerated by the patient with observation of the BP and heart rate (HR).

### *Digoxin*

Digoxin causes inhibition of the sodium potassium adenosine triphosphatase (Na-K-ATPase) membrane pump mainly within the myocardium. This results in increased sodium levels intracellularly producing mild diuretic and positive inotropic effects. Digoxin also augments neurohormonal function and reduces atrio-ventricular conduction [53]. Optimising digoxin dosing is difficult as it is primarily excreted

through the kidneys with low doses producing positive inotropic effects whilst higher doses can give side effects such as confusion, arrhythmias and death [54, 55]. The drug has moved from first line treatment to being reserved for specific indications due to its narrow therapeutic window, increased mortality risk and unclear benefits, despite being associated with reduced hospitalisation [55-59]. The modern use of digoxin is to alter the ventricular rate in patients in AF when other medications have failed.

### *Ivabradine*

Ivabradine inhibits the conduction channels of the heart, specifically the $I_f$ (funny channel) found in the sinus node. This causes a slower HR without the classical changes to BP. Due to its mode of action, Ivabradine is not licensed for use in patients who do not have a sinus rhythm, for example those in atrial fibrillation (AF). It is associated with improved survival in patients who have CHF (LVEF≤35%) with a resting HR ≥ 75bpm [60].

### *Loop and thiazide diuretics*

Loop diuretics act on the Na-K-Cl cotransporter found in the thick ascending limb of the loop of Henle. By inhibiting reabsorption of these molecules, water remains within the collecting duct and passed from the body through urine.

Thiazide diuretics inhibit NaCl symporter in the distal tubules within the kidneys giving a longer but weaker acting mechanism of action than loop diuretics [61]. Caution must be given when these two drugs are prescribed together due to potent synergistic diuresis.

These classes of diuretics have been shown to improve symptoms such as dyspnoea and peripheral oedema. Indeed meta-analysis suggest diuretics may even improve exercise capacity and mortality [62].

### *Mineralocorticoid receptor antagonists (MRA)*

MRA primarily inhibit sodium reabsorption in the kidneys via the collecting ducts. This promotes diuresis which reduces cardiac preload and afterload. MRA are recommended in combination with ACEI and BB for further improvements in mortality and hospitalisation in patients with symptomatic CHF [63]. Caution must be taken in monitoring renal function, particularly potassium levels in CHF patients managed with MRA.

### *Anti-arrhythmic drugs*

CHF patients are more likely to develop ventricular tachyarrhythmias and are at greater risk of sudden cardiac death. However, combining standard treatment such as BB with anti-arrhythmics such as dofetilide and amiodarone whilst helpful in converting AF and reducing hospitalisation does not reduce mortality [64, 65]. Guidance is to use standard CHF treatment including ACEI, BB, MRA and sacubitril/valsartan to reduce rates of ventricular arrhythmia and sudden death.

### *Risk factors*

Modifying risk factors are useful in all patients with CHF. The SPRINT trial has shown that treating hypertension aggressively (aiming for systolic BP<120 mmHg) reduced mortality and hospitalisation rates [66]. This supports earlier findings that controlling BP delays HF development [67].

There is significant evidence that ACEI can stall development of HF and reduce mortality in patients with IHD [68]. Indeed IHD represents a significant modifiable risk factor with primary percutaneous coronary intervention associated with a reduced the risk of HF and impaired LVEF [69]. Medications such as ACEI, BB and MRA are associated with reduced mortality and HF related hospitalisations following MI [70-73]. Statins (HMG-CoA reductase inhibitors) also make CHF less likely to develop [74].

## 2.3 Non-Pharmacological management of CHF

Non-pharmacological management options are often under emphasised in CHF management. Multiple studies have identified lifestyle modifications as effective in reducing both preventing and reducing progression of CHF and cardiac disease [75, 76].

### *Exercise*

All patients with CHF are encouraged to carry out regular exercise. Increasing physical fitness improves exercise capacity and prognosis. This helps to counter the complex syndrome of CHF (neuroendocrine, haemostatic, inflammatory and musculoskeletal) which leads to altered haemodynamic response and muscle wasting [77]. Exercise training has been shown to partially return peripheral abnormalities to normal including mitochondrial function, composition of skeletal muscle fibres and skeletal muscle mass [78]. Furthermore, exercise seems to correlate with reduced risk of HF and related hospitalisations [79]. This is partially explained through the reduced incidence of some of the CHF risk factors of CHF such as diabetes and obesity [80].

### *Alcohol consumption*

Patients should stay away from significant weekly alcohol intake; however modest alcohol consumption (<7 drinks/week) has been associated with a lower risk of future HF [81]. The benefits are less clear in patients without a history of MI and it is likely drinking patterns and genetics that confer risk [82, 83].

### *Smoking*

Smoking is strongly linked to IHD, a significant risk factor for CHF. It has also been independently linked to worse mortality and morbidity with smoking cessation leading to improved outcomes [84].

### *Diet*

Dietary advice in CHF is relatively generic, focusing on eating a well-balanced healthy diet and cautioning away from salt rich foods which is helpful to offset the development of hypertension. Diets that are low in saturated fats and high in fruits and vegetables reduce the incidence of HF and are associated with higher LV function [85, 86].

### *Travel*

Individuals with HF are more likely to develop venous thrombosis during periods of sedentary travel. HF patients are prothrombotic due to the reduced blood flow, altered endothelial wall (such as impaired nitric oxide release) and increased plasma viscosity present in this cohort [87]. Thus, it is important that patients with CHF keep mobile on long journeys and stay well hydrated.

## 2.4 Device therapy in CHF - Cardiac resynchronisation therapy (CRT)

### *The effect of conduction delay and indication for CRT*

CRT is indicated for symptomatic CHF patients with cardiac dyssynchrony. This is a complex phenomenon in which there are prolonged atrioventricular intervals and ventricle-ventricle delays causing pauses and dyssynchronous contraction of the ventricles [88].

Contraction of the ventricles is controlled through cardiomyocytes and the Purkinje conduction fibres. As the contraction signal is passed down, a coordinated muscular contraction occurs giving an efficient powerful ventricular squeeze, generating the CO via SV. This pattern can become uncoordinated due to disease of the myocardium, failure within the conduction system itself or from iatrogenic causes (eg. Right ventricular pacing) leading to reduced LV systolic function [89, 90]. Conduction abnormalities are over-represented in CHF patients with left bundle branch block (LBBB) present in approximately 25% of the cohort [91]. Presence of LBBB is a poor prognostic marker in CHF and has been shown to dramatically

increase 1 year mortality (16.1% vs 11.9% across the general population of CHF patients) with an associated 58% raised risk of sudden death [92]. The poor co-ordination of muscle contraction causes late tissue activation resulting in greater work load requirements (variance in myocyte sarcomere shortening) of the myocardium via canine models [93]. This in turn reduces myocardial perfusion, exacerbating the delayed contraction and reducing SV [89, 94]. CRT synchronising ventricular contraction whilst producing increased energetic efficiency as measured with myocardial oxygen consumption [95].The cumulative effect is worse survival for patients who already have a poor prognosis with CHF and thus requires proactive identification and management [96].

| | **Recommendation** | **Class** | **Level** |
|---|---|---|---|
| Patients in sinus rhythm | **LBBB with QRS duration >150 ms**<br><br>CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment. | I | A |
| | **LBBB with QRS duration 120–150 ms**<br><br>CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment. | I | A |
| | **Non-LBBB with QRS duration >150 m**<br><br>CRT should be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment | IIa | B |

| | | | |
|---|---|---|---|
| | **Non-LBBB with QRS duration 120–150 ms**<br><br>CRT may be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II, III and ambulatory IV despite adequate medical treatment | IIb | B |
| | CRT in patients with chronic HF with QRS duration | III | B |
| Patients in permanent AF | **Patients with HF, wide QRS and reduced LVEF**<br><br>CRT should be considered in chronic HF patients, intrinsic QRS ≥120 ms and LVEF ≤35% who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment, provided that a BiV pacing as close to 100% as possible can be achieved. AV junction ablation should be added in case of incomplete BiV pacing. | IIa | B |
| | **Patients with uncontrolled heart rate who are candidates for AV junction ablation**<br><br>CRT should be considered in patients with reduced LVEF who are candidates for AV junction ablation | IIa | B |

Table 2 – Indications for CRT in patients in sinus rhythm and permanent AF. Adapted from current ESC guidelines [88].

***How does CRT work and improve outcomes?***

CRT devices stimulate both the left and right ventricles via biventricular pacing (BiV) by creating a state of pre-excitation at the LV free wall and right ventricular (RV) septum or apex. The lead into the LV is placed using retrograde insertion from the lateral cardiac vein via the coronary sinus (figure 2). The LV is generally stimulated slightly earlier than the RV to re-create normal contraction of the heart. It is important to note that electrical activation delays create corresponding muscular contraction delays [97]. This is complicated by dyssynchronous contraction due to muscle

damage and contractility weakness even in the context of normal electrical activity [89]. Early RV stimulation leads to greater dyssynchrony particularly impacting the LV [98]. To improve coordination, atrial electrical activity is either measured or paced with a timer followed by ventricular stimulation and thus contraction. Placing the lead in the LV more laterally, coinciding with the most delayed region is effective for outcomes as opposed to an apically positioned lead [89]. However other studies have found apical placement to be associated with improved survival and reduced cardiac events [99]. By improving ventricular contraction, a dramatic improvement in SV and systolic function are obtained. Indeed, both myocardial efficiency and coronary blood flow are improved [100, 101]. These changes result in reduced mortality and morbidity in CHF patients which are promoted further in those with more prolonged conduction [3, 102]. Importantly, functional capacity has been shown to improve following implantation [103]. Symptoms such as breathing are often less severe as validated by lung function tests and breathing patterns analysis post implantation [104]. These improvements are likely due to correction of the dyssynchrony as CHF patients with relatively normal ventricular conduction do not receive a benefit and instead have increased mortality following CRT implantation [105].

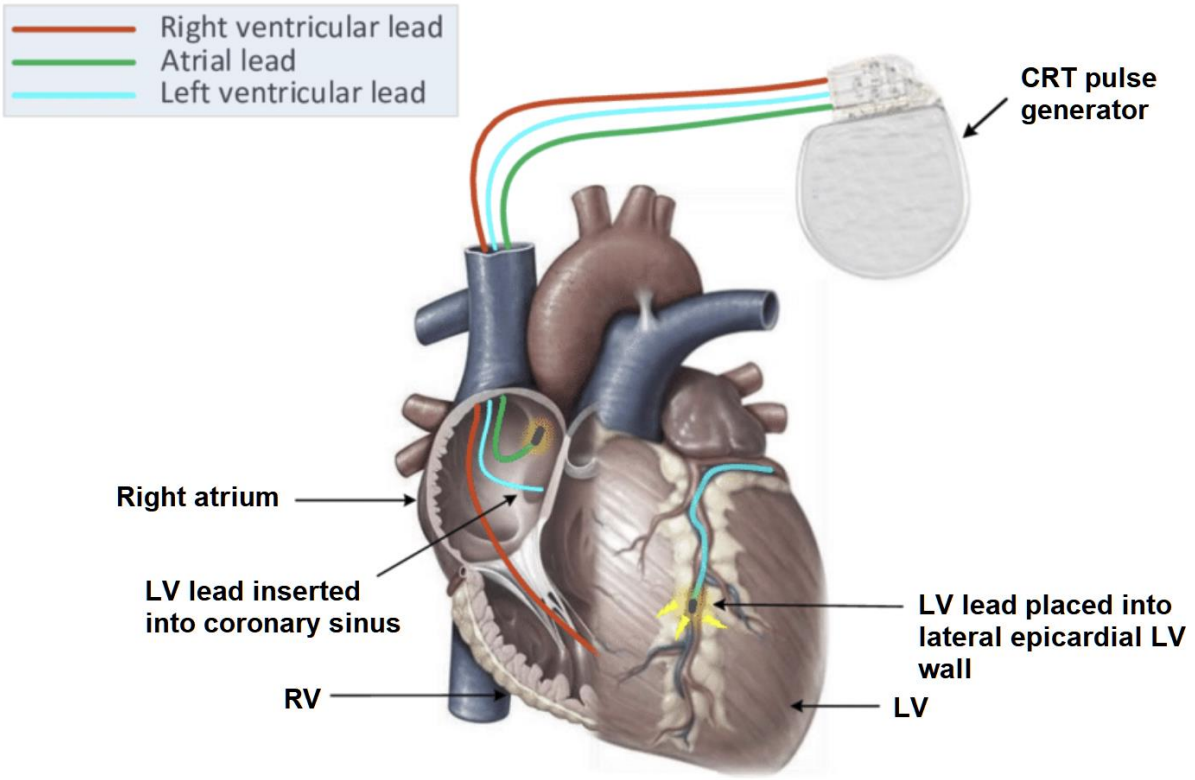


Figure 2 – The lead positions of a CRT device. Adapted from Albatat et al [106]

Fine tuning CRT for the patient involves optimising both the interventricular and atrioventricular (AV) delay at rest and on exercise. The interventricular delay can be optimised using a number of methods including BP or CO monitoring based on echocardiography, invasive measurement of systolic ventricular pressure and algorithms within the device. There are many methods of AV delay optimisation with the target usually depending on the modality chosen such as echocardiography or formula based parameters [107]. A number of studies have shown that optimising CRT is associated with improvements to mortality, quality of life and exercise capacity [102, 108, 109]. Conversely, methods such as AV optimisation has been found to have a neutral effect on echocardiographic and clinical outcomes [110-112]. Furthermore, it remains difficult to evaluate which methods are the most effective and guidance suggests optimisation to be trialled in patients who have a poor response to CRT [3].

CRT is not effective in all CHF patients and a positive long-term outcome is often associated with the degree of reverse remodelling. A number of factors are suggestive of a positive response: Female sex, large QRS width and presence of LBBB [3]. Despite this, approximately 30% of CHF patients do not improve with CRT [113]. This relatively high rate is associated with the lack of knowledge surrounding the multi-modal mechanism of CRT action and the variable definitions of non-response by specialists. Response can be defined by an improvement in mortality, quality of life, reverse remodelling measurements and composite measures. Indeed, only 4 studies evaluating CRT response have a strong agreement end points, which increases to 75% for a weak agreement [114]. CRT effectiveness is also complicated by AF, which is present in approximately a quarter of CHF patients receiving CRT [115]. This group of patients did not receive benefits from CRT when compared with non-AF CHF patients in the RAFT study [116]. The Packer composite score which categorises patients as worsened, unchanged or improved identified improved outcomes in the BLOCK-HF study across all time points when comparing BiV to RV pacing in CHF patients [117].

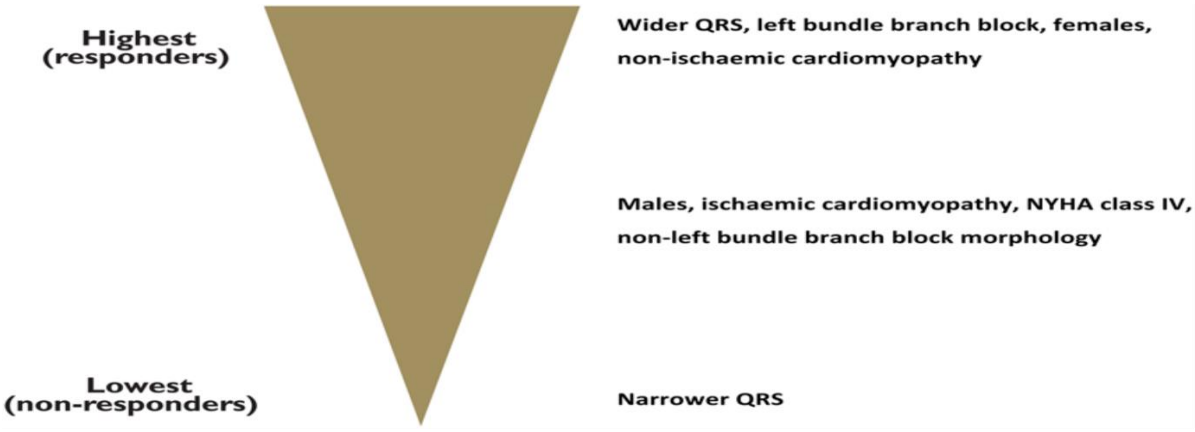



Figure 3 - The factors influencing the response to cardiac resynchronization therapy. Adapted from Brignole et al [88].

## 2.5 Other device therapies in CHF

### *Implantable cardioverter defibrillator (ICD)*

An ICD is an advanced pacemaker that has the ability to shock the heart in order to carry out cardioversion or defibrillation. They are a useful option when medical therapy has failed to restore an acceptable rhythm. Approximately 40% of CHF patients die from sudden or explained death [118]. This is blamed in part due to arrhythmias; however anti-arrhythmic medications have a low success rate and can increase mortality [3].

ICDs are recommended in CHF patients with an ejection fraction < 35%, however they should be avoided in patients who have had a MI within 40 days or those with New York Heart Association functional class (NYHA) IV and are unresponsive to medical therapy [3]. ICDs are effective in reducing sudden death and RCTs indicate mortality reduction of 23% following implantation [64].

### *Left ventricular assist devices (LVAD)*

LVAD are destination therapy or a bridge to transplantation for patients on the waiting list for organ donation. A LVAD is a mechanical pump placed into the LV to support the native heart. Patients must be anticoagulated and treated proactively for pathogens to reduce the otherwise significant risk of pump thrombosis and infection

respectively. LVADs improve survival and quality of life when compared with optimal medical therapy [119]. However, these devices are yet to become easily accessible as only a few centres in the country are capable of implantation and monitoring due to the high capital cost and associated aftercare. This makes it important to ration it to CHF patients who have failed to improve following all traditional therapy options including CRT. It is difficult to gauge implantation rates, however it is believed less than 80 LVADs are implanted in the UK annually [120]. LVADs have complications associated with implantation which fall into 3 main categories: Thrombus formation, infection and device failure. The latter two issues have steadily reduced in incidence through improvements in the device technology, surgical procedure and driveline materials. Stroke remains as a significant lifetime risk for LVAD patients which can be as high as 13.3% though definite numbers remain unclear due to the rapidly evolving device technologies [121]. Patient selection for implantation also requires further refinement as comorbidities that are classically found in CHF patients such as hypertension and chronic kidney disease are associated with higher adverse outcomes and reduced likelihood of receiving a cardiac transplantation post LVAD implantation [122, 123]. It is expected that following more research, LVADs will become more commonplace with a reduced side effect profile (potentially in a broader cohort) through state-of-the-art developments such as wireless power sources and miniaturised devices [124, 125].

# Chapter 3 – Magnetic resonance imaging (MRI) and safety issues

## 3.1 Introduction

MRI scanners are able to produce incredibly detailed images of the body and tissue in humans and animals. The technique utilises non-ionising electromagnetic waves, specifically microwaves and radio frequency waves instead of ionising radiation as found in x-rays and CT scanners. Dr Raymond Damadian theorised that cancerous cells should have higher water content compared to healthy cells which can then be picked up by magnetic resonance (MR) [126]. He then went on to patent and build the machine that produced the first images of the human body (his assistant) which was published in 1977 [127]. MRI is useful in many areas of medicine and is typically used in imaging the brain, spine, heart and musculoskeletal system and is considered unsurpassed at assessing soft tissue. Initially the cost of these machines was prohibitive for most of hospitals, however as the capital cost reduced alongside the potential utility of scanning, the availability of MRI has continued to increase in keeping with the majority of developed countries. In 2017, the UK had 6.1 MRI machines per million people which was less than Germany and USA at >10 and >15 per million people respectively [128]. However, the UK utilises these machines at a rate of 56.3 per thousand people which is relatively in line with the average of sampled countries. Initially the criteria for obtaining a scan was quite restrictive due to the known and unknown dangers which largely revolved around being in close proximity to a powerful magnet. Furthermore, the first few decades of MRI development focused on increasing the field strength of MRI largely under the perception of increasing image quality. This has led to the field strengths of MRI scanners progressing from 0.35T to the clinical standard in the UK of 1.5T to recently publicised 10.5T scanners that are used in the research environment [129, 130]. Much of the research in MRI in the last decade has focused on studying and modifying existing scanning protocols and image acquisition techniques. This has led to superior images, reduced scanning times and many more methods of scanning tissue each with their own advantages and disadvantages. Furthermore, more

experience with scanning, larger safety studies alongside the steady standardisation of MRI compatible devices has created a smaller list of contraindications to scanning than ever before.

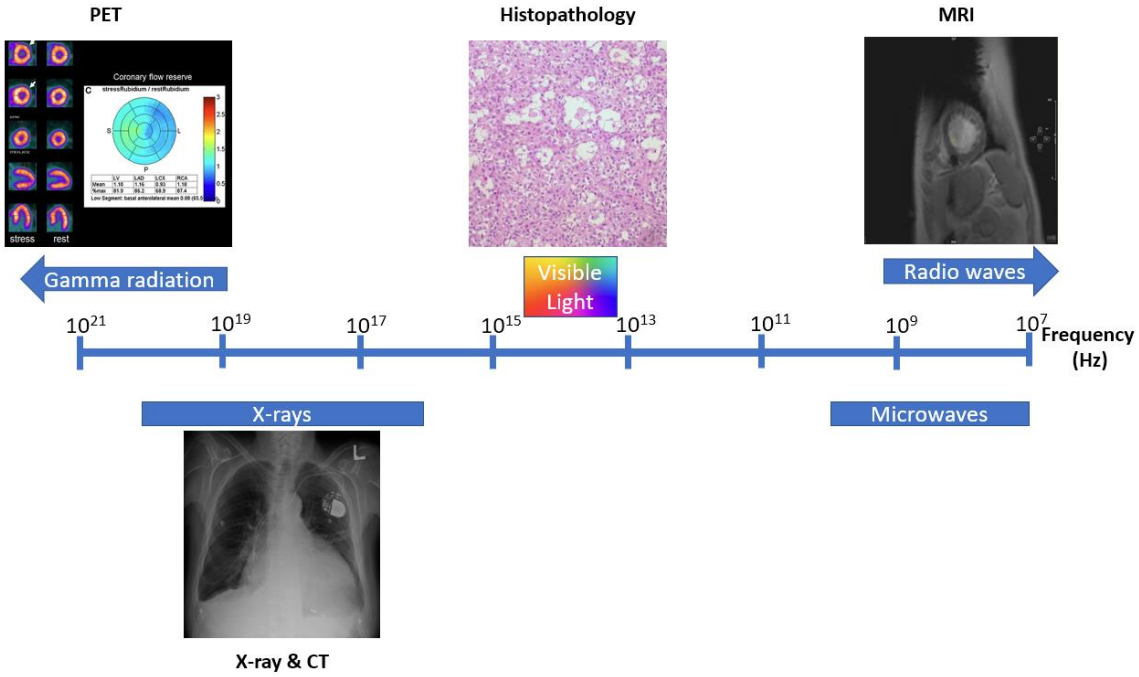



Figure 4 - Frequency range for common cardiac imaging modalities

## 3.2 The basic principles of MRI

MRI is based on the concept of the absorption and subsequent release of energy, specifically when taking place in the radio wave range. The human body is largely made up of muscle, bone, water and fat. MRI relies on imaging the signal produced by hydrogen nuclei from water. The hydrogen atom is a proton with a surrounding electron without a neutron present. The charged state of the nucleus gives a magnetic moment which is usually spinning in a random direction. When exposed to an external, static magnetic field, nuclei of atoms behave like magnets that align in the same direction as the magnetic field or switch to the opposite direction. The larger the magnetic field, the more nuclei that have a magnetic moment aligned in the same direction (low energy state) as opposed to being anti-parallel (high energy

state) [131]. This fact is made more important when considering that in most cases the majority of “noise” or unwanted signal is from the scanned sample rather than originating from hardware [132]. In theory this means that the larger the magnetic field, the higher the number of aligned magnetic moments. Simultaneously, the atoms are spinning on its axis along the primary magnetic field which is called precession. The exact rate of movement is the Larmor or precession frequency which is a product of the static magnetic field strength and the unique spin value of the atom (gyromagnetic ratio) being utilised such as hydrogen.

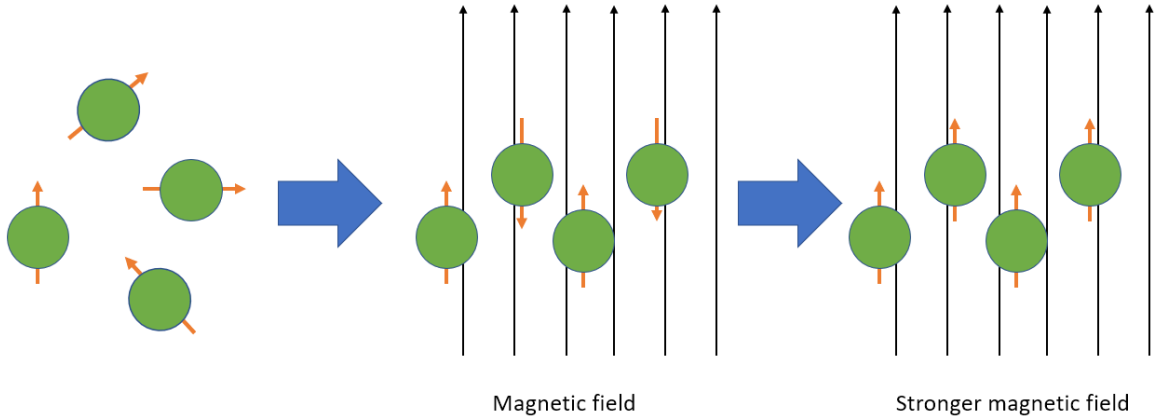



Figure 5 - Exposure to a magnetic field aligns the magnetic moments (orange arrows) of the nucleic (green circle) to the direction of the magnetic field (black arrows).

An MRI scanner at its foundation has different coils to generate the static magnetic, magnetic field gradients and radiofrequency (RF) fields. Within the primary magnet, gradient coils (often one for each plane; x, y and z) provide the spatial encoding for the MRI signal. As discussed, the static magnetic field aligns into the direction parallel to the magnetic field (otherwise known as the longitudinal direction) resulting in the overall net magnetisation being in the same direction. A RF pulse is superimposed which is absorbed by the protons, this rotates the net magnetisation direction into what is known as the “flip angle.” The flip angle is defined by the strength and duration of the RF pulse. Often the flip angle is set based on the scanning technique, for example it is frequently 90° or 180° for spin echo sequences

or inversion pulses which results in a net magnetisation direction in the transverse plane or the antiparallel (anti-longitudinal) direction respectively [133].

Notably, absorption will only take place when the RF frequency is identical to the Larmor frequency (precession frequency). When the RF coil is transiently turned off, the energised nuclei relax into a lower energy state which causes the release of photons, allowing imaging to take place. The rate of relaxation has an exponential curve called the relaxation time. In MRI there are two relaxation processes each with their own constant. The time constant for energised nuclei to reach the neutral or equilibrium point, i.e. return to being in parallel with the magnetic field which is termed as T1 or longitudinal relaxation time. The time constant for the reduction of energy of the spinning atoms as they continue to de-phase and lose magnetisation in the transverse plane is called T2 or transverse relaxation time. Notably T2 is always shorter than T1 and conversely is not related to the field strength.

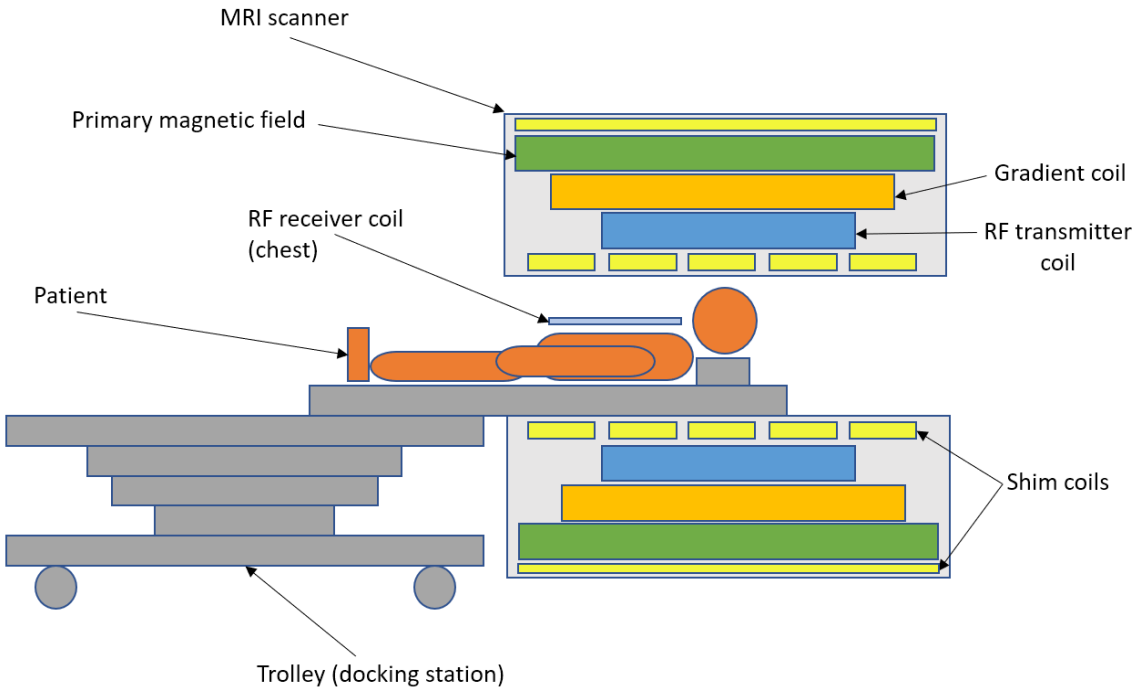



Figure 6 - Components of an MRI scanner

The combination of fields in an MRI scanner enables signals to be encoded and spatially localised, enabling a highly sensitive image of the human body to be formed [131]. Magnetic field strength is measured in Tesla (T). MRI system strengths have

increased from an original 0.5T to field strengths of 7.0T and 10.5T which are generally used in the research setting [130, 134]. Routine hospital MRI for patients utilises 1.5T systems with 3.0T MRI representing the forefront of advanced imaging techniques in patients with CHF [135]. There are however certain situations when a lower strength such as 1.5T may be preferred, for example when a patient has certain metallic implants that have not been safety approved at higher field strengths. A more powerful signal generally gives improved spatial resolution and contrast, resulting in an overall higher resolution. However, by increasing the signal and contrast, new artefacts may appear or become more pronounced. This can be particularly relevant when scanning MRI compatible devices (CRT, pacemakers) [131]. Thus, in reality a higher strength magnetic resonance (MR) field can be both an advantage and hinderance in terms of image acquisition. This is partially why it takes many years after the introduction of a higher strength scanner for studies to identify and modify scanning techniques to maximise the advantages and ensure safety [132].

There are a large number of scanning sequences that can be utilised in CMR to obtain high quality images and identify areas of interest. One of the most common techniques is steady-state free precession (SSFP), a modified version of the older gradient echo method (GRE). SSFP created a paradigm shift in MRI through its use of both longitudinal and transverse magnetisation that form multiple types of signal leading to high SNR and rapid scanning whilst also offering a robust contrast to noise ratio [136]. The scanning method also has inherent flexibility, with utility in foetal and abdominal imaging. Despite these advantages, GRE is often utilised in patients with cardiac implantable electronic devices (CIED) due to the higher rate of diagnostic grade images and fewer artefacts when compared with SSFP [137].

## 3.3 Safety Issues regarding MRI

Safety in MRI devices has long been a concern due to the association of strong magnetic fields and metal objects. This led to cardiac devices being considered as a strong contraindication for CMR. One of the main concerns around an implanted metal device is MRI induced heating. RF energy is absorbed and focused in the metallic object and due to a lack of tissue conductivity, heat accumulates which can

cause damage to both tissue and the device [138, 139]. Animal studies in pigs have shown that during CMR, cardiac leads can heat up by 20°C [140]. This was associated with initiation of tachycardia and a significant change in lead impedances post scanning. Local tissue injury around the leads have also been occasionally noted, however, it is difficult to differentiate heat damage from potential trauma during implantation. Studies in humans have found that abandoned leads in patients heat up during CMR [141]. CIED such as dual chamber pacemakers can become damaged in terms of the circuitry, leads or battery. The heating effect can also damage the human heart itself.

There are other safety concerns with regards to MRI. Due to the strength of the magnetic field, magnetic objects of various sizes can be attracted to the scanner, placing the patient at potential harm. This has led to careful design of the scanning area and the control room with strict restrictions on the personnel present in the environment, mandatory training for staff and the material composition of the equipment utilised in this setting. This issue also has significant bearing on the contraindications list for scanning patients. For example, patients with a metallic brain aneurysm clip are often unable to be scanned with MRI. An expanded list of risks and considerations for MRI is found below (figure 7). These issues range from a relative to absolute contraindication and thus require a case-by-case evaluation with the MRI radiographer and medical physics to ascertain safety. In general, safety is assessed in a protocolised fashion such as a patient completed questionnaire with any positive risk factors then discussed in detail to agree on feasibility in scanning. Issues such as difficulty in breath-holding can often be managed by modifying the scanning protocol with the use of free-breathing techniques or increasing the time between breath-holds [142].

The scanning duration must also be considered carefully in patients, not only for comfort and feasibility issues but to appreciate the specific absorption rate (SAR). This is a calculation of the amount of electromagnetic energy absorbed by tissue during scanning. This is a relatively complex calculation that attempts to take into account varying tissue types (due to the various absorption rates) as well as other factors such as the scanning protocol itself which can cause significant variance in energy absorption [132]. The British Institute of Radiology recommends a SAR limit of 2W/Kg for general full body scanning [143]. Higher intensity scans such as 4D

scanning or longer scanning protocols give a higher risk of exceeding SAR limits. Modern scanners have in-built SAR logging software that result in warnings, inability to start the scan and potential forced termination of scanning if exceeded [131].


Figure 7 - Safety issues for patients with MRI scanning

## 3.4 Developments in safety around MRI and CIEDs

Over the last two decades, significant strides have been made in making devices more resistant to damage or harm under MR exposure, subsequently labelled as “MR-conditional” with an indication of the field strength it has been tested to. The developments include reduction of magnetic material within the devices, filters to reduce RF absorption, reed switches to enable safe function when exposed to significant magnetic field strengths and advanced programming modes for the device to function safely during planned procedures [144]. Large reviews have shown that if

careful considerations to the scanning protocol are made on a case-by-case basis, it is often reasonable to scan patients with CIEDs [145]. Our group have shown that the majority of large studies investigating safety in scanning patients with CIED have identified few side effects across a range of protocols, from general body MRI to CMR at a variety of magnetic field strengths [146]. Modern MRI has continuous electrocardiogram assessment, live patient monitoring and allow for regular BP checks to ensure that the patient is alert and comfortable. A two-way microphone system is also built in to ensure continuous communication is possible between the patient and scanning team. Protocols are also developed around the scanning environment to avoid unexpected issues. For example, if the patient were to experience an MI, there is a set procedure for all hospitals to follow that would avoid the CPR team potentially causing increased harm through exposure to the magnetic field. This has led to relatively safe operation of MRI worldwide, enabling the technology to be utilised in an ever expanding set of scenarios when conducted in a cautious manner [147]. The logging of minor and major incidents has been key in developing safety standards with a modern rate of incidents reported as below 0.5% across large scanning sites and a fatality rate less than 0.07% with the UK generally reporting some of the safest rates of operation [148, 149].

| Author | Year of publication | N | Device type | MRI conditional | MRI scanning protocol | Significant complications |
|---|---|---|---|---|---|---|
| **Lupo et al [150]** | 2018 | 120 | PM & ICD | No | Routine including cardiac | No adverse events were observed. One temporary communication failure was observed (0.08%). |
| **Nazarian et al [151]** | 2017 | 1509 | PM & ICD | No | Routine including cardiac | In 9 examinations (0.4%) the device reverted to a transient back-up programming mode without long-term effects. |
| **Ching et al [152]** | 2017 | 140 | PM | Yes | Cardiac | None (No adverse events were observed |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | or change to device performance) |
| **Mason et al [153]** | 2017 | 178 | PM & ICD | Mixture (82% non-conditional) | Routine including cardiac | None |
| **Russo et al [154]** | 2017 | 1246 | PM & ICD | No | Routine excluding thoracic | One patient required generator replacement following scanning whilst in unsafe device settings. In 6 examinations (0.04%) the device reverted to a transient back-up programming mode without long-term effects. |
| **Schwitter et al [155]** | 2016 | 156 | ICD | Yes | Cardiac | None |
| **Higgins et al [156]** | 2016 | 398 | PM & ICD | No | Routine including cardiac | None |
| **Bailey et al [157]** | 2016 | 221 | PM | Yes | Cardiac & Thoracic spine | One adverse event (0.4%) possibly related to the implanted system and scan. |
| **Awad et al [158]** | 2015 | 153 | ICD | Yes | Cardiac & Thoracic spine | None |
| **Shenthar et al [159]** | 2015 | 177 | PM | Yes | Routine including cardiac | None |
| **Friedman et al [160]** | 2013 | 171 | PM | Mixture | Routine including cardiac | None |
| **Schwitter et al [161]** | 2013 | 150 | PM | Yes | Cardiac | None |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Gimbel et al [162]** | 2013 | 177 | PM | Yes | Chest and head | None |
| **Nazarian et al [163]** | 2011 | 438 | PM & ICD | No | Routine including cardiac | In 3 patients (0.007%) the device reverted to a transient back-up programming mode without long-term effects |
| **Wilkoff et al [164]** | 2011 | 258 | PM | Yes | Head and lumbar spine | None |
| **Strach et al [165]** | 2010 | 114 | PM | No | Routine excluding cardiac | None |
| **Mollerus et al [166]** | 2010 | 103 | PM & ICD | No | Routine including cardiac | One pacemaker reverted to transient back-up programming requiring reprogramming |

Table 3 - Trials (n>100) of MRI scanning in patients with implanted cardiac devices. Complications following scanning are rare regardless of the device being MRI conditional. Adapted from Koshy et al [146]. PM –including conventional and dual chamber pacemaker, ICD – implantable defibrillator, MRI – Magnetic resonance imaging.

## 3.5 How to conduct CMR in patients with a CIED

A patient with a CIED can be scanned using CMR under careful conditions. Patients follow routine protocols prior to scanning such as completing a safety questionnaire however there are additional steps required. The CIED must be treated as a package meaning that not only does the pacemaker itself need to be MR-conditional but also the leads. Furthermore, the pacemaker and leads must generally be tested with each other to maintain MR conditionality. This is often conducted by the manufacturers of the devices through rigorous assessment with the documentation published clearly for subsequent use in the form of downloadable files or an accessible database. In the UK, a device technician is generally required to be

present for the CIED to have a full interrogation. This is important for two reasons; firstly, to check that there are no issues with the device package such as lead dysfunction and secondly to produce a baseline set of parameters pre-scanning. The device is then placed in an MR-conditional or safe mode. The CMR procedure is largely identical to routine scanning with close attention paid to arrhythmia formation. On scan completion, the CIED undergoes full diagnostic checks to ascertain any changes following scanning as well as programming to return to normal function for the patient. Extra care must be taken during scanning and image analysis to mitigate the increased artefact generation associated with CIED such as susceptibility artefacts [167]. The difference in medium with respect to the patient such as metal (CIED) to air causes distortions and areas of void on the image. This can be countered in a number of ways. Simple manoeuvres including the patient resting their left arm underneath their head physically shifts the pacemaker towards the head, giving less artefact around the heart on the image. Different scanning protocols such as GRE are also associated with fewer artefacts [137].

One important issue when scanning CIED patients is to consider the pacing mode. In general, MRI safe modes are RV pacing only which can alter cardiac volumes and haemodynamics [168]. The availability of MR-conditional devices, sophisticated scanners and increasing evidence of safety in scanning patients who have a CIED suggest feasibility in scanning patients whilst biventricular (BiV) pacing is active as opposed to RV pacing alone. Indeed, our group proposed a model (figure 8) for scanning patients with an implanted CRT whilst BiV pacing is active. This model relies on the availability of a multidisciplinary team including a clinician, MRI radiographer, medical physics and cardiac physiologist (device technician).

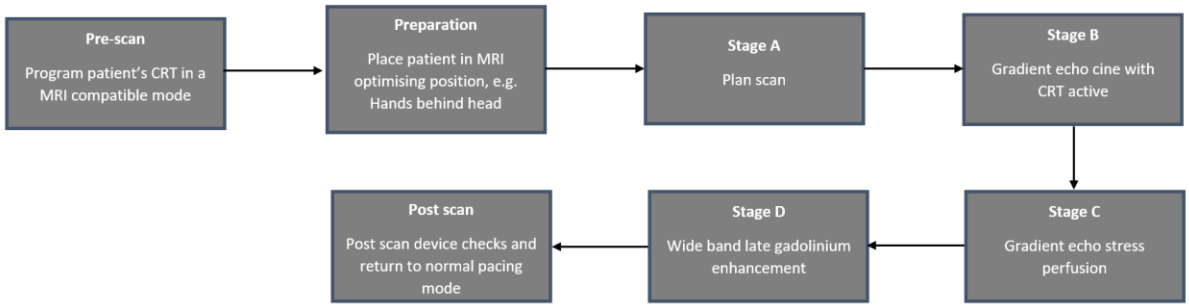



Figure 8 - An approach to scanning patients with BiV pacing active. Adapted from Koshy et al [146].

# Chapter 4 - Magnetic resonance spectroscopy (MRS)

## 4.1 Introduction

MRS employs a similar process to MRI with the same scanning system utilised to generate a chemical map of the desired area. MRS is used to identify metabolic changes found within a voxel (a specific location within a grid of 3-dimensional space). MRS was originally (and sometimes to this day) referred to as nuclear magnetic resonance (NMR), however over time, perhaps in association with clinical practice and distancing from the term “nuclear,” MRS has become the standard way of referring to this technique. MRS identifies metabolites by using the frequency information obtained on scanning whilst MRI encodes the same information to produce the image. Similar to MRI, MRS involves moving electrons that create a magnetic field through exposure of the external magnetic field giving the protons (within the nucleus) a different Larmor frequency. This results in chemical shift which can be analysed as different molecules (i.e., have a different number of protons with surrounding electrons) which resonate at various frequencies due to the variance in applied fields [169]. Chemical shift is the key step that allows identification of different metabolites based on the type of MRS used. In MRS the same nucleus is analysed, i.e. for 31P, phosphorous of ATP, PCr and Pi is investigated. This phenomenon assesses the entire molecule in terms of shielding which is the magnetic field experienced by the molecule. Shielding is comprised of multiple components such as the hydrogen bonding, magnetic anisotropy and the electron field (electronegativity) present [170]. If a nucleus of an atom is less shielded (thus enhanced) by factors such as the surrounding electrons then it has a higher chemical shift whilst if it is shielded well, it has a lower chemical shift. This interplay of variable shielding leads to the diagnostic identification of the chemical structures of the atoms. Following the RF pulse, as with standard MRI, the molecules return to an equilibrium state which produces a signal called free induction delay (FID) [171]. This signal is then manipulated to remove noise and produce identifiable spectra via Fourier Transformation (FT) and subsequent chemical shift (figure).

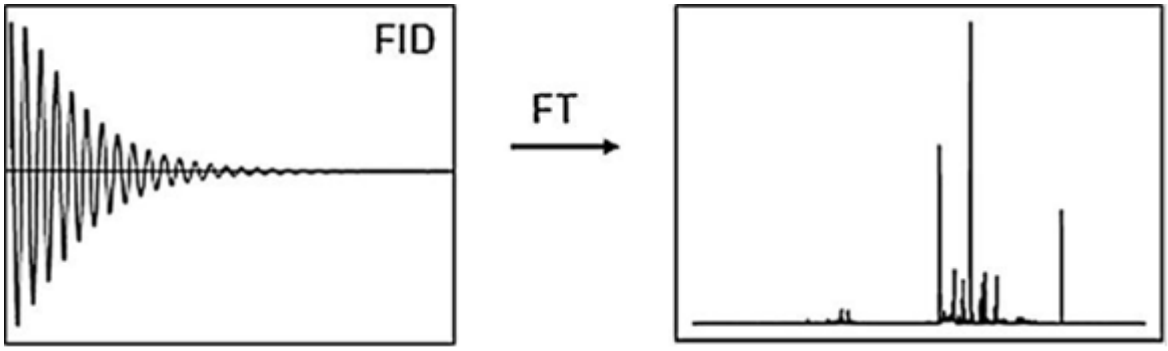



Figure 9 - Converting MRS signal into spectra. Adapted from Tognarelli et al [172]. FID – Free induction delay, FT – Fourier transformation.

Notably, the signal can be both positive and negative. Phase correction is mathematically applied to the signal to produce positive lines that can then be identified. There are multiple corrections that can be made, for example zero order phase correction augments all the peaks in an identical manner whilst first order phase correction has an effect depending on the position in the spectrum which are used in delays (such as the time to switch phase encoding gradients between an RF pulse and the acquisition). Subsequently, areas of interest can be amplified (or background noise can be removed) to increase the SNR [172].

MRS can be conducted using multiple nuclei including: Hydrogen ($^{1}$H), Phosphorus ($^{31}$P), Nitrogen ($^{15}$N), Carbon ($^{13}$C), Fluorine ($^{19}$F) and Sodium ($^{23}$Na). Hydrogen and phosphorus are the most established for academic and clinical assessment. Hydrogen is frequently utilised for energy and lipid metabolism whilst phosphorus is often used in energy metabolism research in cardiac focused scans. MRS has a diverse range of applications as it can assess the presence of metabolites across a variety of medium from isolated cells and body fluids to giving insight into the performance and composition of organs.

Interestingly, in vitro MRS predates clinical MRI with work published in the 1980's [173]. Phosphorous magnetic resonance spectroscopy ($^{31}$P-MRS) was investigated in 1960 as a method of exploring adenosine triphosphate (ATP) [174]. MRS then had application in organelles such as mitochondria and excised organs before proof of concept was shown *in vivo* by Ackerman et al [175] in 1980. Clinical and human based research is becoming more common after significant success in central

nervous system disease [176]. Quantification of metabolites requires a reference point such as a phantom model with known concentrations of inorganic phosphate ($P_i$) to take into account variance in magnetic field homogeneity, coil sensitivity and relaxation time. Hydrogen magnetic resonance spectroscopy ($^{1}$H-MRS) obtains a water supressed and non-supressed spectrum from the phantom to appreciate the variance in the reference model and the acquired analysis [177].

There are some differences in MRS methodology from standard MRI that occur following generation of the MR signal (figure 10). One of the divergent points is shimming which is present in MRS. This is the process of making the primary magnetic field produced by the scanner more homogenous. Shimming can be active, passive or both. Active shimming utilises additional coils that produce and subsequently modify the overall magnetic field, often by varying coil current (usually during MRS scanning). Passive shimming is the use of materials with magnetic properties such as sheet metal to modify the magnetic field as desired, it is particularly useful when the MR system is being installed to ensure that it achieves desired homogeneity. Modern scanners frequently employ both methods to reduce artefact generation and improve signal quality in areas of interest [178]. The main difference between MRI and MRS is that rather than having a read-out gradient as done with MRI which produces the positional information, MRS simply uses the frequency information to determine the chemical spectra of the sample. MRS is also unique in being able to identify metabolites non-invasively using non-ionising radiation when compared with PET scanning. Indeed even within MRI, whilst modern perfusion techniques such as blood oxygenation level-dependent (BOLD) are helpful in identifying areas of reversible ischaemia, $^{31}$P-MRS is unique in being able to investigate cardiac energy reserves and efficiency [179]. MRS has had historical value in the exploration of cardiac work and continues to receive further study due to its distinctive offering that is hoped to enter clinical practice in the next few years.

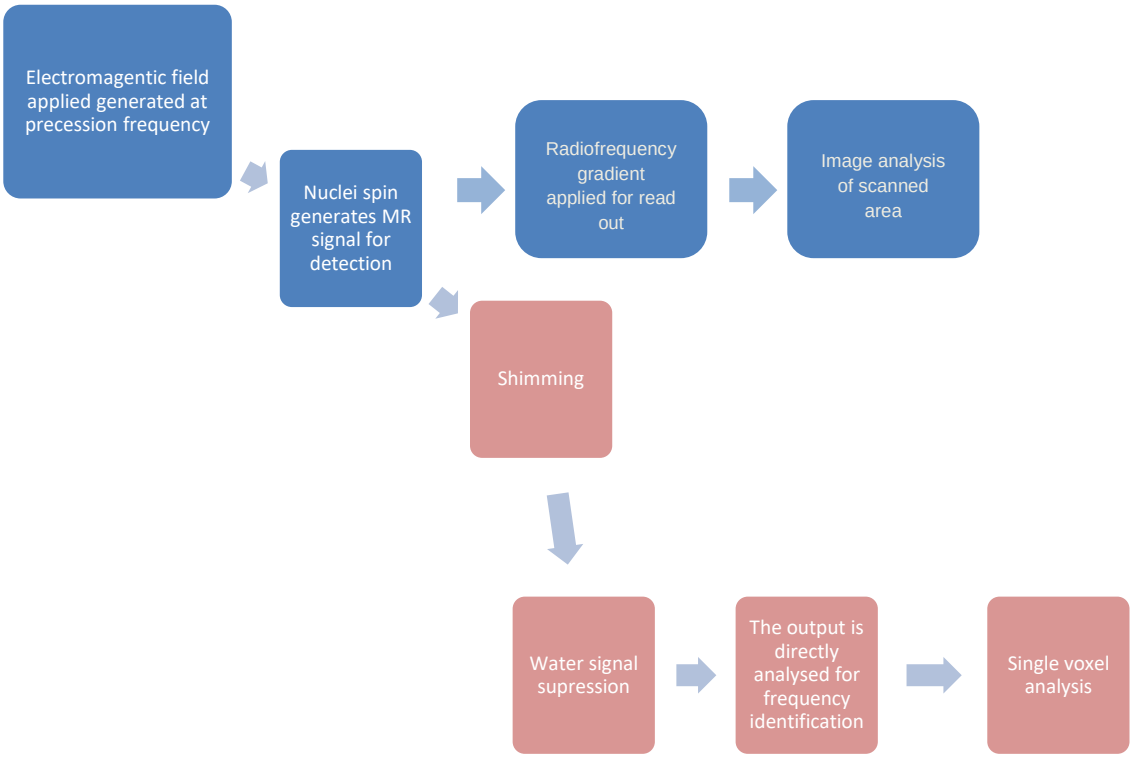



Figure 10 - Flowchart for standard MRI (blue) and MRS spectra acquisition (red).

## 4.2 MRS in clinical research

Research into the application of MRS in HF has been ongoing for over two decades. Due to the versatility of the technique, it can be used to explore a number of cardiac diseases and with CMR overlay can reveal cardiac structure and metabolism more clearly. One of the most common variables to study in terms of cardiac metabolism is the phosphocreatine to adenosine triphosphate ratio (PCr/ATP) through $^{31}$P-MRS. ATP is the primary substrate for cardiac muscle contraction and it is believed that during stress there is transfer of ATP from production in the mitochondria to areas of uptake in the myofibrils. In general, glycolysis produces ATP that is rapidly converted to phosphocreatine (PCr) via creatine kinase (CK) [180]. PCr is a high energy-phosphate that provides storage and transportation with the most popular theory resting on the PCr “shuttle” system [181]. This places PCr with the important role of acting as a transport system for phosphate and ATP from sites of generation to utilisation. Cardiac cells in particular have a higher reliance on oxidative metabolism which gives greater availability of phosphate levels and contractility when healthy

conditions are met [182]. As ATP is used at many sites in the body, the resting rate of ATP hydrolysis is high in the context of relatively low concentrations. Specifically, the ATP hydrolysis rate is ~0.5 µmol/g wet wt/s at rest compared with an ATP concentration rate of ~5 µmol/g wet wt/s during exertion, giving complete cycling of ATP every 10 seconds [183]. Notably, the majority (~70%) is utilised for contraction with the remainder on active electrolyte transfer in channel pumps and within the sarcoplasmic reticulum [184].

Interestingly, the PCr/ATP is relatively uniform across species [185, 186]. CHF conversely is associated with reduced PCr/ATP; in fact the severity of CHF is inversely correlated with the PCr/ATP [187, 188]. A lower PCr/ATP is found in DCM patients when compared with controls [189]. This has led to the notion of PCr/ATP acting as a metabolic state that may be contributing to the progression of CHF [190]. The depletion of PCr is associated with reduced cardiac ability to increase output in response to demand or stress [191]. It is likely that the levels of PCr and CK in particular are controlled to maximise cardiac energy metabolism. Neubauer et al [192] not only confirmed that CHF patients are associated with a reduced PCr/ATP but the reduction was associated with a significantly higher mortality rate compared with CHF patients with a normal PCr/ATP.

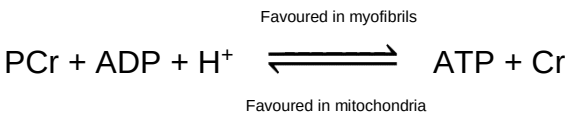



Figure 11 - Production of ATP. Adapted from Zweier et al [191].
ADP – Adenosine diphosphate, ATP – Adenosine triphosphate, Cr – Creatine, PCr – Phosphocreatine,

MRS analysis is fraught with complexity. Low concentrations of ATP and PCr make this technique more insensitive, resulting in saturation effects when compared with water protons in human tissue. The imaging technique has a number of limitations, particularly with regards to variable reproducibility and low spatial and temporal resolution [193]. Some of the common issues associated with MRS are explored below:

- Acquisition time - Due to the low concentration of metabolites in comparison to water protons, the voxel size is large with often repeat scans needed to achieve a satisfactory signal to noise ratio (SNR). This is through obtaining a higher number of signal averages which in turn can lead to long image acquisition or scanning times [172].
- Spatial resolution - Spatial resolution is of critical importance. It is possible for the voxel size to be too large, for example >2 cm which would be problematic when aiming to assess small tumours [194]. Large voxel size is often present in MRS due to limitations in other factors such as acquisition time. This can lead to multiple tissue types being included in the assessment which reduces confidence in quantification of metabolites in a given area (resulting in a contamination like effect).
- Measurement variability - Measurement of spectra can be done in absolute or relative terms through the utilisation of a reference. In general, absolute value measurements are not practical to publish due to the known variance of these values which are associated with differences in field homogeneity and device set up. Specifically, water protons can be problematic as a reference point due to the variability of water content in age groups and disease states [195]. Additionally, metabolite ratios often require assumptions in the values of certain metabolites such as creatine which can change similarly to water in different demographics or disease states [172]. Thus, relative changes in samples are generally of more value across cohorts, however this removes some of the diagnostic value from the tool and does not resolve the issues around obtaining reference values for healthy and diseased patients.
- Motion susceptibility - MRS is significantly limited by motion of subjects, indeed even physiological motion (such as cardiac movement) during scanning can be problematic as it is prone to causing changes in spectra peaks, shifts in frequency and often an increased spectra line width. Additionally, motion can also cause issues around water suppression which is critical for consistent spectra analysis [169]. Motion impacts higher resolution scans due to the smaller voxel size. This can cause significant variance in results from even minor movement. Some of these issues can be mitigated by cardiac gating (ensuring that the analysis begins and ends

in time with the cardiac cycle) and multivoxel spectroscopy, enabling localisation of the voxel to the most appropriate areas in a given scan [196].

- Sampling - Spectra can be obtained from single or multiple voxels within the heart. There are multiple techniques for single voxel $^{31}$P-MRS such as Point RESolved Spectroscopy (PRESS) and STimulated Echo Acquisition Mode (STEAM). These protocols both use 3 RF pulses of various degrees (90 or 180°). Similar to CMR, protocols generally require compromise as higher resolution (or higher SNR) is often at the cost of longer acquisition times. Image-Selected In vivo Spectroscopy (ISIS) utilises FID with multiple acquisitions at different gradients to improve the quality of analysis at the single chosen voxel with subtraction applied to signals from surrounding voxels. This process is unsurprisingly more vulnerable to motion artifact [197]. Magnetic resonance spectroscopic imaging (MRSI) allows multiple voxels to be sampled simultaneously. The advantage of MRSI is that motion and issues around voxel selection can be mitigated with greater appropriate sampling. However the trade-off is often in reduced signal quality and/or longer acquisition time [198]. Modern scanning protocols have dramatically improved acquisition time without significant issues in SNR, however each technique remains with constraints or issues including artefact generation [199].
- Signal isolation - MRS is also vulnerable to a lack of magnetic field homogeneity which is often found as a result of the materials and equipment used during scanning as well as the patient themselves. This issue can be partially mitigated by shimming [169].
- Post processing and specialist expertise - MRS generally requires significant post processing and analysis due to the plethora of variables such as field inhomogeneity and a low SNR [177]. Specialist knowledge and specific scanning systems need to be in place to take into account the various experimental parameters which makes reproducibility difficult [177]. This can dramatically increase the cost and indeed restrict options for purchasing MRI systems that are able to handle the variety of scanning protocols required.

However, there are reasons for $^{31}$P-MRS to have significant utility. Phosphate nuclei have distinctive spectral peaks which makes quantification manageable [199]. Furthermore, it is able to derive molecular activity without requiring ionising radiation or contrast [177]. Alternatively, $^{1}$H-MRS has been effective in identifying steatosis in patients with pre-diabetes and in advance of cardiac dysfunction [200]. This finding highlights the value of MRS in being able to correlate visceral fat with myocardial triglyceride content, thus a potential early mechanism to a number of cardiac diseases.

| | $^{1}$H- MRS | $^{31}$P-MRS |
|---|---|---|
| **Number of stable atomic isotopes** | 3 | 1 |
| **Gyromagnetic ratio value at 1T** | 42.6 MHz | 17.2 MHz |
| **General use** | Most popular form of MRS | First form of MRS that showed clinical utility and close second in popularity |
| **Recommended magnetic field strength** | ≥1.5T | ≥1.5T |
| **Relative sensitivity** | 1 (standard) | 0.07 |
| **Range of spectral peaks** | Narrow (0 to 5 parts per million) | Wide (-5 to 25 parts per million) |
| **Equipment required beyond standard MRI scanner capable of spectroscopy** | None | Separate set of RF coils and amplifiers to receive lower frequency signals |
| **Number of identifiable peaks** | >25 | <10 |
| **Examples of analysable metabolites** | Lactate, glutamate, lipids, creatine, n-acetyl aspartate, choline and glutathione. | Cr, PCr, ATP, Nicotinamide adenine dinucleotide and cell membrane precursors such as phosphomonoesters |
| **Common issues** | Frequently contaminated by water and fat that subsequently requires | Often impacted by “J-coupling” which is related to chemical connections between atoms |

| | | |
|---|---|---|
| | suppression techniques | (such as hydrogen and phosphorus) causing reduction or splitting of signal. This is mitigated through de-coupling techniques. |

Table 4 - Comparing clinical $^{1}$H-MRS against $^{31}$P-MRS.

## 4.3 P-MRS in heart failure

$^{31}$P-MRS is the most utilised form of MRS for CHF due to its ability to assess energy and work efficiency. One of the earliest studies was conducted by Wilson et al [201] in 1985. This identified altered metabolic activity in CHF as a result of blood flow changes to skeletal muscle and reduced muscle mass as opposed to simply distorted central haemodynamics. A follow up study was carried out by Wiener et al [202] in 1986. 21 CHF patients had their forearm scanned at rest and during exercise (weighted wrist flexion). It identified CHF patients as having a higher $P_i$ to PCr ratio ($P_i$/PCR) when compared with controls whilst muscle blood flow was relatively unchanged. This suggests that there may be either a maldistribution of blood flow or altered metabolic activity within muscles. These findings led to the seminal work by Mancini et al [203] in 1989. CHF patient underwent gastrocnemius muscle biopsies and $^{31}$P-MRS during calf muscle exercises. CHF patients had a higher proportion of Type IIb fibres which are glycolytic and easily fatigable with associated atrophy of Type I and IIa muscle fibres. Using $^{31}$P-MRS it was found that CHF patients had higher $P_i$/PCr in relation to oxygen uptake and exercise. As the $P_i$/PCr relates to oxidative metabolism, it shows that the skeletal muscle in CHF patients is likely to be less efficient than in controls. The team went on to show that CHF patients generally have both altered metabolic function in skeletal muscle in addition to significant atrophy, giving a lower muscle mass in this cohort [204]. Furthermore, the PCr level recovery post exercise was also altered indicating that there are complex factors such as weakened metabolic activity and peripheral blood flow that explain the reduced exercise performance found in CHF patients [205].

Weiss et al [206] investigated if there is energy deficiency (concentration of ATP and ATP flux) in CHF patients. CHF patients had a reduced PCr concentration and ATP flux whilst ATP concentrations were relatively similar when compared with controls. Specifically, CHF patients have reduced ATP regeneration via CK reaction. Notably myocardial $P_i$ levels were not able to be calculated due to the low resonance obtained and difficulties around delineating signals. Reductions in ATP concentration have been noticed in CHF patients [207, 208]. It is believed that measuring $P_i$ levels consistently in CHF will give a more definitive understanding. Regardless, ATP is appearing to be less of a major factor as measured biopsy concentrations remain above minimal levels for normal performance suggesting other measures such as PCr concentration or ATP flux are of greater importance [209]. Subsequent studies have shown that increased hand exercises cause a depletion in PCr and increased $P_i$ concentrations [210]. Exercise training is also associated with a reduction in $P_i$/PCr resulting in positive metabolic adaptions such as muscle oxidative capacity over short time frames.

The $P_i$/PCr looks to be altered in a couple of diseases such as CHF and chronic lung disease with an exaggerated response during exercise [211]. Interestingly, the half time of $P_i$/PCR during recovery from exercise is proportional to the halftime of $VO_2$ recovery ($r = .70$, $P < 0.01$) [212]. Chati et al [213] confirmed that increased $P_i$/PCr is associated with CHF patients when compared with controls but importantly the ratio reduces when the participants are trained, presumably through reduced deconditioning. These findings suggest that metabolic adaptations occur during short and long-term exercise or conditioning. The $P_i$/PCr is even higher in CHF patients with iron deficiency anaemia, potentially leading to skeletal myopathy and symptoms [214]. There seems to be lower phosphorylation rates in CHF patients which can explain the depletion of energy storage and lower $O_2$ uptake in patients as opposed to controls [215]. Nanbu et al [216] found that with increased HR via dobutamine, circumferential fibre shortening occurred whilst the PCr/ATP did not change meaning that the energy demand was met by supply in both controls and CHF patients.

These studies show that metabolic function is altered in CHF and are likely related to the severity or duration of disease leading to peripheral and systemic changes. The ability to monitor metabolic function whilst altering HR gives a powerful opportunity to

explore mechanisms that underlie the various cardiac mechanics that occur as a response.

# Chapter 5 – Force Frequency relationship (FFR)

## 5.1 Introduction

During exercise, the healthy heart increases performance and CO primarily through increased β-adrenergic stimulation resulting in higher HR and contractility via increased end systolic pressure and volume [217]. When combined with vascular changes including decreased vascular resistance and increased venous return, 4-6 times increases in CO can be achieved from rest. The force frequency relationship (FFR) also known as the Treppe (staircase) phenomenon or Bowditch effect is a crucial physiological relationship between the rate of contraction and the force of contraction in cardiac muscle cells as outlined:

↑Frequency or Heart rate ∝ ↑Contractility

FFR was first discussed by Henry Pickering Bowditch in 1871 through experimentation with a frog heart [218]. Muscle contraction (depolarisation) occurs through the release of calcium ions from the sarcoplasmic reticulum (SR). Relaxation occurs when calcium ion levels in the cell are returned to the SR via channels such as sarco/endoplasmic reticulum Ca2+-ATPase (SERCA). There are 3 main forms of the SERCA gene, SERCA 1, 2 and 3. SERCA1a and SERCA1b are associated with fast twitch skeletal muscle and embryonic growth stages respectively [219]. SERCA2a is primarily associated with cardiac tissue and slow twitch skeletal muscle whilst SERCA2b is found in non-muscle cells. SERCA3 is found almost exclusively in epithelial and endothelial cells. For the purpose of this thesis, SERCA will refer to SERCA2a which is most relevant for cardiac analysis. SERCA acts as a calcium transporter within the SR. During systole, calcium influx occurs with simultaneous calcium release from the SR. Calcium ions then attach to troponin C in a crossbridge manner that generates force and subsequent contraction.

Calcium levels are also reduced via action of the Na/Ca exchanger (NCX) and mitochondrial uptake [220]. However, SERCA is associated with over 70% of the calcium level removal and so is critical in myofilament relaxation [221].The efflux of calcium followed by the influx of calcium and sodium during early diastole seems to

be one of the key steps that produce the FFR. As the HR increases, the higher rate of action potentials produces higher levels of sodium and subsequent reduction in calcium efflux through the inherent limiting refractory rate of NCX activity (whilst continuing movement in the other channels). This results in higher SR uptake and more calcium present for subsequent contraction [222]. It is likely that the increased calcium levels within the SR due to the higher HR is a consequence of the influx rate of calcium ions being greater than the efflux. Importantly, higher calcium levels are often associated with increased contractility [223]. The less positive and often negative FFR that is observed in humans with various diseases is believed to be through reduced SERCA activity via lower rates of phosphorylation of control proteins by calmodulin kinase [224]. Interestingly, higher frequencies seem to produce reduced L-type $Ca^{2+}$ channel transfer in healthy mouse cardiac tissue. This effect has been noted in human myocytes from CHF patients (including those with RVF) resulting in a leftward shift in FFR and reduced L-type $Ca^{2+}$ channel activity at the higher frequencies [225, 226]. The reduced interval at diastole associated with higher HR leads to higher calcium levels that generate more binding of calcium to thick and thin myofilaments via troponin C [227]. This phenomenon is also present in skeletal muscle, however there are differences. Cardiac myocytes have a network effect of grouped contraction that is consistent, whereas skeletal muscle can be activated further at higher HR to increase the force of contraction. Notably, skeletal muscle is modulated by intracellular calcium levels alone converse to cardiac muscle which is also influenced by extracellular calcium levels.

The HR itself has significance. Levy et al [228] were one of the first to identify the risk of increased HR to prognosis. Participants that had transient tachycardia both independently and as part of hypertension had a higher mortality rate. In fact meta-analysis and large trials have shown that a higher resting HR is associated with increased risk of cardiac and all-cause mortality in the general population [229, 230]. The issue around this finding is if HR should be treated as an endpoint or as a marker of disease with the answer likely to be both. Vazir et al [231] showed in 7599 CHF patients that a higher HR was associated with a larger all-cause mortality and subsequent reduction in HR reducing this risk. The SHIFT study discovered that CHF patients taking Ivabradine had a 16% reduction in HR compared with a 6.3% reduction with placebo. The HR reduction via Ivabradine was associated with a

reduction of 26% in HF related death and 10% in all cause death when compared with placebo. In both studies, the level of HR reduction was not only proportional to mortality benefits but more specifically seems to reduce HF events suggesting that HR reduction could slow disease progression. On the other hand, HR rises during exercise, infection and mental stress [232]. Increases in HR are also associated with a predisposition towards obesity and diabetes, both notably associated with CHF [233, 234]. With progression of CHF, there is increased sympathetic activity leading to increases in the HR and due to the positive feedback loop that forms with sympathetic overdrive, HR continues to rise [235].

## 5.2 Changes associated with CHF

Recent work by Balcazar et al [236] investigated the role of SERCA in FFR using fruit flies. By causing 2 mutations to SERCA via heat shock on conditional mutants for the Drosophila SERCA gene (dSERCA, Ca-P60A), two completely different patterns of the FFR were obtained. Specifically, one mutation caused a dramatic positive FFR whilst another gave a higher negative FFR effect. This in itself suggests that the FFR can vary amongst species and be affected by external factors such as epigenetics. CHF is associated with reduced presence of SERCA. Hasenfuss et al [237] investigated the FFR in human cardiac tissue obtained from patients undergoing heart transplantation for CHF as a result DCM or IHD (figure 12). The tissue underwent stimulation at different rates (30 – 180 bpm) whilst at a physiological temperature, with concurrent analysis of SERCA expression and calcium uptake by the SR. The twitch tension was higher in non-failing hearts with a delayed peak when compared with CHF hearts. It is important to note that there was significant variation in twitch tension and SERCA levels within the groups. Despite this variation, SERCA levels were on average 36% lower in CHF patients when compared to non-failing hearts. After normalisation for expression of contractile proteins (β-myosin heavy chain), CHF patients had 32% lower SERCA levels than non-failing hearts. This should be considered in the context of the SR (within myocardium) being the major source of calcium required for systolic contraction and the excitation-contraction coupling phenomenon between proteins and contractility [238]. The aptly named excitation-contraction coupling is a process by which the increased calcium levels and neurohormonal activity is converted to mechanical contraction [239]. The persistently high levels of norepinephrine (NE) as part of CHF

alters the excitation-contraction coupling which results in weakened rather than supportive changes to FFR [238]. It is therefore likely not a coincidence that the failing heart has lower mRNA levels with respect to SERCA and calcium release channels which in turn is linearly linked to myocardial function [240]. The neurohormonal component cannot be understated in CHF, especially with regards to FFR and being a condition of sympathetic overdrive [241]. Exposure to NE over a couple of days results in a significant (40%) drop in mRNA for SERCA and can partially explain the changes associated with progression of CHF [238, 242]. The sustained demand for higher CO causes persistently raised sympathetic activity and NE which results in reduced SERCA in turn leading to reduced contractility and a left shifted, blunted FFR. This develops into a positive feedback loop of higher NE levels, causing further negative shifts in FFR with an almost inevitable journey to decompensation at resting levels. As partial validation, BB improve calcium transportation and helps normalise SERCA activity [243]. It would be interesting to investigate if this change is independently associated with haemodynamic and mortality benefits. This could be explored through an observational study comparing SERCA activity via biopsy in CHF patients with subsequent cardiopulmonary exercise testing and follow up for up to 5 years. Notably, ventricular tissue in CHF patients have significantly lower levels of β receptor density (both $\beta_1$ and $\beta_2$) than controls [244]. It is therefore relevant that some BB are found to reduce the inflammatory response in terms of circulating levels of cytokines [245].

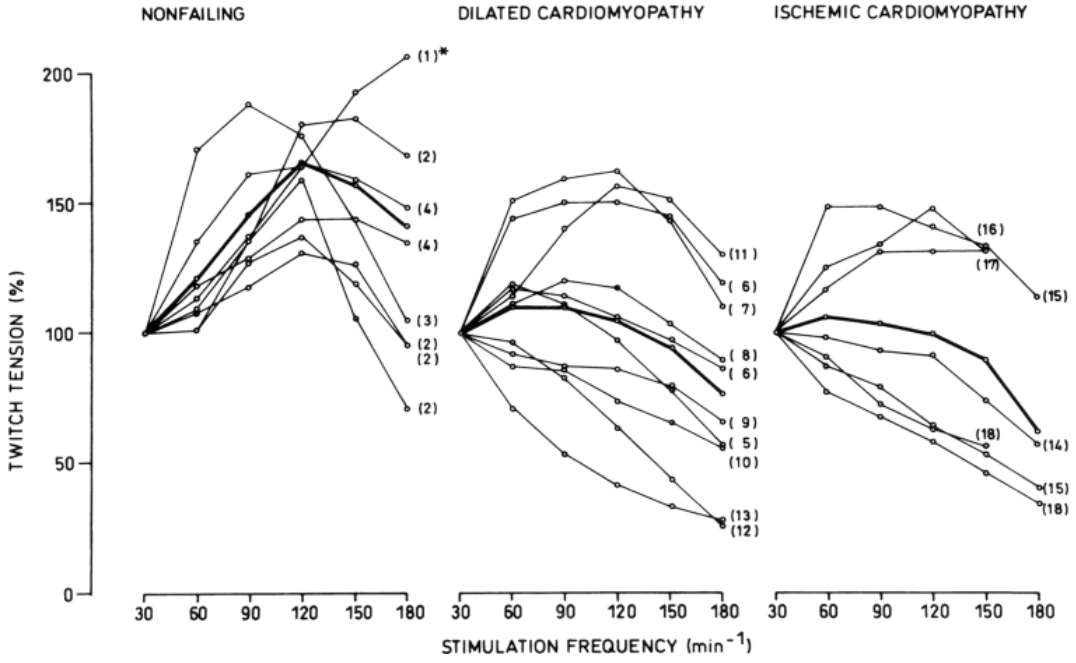



Figure 12 - Comparing cardiac myocyte FFR in CHF (DCM & IHD) and non-CHF at different stimulation rates. Adapted from Hasenfuss et al [237]

There are other factors associated with a flatter, left shifted FFR such as the role of phospholamban and cardiac troponin I (cTnI). Phospholamban is a protein that reversibly phosphorylates the cardiac SR, in turn regulating SERCA activity [221]. Under-expression of phospholambin is associated with increased contractility (in this case, the rate of myocyte shortening and lengthening) through increases in the binding ability of SERCA to calcium [246]. Interestingly, phospholambin levels are relatively unchanged in HF [237, 247]. However, the diminished levels of SERCA lead to a higher ratio of phospholambin to SERCA in HF which in turn creates reduced affinity for calcium and a downward shift in FFR. cTnI plays a control role (inhibitory) within the troponin structure which is a principle component of contraction [248]. Protein kinase A phosphorylates cTnI which in turn reduces myofilament binding to calcium [249]. A study by Takimoto et al showed in transgenic mice that over expression of cTnI improved FFR at higher stimulation frequencies [250]. It is believed that cTnI via β sympathetic activity increases relaxation and contraction velocity [251, 252]. This is important as HF is associated with reduced levels of phosphorylation of cTnI [253, 254]. Therefore, at higher frequencies or HR it would be expected that β-activity would shift the FFR upwards and to the right whilst conditions such as CHF would shift it down and left.

## 5.3 Clinical investigation into FFR

LV contractility is associated with survival and can be measured in a number of ways [255]. Laboratory based studies frequently assess twitch tension which was historically measured by LV end-systolic elastance (Ees). Ees is the gradient between the point at which LV pressure starts to rise with LV volume increase and the LV pressure at left ventricular end systolic volume (LVESV). In vivo studies have shown Ees to increase during exercise [256]. Assessing Ees generally requires explantation of the heart with arduous preparation to derive contractility from water exchange and pressure measurements [257]. The often-utilised LVEF is seen as a surrogate of contractility, however it has significant constraints around variable cardiac loading and erratic measurements (depending on imaging modality) and so would not be appropriate as an independent variable for contractility [258, 259]. More commonly, contractility is derived in the patient via LV dP/dtmax measurement which assesses the rate of LV pressure whilst isovolumetric contraction is taking place. This gives a strong measurement of the inotropic state. LV dP/dtmax is obtained invasively via measuring pressures of the LV using a catheter tip positioned in the LV apex. This method allows Ees to be derived albeit through complex analysis (slope assessment of pressure-volume measures via linear regression of peak elastase within the cardiac cycle). More recently it has been suggested that peripheral measurement (radial and femoral) of dP/dtmax has a strong correlation with LV Ees. Despite the multiple measures of contractility, they are generally rendered unfeasible by the level of invasiveness and complexity of analysis which may explain why they are not commonly utilised in clinical practice. One of the more modern measures of contractility is the FFR calculation which is obtained by the relationship between the systolic blood pressure (SBP), LVESV and body surface area (BSA) via the following formula which has been validated against gold standard invasive measures of contractility [260, 261]:

Contractility = SBP / LVESV / BSA

Using early data from Higginbotham et al [262] and the above formula, the contractility in the normal man can be derived as 4.86 vs 11.58 when at rest and peak exercise respectively. Participants reached a mean HR of 167 bpm compared

with 73 at rest. Many studies investigating FFR have been conducted in animals. Kambayashi et al [263] investigated FFR in dogs who underwent atrial pacing at different rates with dobutamine infusions (β1-agonist agent), thus increasing cardiac activity by acting as a positive inotrope [264]. This study showed that there were limited increases in FFR with a rise in HR through pacing; however the addition of dobutamine had a significant dose dependent increase in contractility. The same team explored the effect of using a rate limiting agent, zatebradine [265]. This drug reduces pacemaker activity on the $I_f$ channel without directly reducing myocardial contractility [266]. Reducing the HR was associated with a reduction in the FFR showing that the linear relationship between contractility and HR does indeed exist in both directions. Subsequently a study in pigs found that increasing the load on myocytes caused decreased velocity in sarcomere shortening in both controls and CHF specimens, however the effect on the CHF group was more pronounced at both lower and higher loads [267].

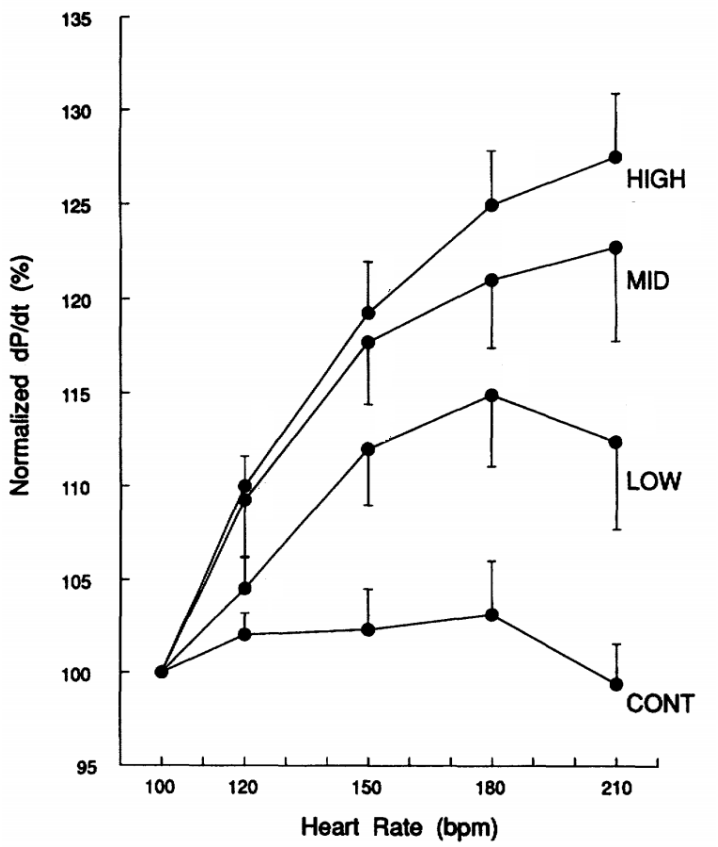



Figure 13 - Change in contractility in canine hearts with varying HR via atrial pacing and the influence of dobutamine. Adapted from Kambayashi et al [263].
Cont – control, Low – Low dobutamine infusion dose, Mid – Medium dobutamine infusion dose, High – High dobutamine infusion dose.

Early work by Ginzeton et al [268] showed that contractility is generally higher in normal subjects compared to cardiac patients (IHD). Furthermore, during exercise, control patients were able to raise their contractility at a much higher gradient than patients post MI. In vitro studies have validated the notion of different cardiac conditions (including CHF aetiologies) being associated with various myocardial function when HR is increased [238]. In general, samples with a CHF aetiology had reduced myocardial reserve (a specific method of assessing contractility variance from 60 to 120 bpm). It is also notable that that conditions associated with a lower myocardial reserve also had a lower optimal frequency.

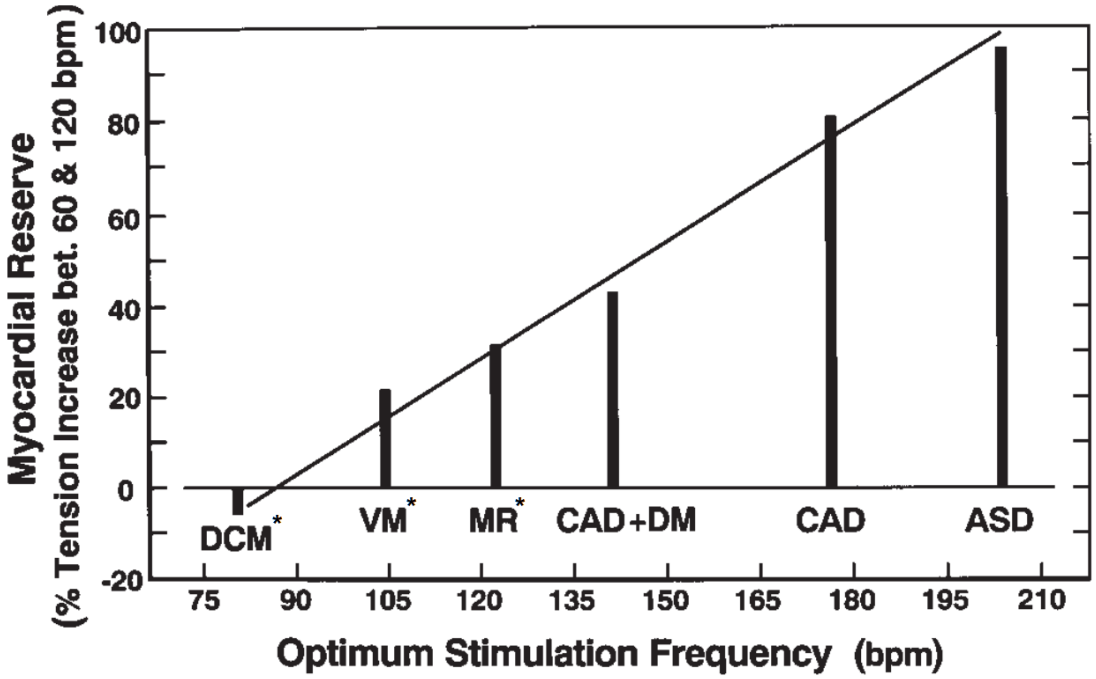



Figure 14 - The optimal stimulation frequency in different cardiac conditions with the subsequent myocardial reserve. Adapted from early work by Alpert et al [238]. ASD – Atrial septal defect, CAD – Coronary artery disease, CAD + DM - Coronary artery disease with insulin dependent diabetes mellitus, DCM – Dilated cardiomyopathy, MR – Mitral regurgitation, VM – Viral myocarditis. *Patients with HF.

Bombardini et al [269] pioneered the modern technique non-invasive analysis of contractility via exercise echocardiography in 2003 by comparing control and cardiac patients. This is also when the concept of the critical heart rate (CHR) was coined which refers to the HR at which contractility peaks. This confirmed a positive FFR in

control participants whilst patients referred for cardiopulmonary exercise testing with a subsequent negative exercise stress test had a flatter FFR and patients with a positive stress rest had a left shifted FFR. The same team went on to assess contractility in patients with permanent pacemakers (PPM) who were either normal, had a history of IHD or DCM accounting for 7, 8 and 11 patients respectively [270]. Using echocardiography, it was again found that the FFR in controls was higher with a positive linear relationship when the HR was increased via atrial pacing when compared with both IHD and DCM patients who had a lower and relatively static change in contractility with HR. Around the same time an invasive study by Esfandiari et al [271] showed that HR increases by RA pacing from rest produced a linear response in control participants whereas CHF patients had a flat FFR.

More recently Gierula et al [272] investigated the effect of rate response programming in patients with CHF. In this study it was shown once more that control participants had increasing contractility with higher HR whereas CHF patients had a relatively static FFR throughout. Notably the CHR was 126 bpm vs 103 bpm in control and CHF patients respectively. Appreciation of the CHR through personalised rate adaptive programming was shown in this study to improve exercise time and even peak oxygen consumption.

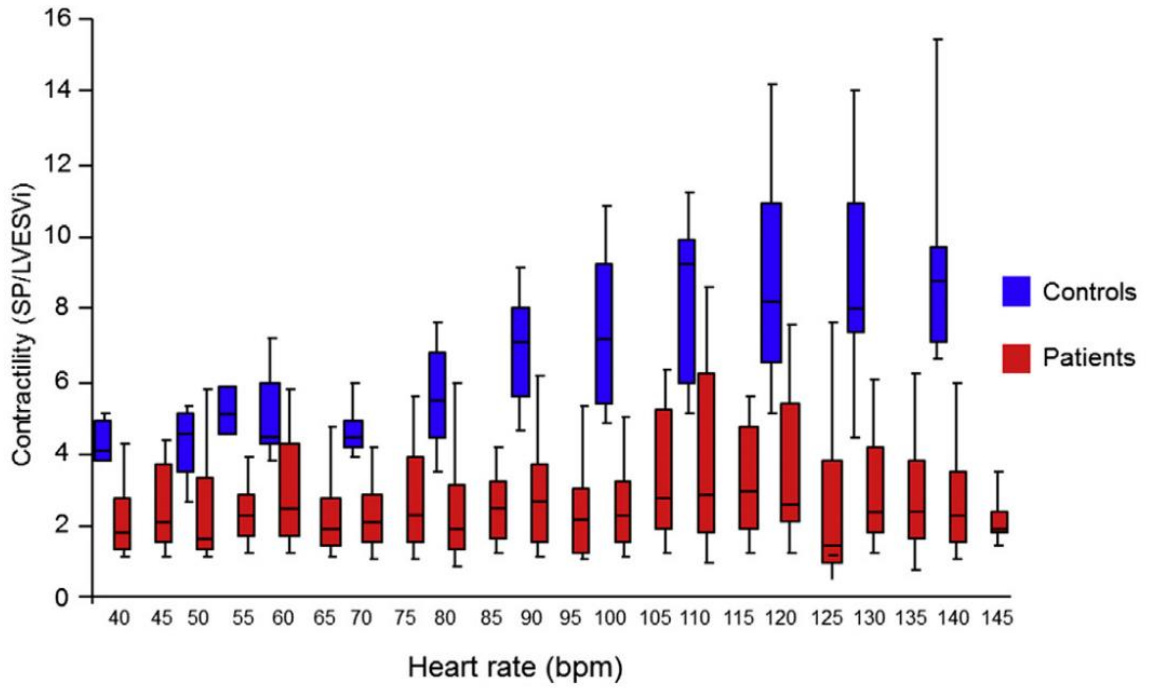


Figure 15 - Increasing FFR compared with static FFR in control and CHF patients respectively with increasing HR. Adapted from Gierula et al [272].

# Chapter 6 – Assessment of safety in scanning patients with CRT active and disabled

## 6.1 Background

CRT devices are indicated in approximately 26.8% of CHF patients and present in 6.8% [273]. Implantation is associated with improvements in functional capacity, QoL and survival [3, 102, 103]. The mechanism by which these changes are achieved are not fully understood. It would be expected that with a more synchronised contraction of the ventricles, a higher LVCO is generated, resulting in improved clinical outcomes. It would therefore be useful to investigate CRT and HR augmentation using fidelity that CMR offers. In order to explore this, CRT devices must be programmed to retain BiV pacing whilst in the scanner. This is not routine practice in the MRI setting, thus an important step would be to assess safety of BiV pacing during CMR.

Developments in CMR and pacemaker devices have improved dramatically in the past 3 decades. When combined with an experienced team of clinicians, radiographers and medical physics, the risks of CMR on a CIED and the patient are generally seen as minimal.  Despite these advances, common practice in scanning patients with a CRT device is to switch the device pacing mode from BiV to RV only pacing as an effort to reduce risks of harm to both patient and device [146]. This approach is problematic as not only is RV only pacing expected to give a falsely low overall CO in CHF patients but specifically will mitigate the impact CRT has on LV function in this cohort during scanning. MR-conditional devices are standard in developed countries and in theory it is possible to program many devices into a relatively “normal” BiV mode that is safe in the MRI setting. In the UK, this is generally only viable in the hands of an experienced cardiac physiologist who manages CRT devices as well as a skilled MR radiographer to ensure safe procedural activity and levels of MR exposure are as minimal as possible. Conducting CMR in patients with BiV pacing would give insight into the mechanical improvements made by the heart with this therapy as well as enabling the exploration of HR changes on cardiac mechanics. This work must be done with care

to avoid the historical issues associated with scanning a CIED such as heating or arrhythmia formation [274].

MR-conditional pacemakers started to be formally approved by safety regulators in 2011 following rigorous testing by manufacturers [275]. Major vendors produced devices that had modified reed switches, RF filters and reduced ferromagnetic materials in order to reduce the effective exposure of the device to electromagnetic radiation associated with CMR scanning. Importantly, efforts were made by the vendors on the programming modes of the devices to ensure reliable functionality of the device in this environment. Developments in scanning have allowed for shorter scanning periods as well as strict safety practices (such as investigating compatibility, awareness of other implanted devices and a safe working area). These improvements have led to many large studies identifying relative safety in scanning patients with a CIED implanted, indeed even in the context of a non-MR conditional device being in situ [151, 276].

Modern CIEDs can be interrogated with a device programmer to assess device and lead parameters such as battery voltage and lead impedance. In general, current practice suggests most of the variations following an MRI scan from the pre-scan values are clinically non-significant, especially when standard scanning protocols are followed [275]. Based on this information we proposed that scanning patients with a CRT device and BiV pacing active should be relatively safe if conducted with experienced healthcare practitioners and a robust selection and scanning protocol [146].Should this be viable, it would not only allow patients to be reviewed with CMR using relatively similar programming to their usual settings (thus giving a more representative impression of cardiac function) but also allow for greater insight into the mechanism by which CRT improves cardiac function in most CHF patients. We received research and ethics approval (Appendix 2) to bring CHF patients in for CMR scanning whilst CRT remained active and HR augmentation takes place. This chapter will focus on safety, specifically the monitoring of symptoms or clinical changes in the patient in addition to examining device or lead parameter variation during and following CMR scanning.

## 6.2 Methodology

CHF patients with CRT devices were recruited from outpatient heart failure clinics at Leeds General infirmary, Leeds, UK. A patient information sheet that was approved by the research and ethics committee (17/SC/0612) for the study was given to the patient to ensure informed consent. A full explanation of the rationale, purpose and structure of the study was also given prior to recruitment.

Inclusion criteria:

- Patient over the age of 18
- Implanted with a 3.0T MR-conditional CRT-D
- CIED in situ for greater than 3 months
- Baseline LVEF less than 45%
- Ongoing symptoms with at least 3 months of optimal medical therapy

Exclusion criteria:

- History of uncontrolled arrhythmias
- Acute myocardial infarction or cerebrovascular event within 1 month
- Patient is unable to lie flat
- Patient is unable to tolerate the CMR environment
- Patient is NYHA 4

Once the patient agreed to take part in the study, a suitable day was booked that would enable scanning to take place ensuring:

- The patient was available to attend the advanced imaging centre at Leeds General Infirmary.
- The 3.0T SIEMENS Prisma scanner housed at the advanced imaging centre at Leeds General Infirmary was available
- A suitably trained radiographer was available for a maximal period of 2 hours set aside for the visit
- A suitably trained cardiac physiologist was available for the approximate 2 hours set aside for the visit

Transportation (private taxi) was also organised as required by the patient to aid recruitment and patient participation. Contact details were given to the patient and obtained to maximise communication and awareness of any change in circumstances.

The patient arrived in the department (Advanced Imaging Centre, Leeds General Infirmary) after the patient's pacemaker details were confirmed with their records. A case report form for the patient was completed which included the patient's past medical history, HF history, medication history and drug sensitivities in addition to discussing the aims of the project and patient information sheet. This helped in reminding the patient of the plan for the scanning session and ensured informed consent was reached. I conducted a cardiovascular examination and fluid assessment was completed to assess cardiac rhythm and confirm that the patient was fit to lie down in the scanner. I collected the following baseline data:

- Age
- Weight
- Height
- BP
- Heart Rate
- Resting rhythm
- NYHA class
- Smoking history

As per standard procedure in all hospitals across the country, an MRI safety questionnaire was completed by the patient to confirm if any additional risks beyond the CIED were present before scanning. Any identified issues were discussed between myself, the MRI radiographer and medical physics before proceeding.

All scans were conducted at the advanced imaging centre at Leeds General Infirmary. One of the advantages of this scanner beyond being able to conduct standard CMR & MRS is that the trolley has undocking capabilities. This allowed our study to proceed with efficiency in terms of the device interrogation to patient scanning. Specifically, we laid down the patient on the scanning trolley within the operating room, enabling programming and interrogation to take place in this safe

area. This serves three purposes. Firstly, it confirms the device and lead details held on the system to ensure that the expected CMR compatibility is indeed present. Secondly, the CIED interrogation produces updated lead impedance and capture thresholds. These have to be within safety limits such as the device must have 10% battery longevity and reasonable lead parameters (specific to each lead and manufacturer) to ensure safe function during CMR scanning. The scanning visit was cancelled if not achieved [277]. For example as this study scanned patients with Medtronic MR-conditional leads, patients were not able to be scanned if the lead threshold was above 2.0V at 0.4ms or there were signs of lead fracture as per the Heart Rhythm Society expert consensus statement and Medtronic published guidance [277, 278]. Finally, the interrogation also creates a baseline set of device and lead variables including capture thresholds, impedance, pacing mode and battery voltage to assess for changes post scan. All patients completed a safety questionnaire with their device and lead components treated as a package for 3.0T MRI scanning. To assess for compatibility, documentation and databases were accessed from the manufacturer's published resources. Any doubts or complicating factors were discussed with both the MR radiographer and medical physics. Once the device interrogation was completed, the CIED was programmed by the cardiac physiologist into an MRI compatible mode through the manufacturer's programming device with CRT active or disabled (randomised). If CRT was disabled, the patient was placed in asynchronous pacing of the atria with ventricular pacing if there was a lack of atrioventricular conduction. The first HR assessed in the study was always the baseline HR of the patient.

The participant was then wheeled into the scanning area without any change in position. Preparation for scanning involves ECG electrodes placed on the chest (± chest hair removal for increased conduction) to enable cardiac monitoring and timed image acquisition through ECG triggering. An MRI coil over the thorax and abdomen was placed on the patient followed by a set of headphones (with noise cancelling) and a BP cuff. Symptomology was monitored with face to face and microphone communications between the control room and MRI scanning area. Once the survey scan and baseline scan are completed, the patient is undocked from the scanner whilst remaining on the scanning trolley. This allows the patient's CIED to be reprogrammed to an alternative heart rate (HR) without requiring the patient to

change position. The HR assessed in this study were: 75, 90, 100, 115, 125, 130 and 140 bpm. 3 patients had a higher baseline and were started at 90 bpm with the order of HR following the baseline HR randomised to ensure maximal statistical value and avoidance of cardiac fatigue [279]. Once the CIED was re-programmed to the randomised HR, the participant was re-docked into the scanner with the same scan protocol conducted. Each scan took approximately 4.5 minutes and the BP was checked at the first minute of scanning at each HR to monitor for variance and patient stability. Notably, the patient's position was not changed in relation to the docking trolley during or between HR programming (due to positional memory of the scanner). This allowed scanning to proceed without duplicate scanning which greatly increased the efficiency of the study visit as a whole. Indeed, it is generally perceived that studies should avoid scanning participants for greater than 1.5 hours, as commonly after this point, patients become fatigued, bored and less likely to engage in further research. Scanning was stopped if the patient felt symptomatic (chest pain, generally unwell, light headed) or if any significant arrhythmias such as asystole or ventricular fibrillation were noted. Following completion of the various HR, the cardiac physiologist completed a full post scan device interrogation to assess for changes in device or lead parameters with the patient's device returned to normal programming (as per pre-scan). The patient was then encouraged to gradually sit up, re-hydrate as needed and return to the observation area and changing room. This period was taken with care as our cohort of patients were generally over the age of 50 and susceptible to balance or vasovagal episodes after a period of lying supine, thus a period of observation (approximately 30 mins) was completed to ensure patient safety. A debrief then took place to ensure patient feedback was obtained and symptoms were not missed.

CIED patients returning to the department for a repeat scan as part of the study underwent an identical pre scan process of the following:

- Completion of MRI safety questionnaire, informed consent and the case report form
- Clinical examination
- Pre and post CIED interrogation. The device was then programmed to either CRT active or disabled (opposite of first scan)

- CMR scanning at baseline HR, 75, 90, 100, 115, 125, 130 and 140 bpm with BP assessment at each HR.

On completion of the second visit, patients once more completed an observation and debrief period to ensure feedback and safety was maintained as a priority.

***Scanning protocol***

Scanning started with a series of planning scans including a vertical long axis, horizontal long axis and short axis scan of the heart. A 4-chamber view at the mid ventricular slice was used for further positioning and strain analysis. Real-time free-breathing GRE scanning with binning was utilised as the main sequence for scanning participants with CIEDs in this study. Specific CMR parameters are included (Appendix 1). This sequence was made available to us via the CMR team within the University of Leeds and collaboration with Kellman et al [280, 281]. The sequence relies on R-R interval and utilises powerful retrospective cloud computing to reconstruct the full imaging stack. This method was chosen as our cohort of CHF patients would not be able to manage the multiple breatholds required in traditional segmented scanning to analyse cardiac mechanics at multiple HR.

## 6.3 Results

Following informed consent, 19 patients with a CRT device completed a full CMR sequence over the two visits. We are pleased to report that no significant changes in device parameters or patient symptomology were observed with results in keeping with published observational datasets [282]. All patients were able to be returned to routine device programming without issue. Patients did not report a sensation of device heating nor were any arrythmias identified immediately prior to, during or following scanning.  None of the patients identified any issues in their device or symptomology between the first and second scan. Regular BP monitoring of patients did not identify any significant drops (>10%) from baseline. A non-significant change of -0.05% (p=0.15) in battery voltage was observed between visits.

| | Atrial impedance | RV impedance | LV impedance | Battery voltage |
|---|---|---|---|---|
| **CRT active (Mean % change from pre-scan)** | -0.08±7.13 | 4.03±4.87 | -1.22±3.17 | -2.90±1.00 |
| **CRT disabled (Mean % change from pre-scan)** | -2.68±7.55 | -2.66±7.92 | -1.08±4.89 | -2.92±0.98 |
| **P-value** | 0.64 | 0.12 | 0.86 | 0.55 |

Table 5 - Change in lead impedance and battery voltage following CMR in the CRT cohort whilst CRT was active and disabled in a paired cohort.

## 6.4 Discussion

As the first study to investigate the cardiac response to changing HR in patients with CRT active, it was reassuring to find that assessing patients with BiV pacing active in the context of 3.0T CMR appeared safe. Patients did not experience any significant side effects during scanning and there were no incidences of arrhythmias or device failure. It is notable that the battery voltage change was similar regardless of CRT being active or disabled. This suggests that the additional energy required and subsequent possible interference of LV pacing represents a negligible effect on battery as opposed to general functioning of the device in the MRI environment. Similarly, switching off BiV pacing does not seem to be associated with any difference lead variation post scan suggesting that the exposure to the MRI environment may well play a greater role than the functionality of the lead during scanning. Indeed, all the measured changes were not found to be significant when comparing CRT active against disabled. Seewoster et al [283] found that atrial and ventricular amplitudes and impedances did not change significantly 6 months after CMR in ICD and pacemakers. The trends observed were similar to patients not

undergoing CMR as part of routine follow up. Furthermore, the battery voltage reductions that are noticed acutely post CMR are thought to be associated with the RF energy emitted during scanning, resulting in a temporary drop that generally resolves after weeks [154]. It is notable that Shah et al [282] found that in patients with non-MR-conditional devices, exposure to CMR was associated with wide range of battery and lead parameter changes which in the vast majority of cases were insignificant statistically and clinically. Significant events when occurring were associated with older devices (pre-2010) which would predate any device present in my cohort of patients.

In many respects the results are not surprising as the CRT devices are being exposed to a magnetic field strength that the devices have already been strenuously safety tested in by the manufacturers. The changes observed in my study are similar to those found in previous work investigating safety in patients with a CIED in the context of MRI scanning [146, 163]. At an approximate 1 hour to complete the full sequence of scans (per visit) in my study, this work is relatively representative of academic research protocols (often shorter in clinical scans) and is the upper limit of time for patients to comfortably undergo cardiac scanning. This is even more relevant in patients with CHF and/or CIED implanted where extended periods have significant risks such as breathlessness from pulmonary oedema. It must also be considered that for a CIED to be scanned in the CMR setting, sensing and thus anti-tachycardia therapies are disabled setting a contraindication for prolonged scanning periods in this cohort of patients. Unfortunately there are no published data on time limits for scanning and it is hoped as CIED scanning becomes more common place that further research in this area takes place. We carried out this work with a high level of caution which may have played a role in the reassuring results that we have obtained. Technical colleagues from the device manufacturer were present during the first few scans just in case any issues arose. Additionally, we obtained direct contact details should there be a need for further advice or resources. Beyond the study methodology, routine CMR procedure for CIED was followed in this study which mitigated any additional risk to participant, staff and the scanner itself. The risks to the patient were also potentially reduced by having a participant focused approach. Patients were aware to disclose any symptoms pre, peri and post scanning as a matter of importance. Importantly scanning patients with a CIED was

not associated with exceeding the SAR limit and we were able to complete relatively routine CMR sequences without issue.

I believe scanning patients with BiV pacing active will become common place. Not only does this approach show “true” cardiac performance and response in the context of CRT but could also make CMR imaging feasible in a larger cohort of CHF patients than ever before. CHF patients often have issues with lying supine due to the combination of weak hydrostatic pressure present in in this cohort and gravity causing increased pulmonary oedema and altered pulmonary mechanics giving rise to breathlessness and discomfort [284, 285]. Having active CRT would be expected to result in an increased CO for most implanted patients, thus logically resulting in a higher net pressure towards fluid movement into tissue and reduced pulmonary pressure. This should help CHF patients lie supine more comfortably for longer periods and potentially prevent deteriorations during scanning whilst giving rise to more representative cardiac imaging.

## 6.5 Limitations

This was a relatively small sample size of CHF patients with CRT devices without long term follow up and so whilst the methodology appears safe, it must be taken with care in case there are drops in device parameters such as battery voltage over time. This would be relatively unexpected due to the short time frame in which the patient was placed in the MRI environment in addition to the published studies indicating minimal changes post CMR. All of the devices were one of two models made by one manufacturer; thus, these findings cannot be readily applied to CRT devices in general until larger studies take place.

## 6.6 Conclusion

Scanning patients with a CRT-D programmed to BiV pacing appears to be relatively safe when conducted by an experienced team with careful protocols in place including a thorough assessment of the patient, device package and scanning technique used. Further studies are required over longer term follow up to confirm

safety. This approach could not only give a more accurate visualisation of cardiac performance in the implanted patient but also a quality insight into the response and value of CRT as an intervention in CHF patients.

# Chapter 7 – Cardiac response to HR with CRT active and disabled using 3.0T CMR

## 7.1 Background

CRT was adopted into clinical practice relatively swiftly due to the weight of evdicen in improved outcomes without necessarily full clarification of the underlying mechanisms [286]. It is also one of the few therapies in cardiology that both improves cardiac performance and survival. Notably, the FFR appears to be flat in CHF patients when compared with controls [217]. Despite the intrinsic value of the FFR in CHF as a marker of cardiac performance, inotropy and even disease progression, limited study has taken place in this area. Exploration of the FFR in the context of CRT provides a unique opportunity to understand cardiac mechanics in response to HR in the CHF population via CIED programming, offering an experimental level of control in HR. Additionally, CMR is the gold standard for cardiac volume and flow analysis [3]. Despite CIED being labelled as MR-conditional, special considerations and protocols must be taken to scan patients with CIED. In particular, routine CMR scanning would require the CRT device to be re-programmed from routine BiV to RV pacing. Large scale studies, review articles and statements from imaging boards throughout the world have generally indicated the relative safety of scanning CIED if appropriate precautions and operating procedures are in place [146, 163, 287]. We have suggested that scanning patients with CRT active is likely to not only be feasible but insightful into physiological cardiac mechanics in CHF patients and the value CRT may bring to improving cardiac performance via the high fidelity that CMR offers [146]. This chapter will focus on the cardiac response to HR augmentation and CRT in patients with CHF. Full approval for conducting CMR in patients with CRT devices and BiV pacing active whilst modulating HR was received by our team on 16/01/2018. I believe we are the first group internationally to receive this permission. Scanning patients with CRT active enables us to explore cardiac mechanics, the FFR and response to CRT in patients with CHF. The ability to change HR allows study of the CHR and observe the potential benefit BiV pacing gives to patients.

## 7.2 Methodology

CHF patients with CRT devices were recruited from outpatient HF clinics at Leeds General infirmary, Leeds, UK. A patient information sheet that was approved by the research and ethics committee (17/SC/0612) for the study was given to the patient to ensure informed consent (full methodology 6.2). An explanation of the rationale, purpose and structure of the study was also given prior to recruitment.

Inclusion criteria:

- Patient over the age of 18
- Implanted with a 3.0T MR-conditional CRT-D
- CIED in situ for greater than 3 months
- Baseline LVEF less than 45%
- Ongoing symptoms with at least 3 months of optimal medical therapy

Exclusion criteria:

- History of uncontrolled arrhythmias
- Acute myocardial infarction or cerebrovascular event within 1 month
- Patient is unable to lie flat
- Patient is unable to tolerate the CMR environment
- Patient is NYHA 4 class

Patients had a full device interrogation before and after the CMR sequence. The patient's pacemaker details were validated on the Leeds General Infirmary hospital records system. Specifically, the patient's CRT device and leads were checked for compatibility for a 3.0T CMR scan. The CRT device had to be MR-conditional to 3.0T including all implanted leads creating a valid compatible package for MRI scanning as mandated by the NHS trust (study sponsor). This is significant as leads are generally left in situ whilst the CRT device may be upgraded over the patient's lifetime. The pacemaker package (CRT & leads) were checked for each patient and validated by the manufacturer's published documents or official compatibility databases. Notably, the validity of MR conditionality was also reliant on all of the components made by the same manufacturer to remain consistent with the manufacturer's testing and subsequent approval. For the purpose of assessing

safety, we decided to focus on one of the major CRT manufacturers, Medtronic and specifically the Amplia MRI CRT-D (DTMB1QQ/DTMB1Q1) and Compia MRI CRT-D (DTMC1QQ) models. These devices were chosen as they are 3.0T MR-conditional, known to be well tolerated and have a relatively high prevalence in our region.

Once the patient arrived at the Advanced Imaging Centre at Leeds General Infirmary, a full diagnostic CIED interrogation was conducted to identify changes to the device (such as battery voltage) and leads (such as impedance). The CIED check was conducted by a cardiac physiologist and myself with the appropriate manufacturer's programmer.

The patient then completed the full protocol for CMR across multiple HR with a scan conducted for each HR with CRT randomised to active or disabled (for the entire session). The scanning protocol took approximately 1 hour to complete from the first survey scan to the final HR in the scanning protocol (full methodology 6.2). Scanning was stopped if the patient noticed any significant clinical symptoms, signs of shock or an indication of device malfunction or arrhythmia formation such as asystole or ventricular fibrillation. Cardiac, BP, verbal and visual monitoring was maintained throughout the patient's scanning period with observation following the scan in keeping with standard procedure when scanning individuals with a CIED. Once completed, the patient underwent a full CIED interrogation. The participant then returned to the department within a month for a repeat completion of the protocol with the CRT device placed in the opposite mode (active or disabled) from the initial visit.

***Statistical analysis***

Analysis was conducted and graphs generated using SPSS v.24.0 (IBM Corp., Armonk, NY, USA). Normality for continuous variables was visually explored by distribution plots, tested using the Shapiro-Wilk test and skewness and kurtosis levels were confirmed at <1 for all key variables. After testing for normality, continuous baseline characteristics were reported as mean and standard deviation (mean (SD)). Categorical variables were reported as frequency and percentages. Loop diuretic dose and critical heart rate are median and IQR. Changes in the cardiac mechanics were analysed as a percentage from baseline with paired T test utilised to derive statistical significance between CRT on and off at each HR as not

all participants could be scanned at every HR. Error bars when presented are standard error of means. The statistical methods employed were independently verified by a statistics research fellow at Leeds University.

## 7.3 Early experience

As the concept of CMR in patients with CRT active with HR augmentation is novel, a number of minor discoveries were made with subsequent iterative changes to the methodology. Our first scans included patients with CRT-P devices, specifically the Medtronic Percepta (W1TR04/ W4TR04) model. This was hypothesised to give fewer scanning artefacts (such as susceptibility artefacts) than CRT-D due to being physically smaller in size and having less ferromagnetic content. We were fortunate to obtain interpretable scans in our first attempt, however, we discovered that patients with that specific generation of Medtronic CRT-P devices switched into “magnet mode” (fixed pacing at 70 bpm) due to the detection of significant levels of electromagnetic radiation (without the ability to utilise a viable MRI safe mode). This meant that altering the HR via pacing would not be possible in patients with these devices.

Whilst scanning patients, the heavy reinforced door to the MRI scanning area is closed for safety reasons in addition to mitigate signal interference. This resulted in a loss of the wireless signal between the device programmer and patient’s CIED. During the subsequent scanning sessions, I made a minor discovery that the programmer would hold the connection for exactly 5 minutes. This means that if for example the scanner door was opened within 5 minutes of closing, the programmer would easily wirelessly reconnect to the device. Whereas beyond 5 minutes, the programmer would need to be re-paired to the CIED through use of the probe being placed proximal to the CIED. This information focused our team effort into keeping the individual scan sequences for each HR as efficient as possible which led to further savings in time which in turn gave a more enjoyable experience for the patient.

Some of the early scans produced significant artefacts appearing as void that occasionally entered the cardiac margins thus negatively impacting analysis. We found that positioning the patient with their left arm raised behind their head led to

improvement in the images. This is due to the CIED being moved superiorly in turn shifting the artefact upwards and generally beyond the heart on the CMR image. This manoeuvre can be found as best practice for improving image quality [146, 288]. Notably this manoeuvre was retained for patients for whom the cardiac margins were affected by susceptibility artefact due to the discomfort it produces after a prolonged period. Indeed many of our cohort also struggled with this position due to existing joint issues. Furthermore, our early CMR scans in patients utilised SSFP as the scanning technique as it is the industry standard. This scanning method allows for relative fast scanning combined with high quality images and the option of normal breathing (as opposed to breath-holding) for participants. As suspected, this scanning technique often created a high amount of artefact which rendered significant sections of the image impossible to analyse with confidence. We switched to GRE which does compromise SNR but dramatically reduced the rate of artefacts encountered.

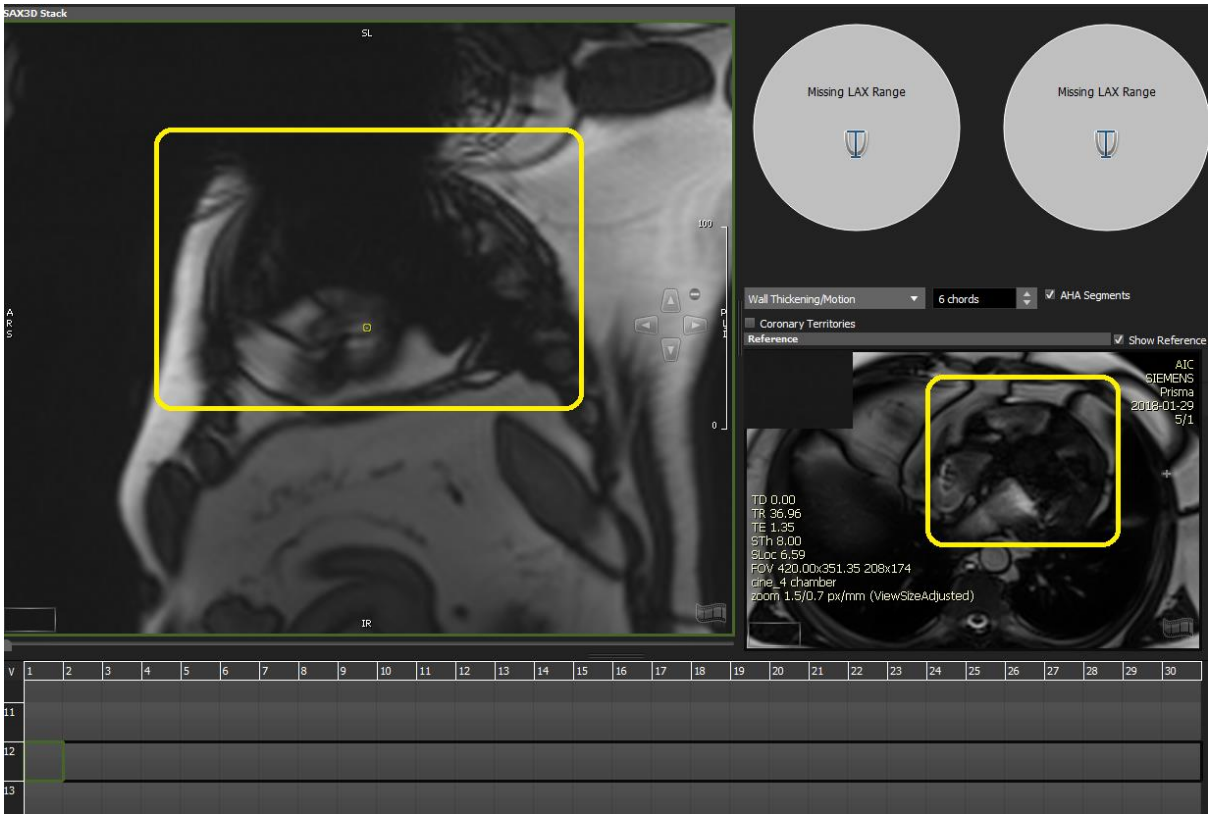



Figure 16 - Areas of susceptibility artefact distorted the cardiac image (yellow highlight) in a SSFP scan of a CHF patient with a CRT.

As this study broached multiple new areas of clinical practice, I ensured that we had device technicians from Medtronic present to assist with any technical issues during the first couple of scans. This gave the team confidence to continue independently as it became clear the protocol fell within our collective competency without obvious issues raised and the availability of assistance should it be required. Indeed, our team is likely unique in this niche area of CMR scanning CIED during normal functioning with frequent re-programming of the device.

## 7.4 Process of contouring

Image analysis was conducted using Circle Cardiovascular Imaging (cmr42, Circle Cardiovascular Imaging Inc, Calgary, Alberta, Canada). This is a well validated tool for cardiac assessment [289]. This tool enables an ellipse to be drawn that neatly defines the LV endocardial border and referred to as a contour. A contour of the LV is created at systole and diastole for each slice ensuring coverage throughout the heart. The same process can be applied for the RV. The contours produced in this fashion build the cardiac dimensions at systole and diastole, thus producing the left ventricular end diastolic volume (LVEDV) and left ventricular end systolic volume (LVESV). Many software packages also support automation or semi-automation of this process. This feature was avoided in my research, with the contours instead defined manually (albeit with edge smoothening) so as to enable consistency through the high number of measurements made. Manual contouring also developed my own skills and also gives more confidence to the moderation process, especially with respect to the presence of CIED likely complicating the automatic mode. Care was taken throughout the contouring process. Not only is contouring a time intensive process but it is a cornerstone for analysis and the project as a whole. One phenomenon that was occasionally noticed with the images was ECG or cardiac mis-triggering. This meant that despite the software reconstructing the cardiac cycle, the images can become discontinuous. To counter this issue, I reviewed every cine (series of frames of cardiac scan) to ensure that the point of systole and diastole were correctly analysed.

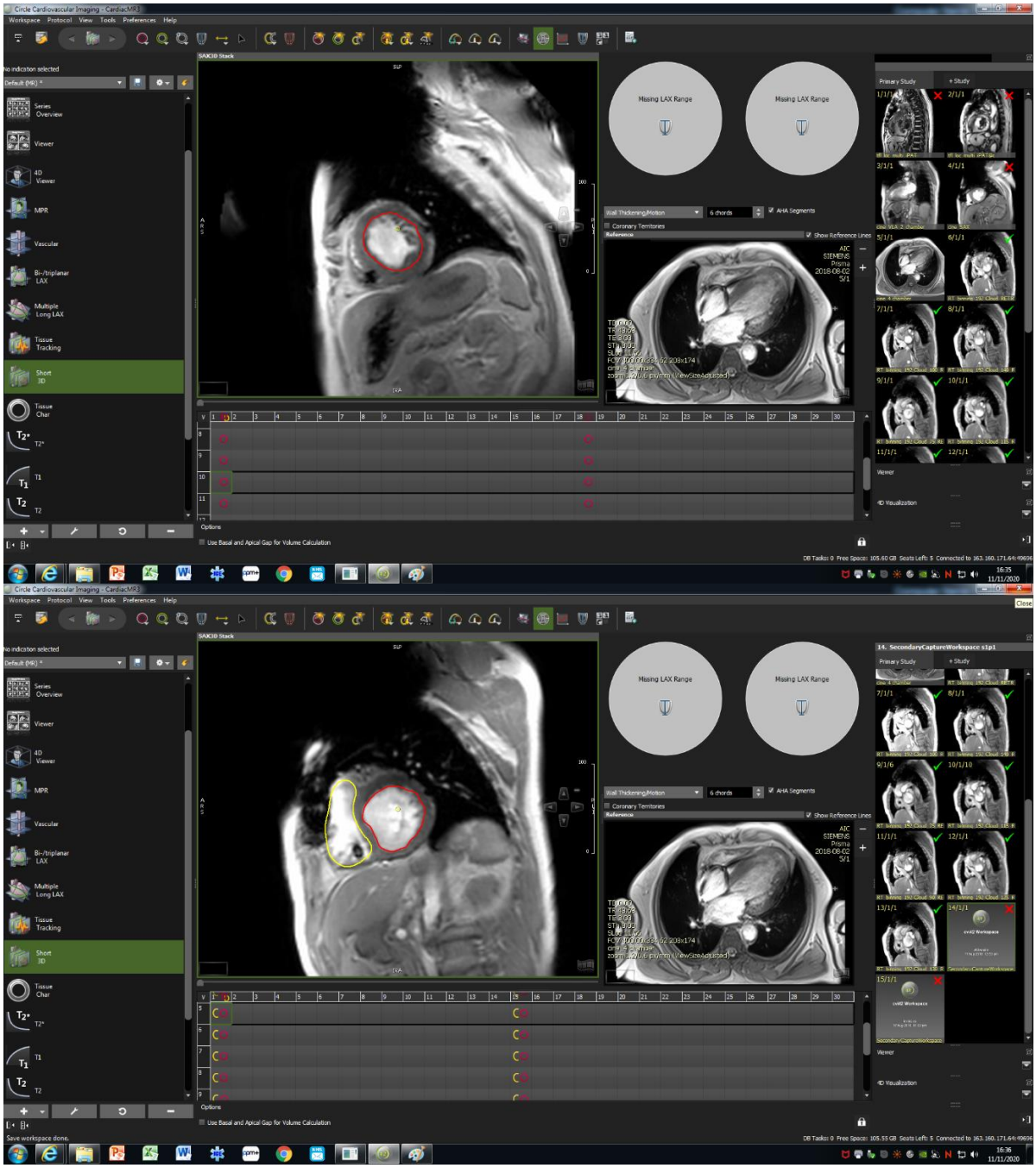


Figure 17 - Screenshots of image analysis software enabling dimension measurement of the LV (red contour) and RV (yellow contour).

The majority of physiological parameters in this research project were derived from the LVEDV and LVESV. I was fortunate to receive one on one mentoring on this process from my PhD supervisor, PS, the CMR lead for our institution as well as other senior registrars and lecturers in this field. After learning the basics of cardiac anatomy, appropriate margins, image manipulation, magnification, consistency and smoothening of edges, I proceeded to contour the participants enrolled in the study.

The contours were then moderated by PS and other senior researchers with experience in MRI analysis to maintain standard practice [290]. Contouring is a painstaking process that requires multiple reviews to maintain consistency. This research project in particular had a high intensity of contours, for example each patient has approximately 11 slices with approximately 6 different HR leading to 132 contours per scanning session for just calculating the LVEDV and LVESV. This suggests that I completed in excess of 4500 contours for the primary analysis of this chapter excluding recontouring for reviewing or reliability.

## 7.5 Calculations

Calculating the LVEDV and LVESV enables the left ventricular stroke volume (LVSV) to be calculated:

LVSV = LVEDV – LVESV

The left ventricular ejection fraction (LVEF) can be calculated with the following formula:

LVEF = LVSV / LVEDV X 100

As the HR was set by the pacing rate, the cardiac output (CO) could also be calculated with confidence:

CO = HR X SV

LV contractility is related to the SBP, LVESV and body surface area (BSA) of the patient through the following equation [272]:

LV contractility = SBP / (LVESV/BSA)

I created an advanced Excel spreadsheet to handle this dataset which would automate data aggregation for easier statistical analysis. Specifically, this database would automatically selectively transpose data for each patient into ordered groups by assessed parameter.

## 7.6 Results

In total 17 CHF patients with CRT devices completed the two visits giving a randomised crossover dataset.

| | Paired CRT cohort (n=17) |
|---|---|
| **Sex (male [%])** | 17 (76.4%) |
| **Age (years)** | 65.1±12.1 |
| **Height (cm)** | 167.9±10.4 |
| **Weight (kg)** | 87.1±13.8 |
| **Body Mass Index (kg/m$^2$)** | 31.2±6.5 |
| **NYHA class** | |
| **I** | 3 |
| **II** | 10 |
| **III** | 4 |
| **Ischaemic aetiology (n [%])** | 9 (52.9%) |
| **Atrial fibrillation (n [%])** | 4 (23.5%) |
| **LV ejection fraction (%)** | 33.7±11.1% |
| **ACEi/ARB (n [%])** | 14 (82.4%) |
| **ARNI (n [%])** | 1 (5.9%) |
| **Betablocker (n [%])** | 17 (100%) |
| **MRA (n [%])** | 14 (82.4%) |
| **Loop diuretic (n [%])** | 11 (64.7%) |
| **Median Loop diuretic dose (mg)** | 40 (40-80) |

Table 6 - Demographic information of the CRT patients who completed the scanning protocol with CRT active and disabled.

The demographics table for our CRT cohort is reassuring. The BMI and aetiology are quite typical of the patients seen in outpatient CHF clinics, however our cohort is younger than the average CHF patient which is closer to 75 years which may be related to the presence of a CRT device [291, 292]. Local data on the epidemiology of patients with devices is not available. This cohort was relatively well optimised pharmacologically with above 80% on an ACEi/ARB, BB and giving further value to the results. Women only represent 23.7% of the participants recruited in this study. Women were approached as often as men to take part in the study if not more as recruitment was non-selective (based on women representing the majority of CHF patients [3]). Data from those who were not interested in taking part including the reasoning was not recorded.

Initial analysis was conducted in absolute values. This data was accepted and presented at the European Society of Cardiology conference in Paris (2019) and subsequently won the best moderated poster award in the CHF category.

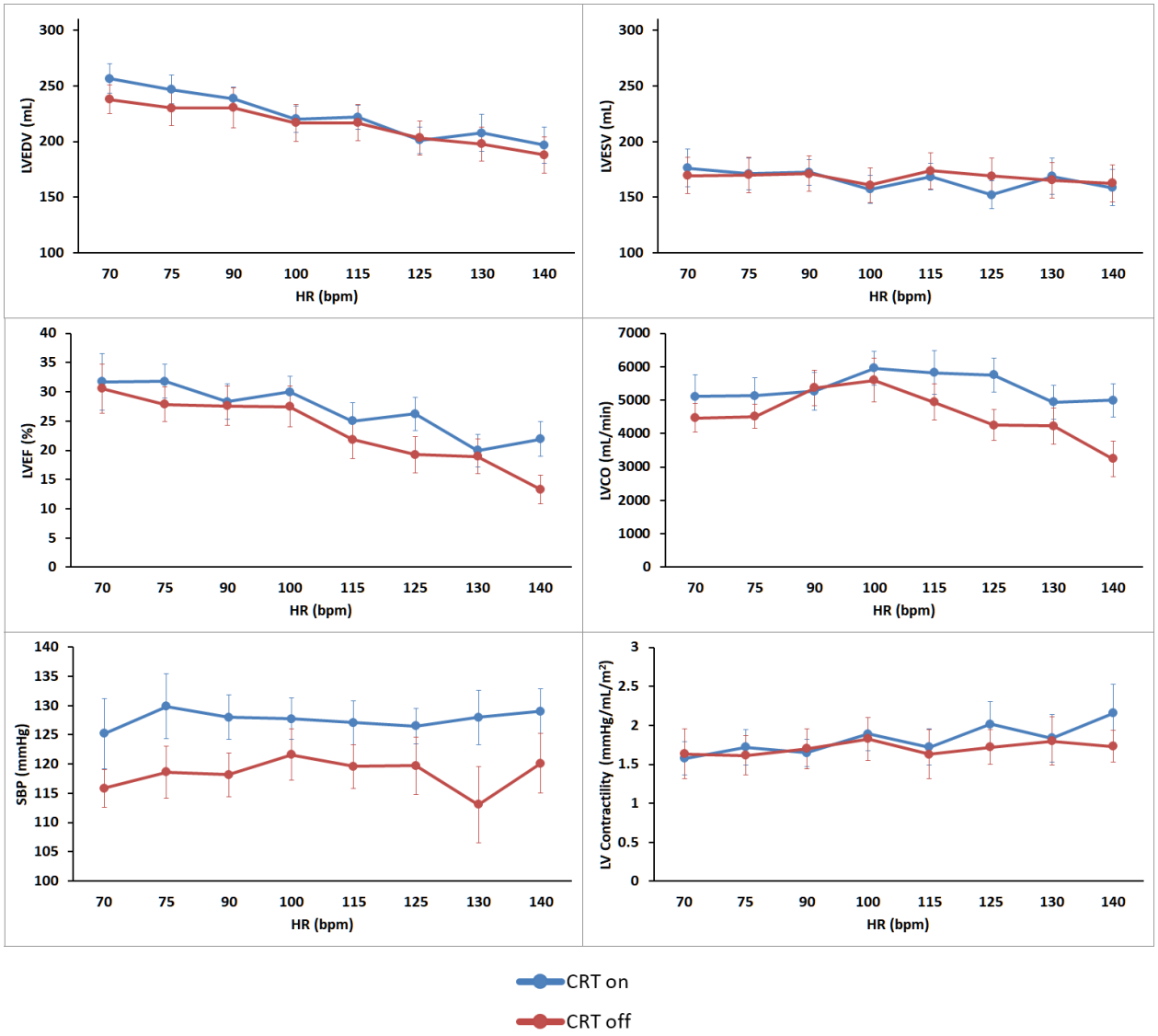



Figure 18 - Cardiac response (absolute values) to varying HR with CRT active and disabled.

The feedback received from presenting these results at the 2019 European Society of Cardiology's Conference strongly recommended that relative change from baseline for each parameter would be more useful than absolute values when presenting the change in cardiac mechanics with augmented HR.

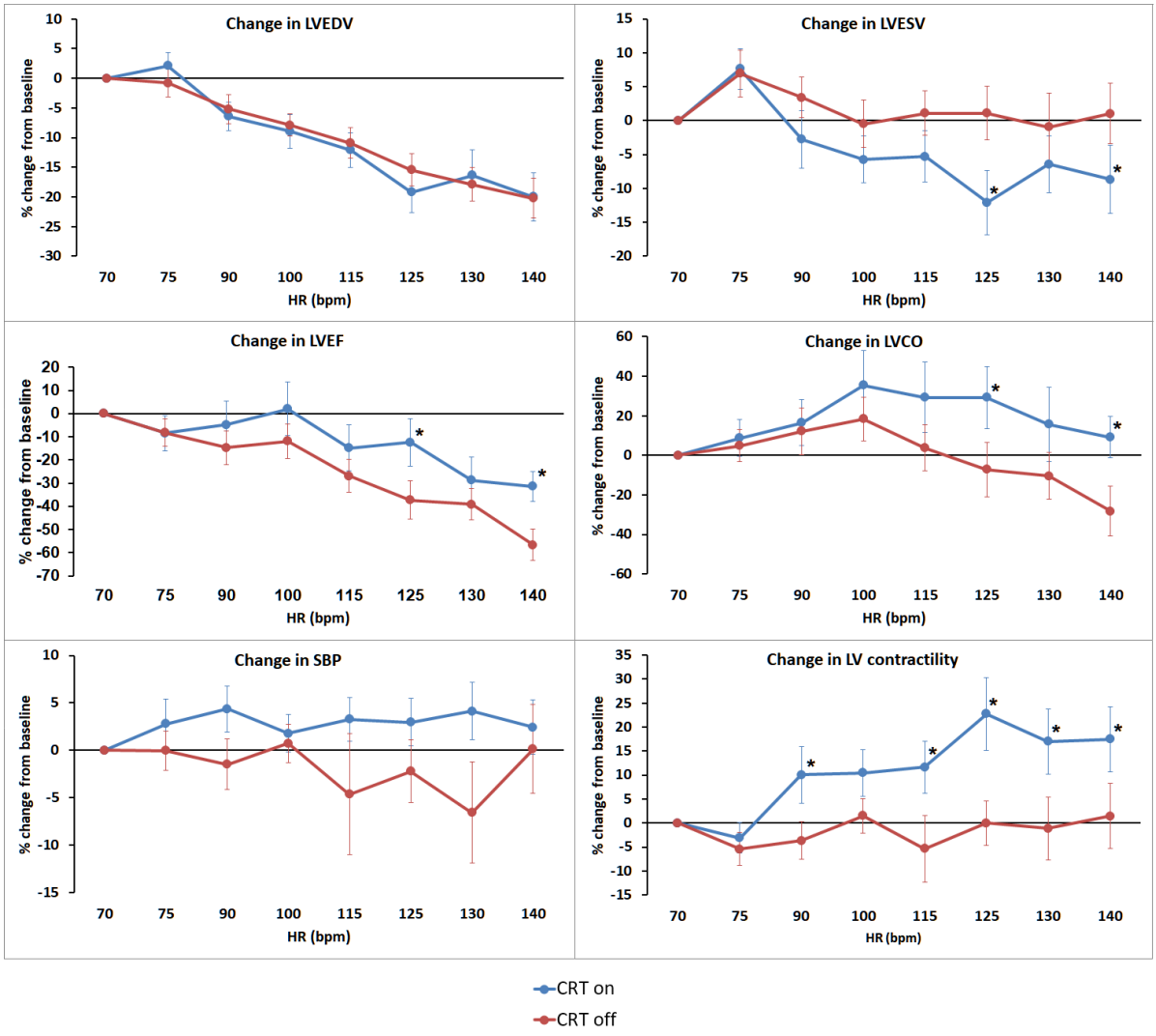



Figure 19 - Cardiac response (% change from baseline) to varying HR with CRT active and disabled. *p<0.05 between CRT on and off.

## 7.7 Discussion

These results are novel and each parameter is discussed below:

- LVEDV & LVESV– CRT on did not acutely alter LVEDV. The diastolic volume seems to reduce linearly with increasing HR regardless of CRT activity. This can be explained by a reduced diastolic filling time which has been observed previously when increasing HR via atrial pacing [293]. LVESV appears to vary with increasing HR with a maximal reduction obtained at 125 bpm. This suggests that BiV pacing is able to cause a higher ejection volume. The fact that ventricular dimensions particularly in systole appear to reduce as the HR

increases via atrial pacing indicates that the mechanism by which the HR increases is likely significant. Whilst exercise induced increases in HR maintain LVEDV with a reduction in left ventricular systolic volume [294], pacing associated HR increases have historically reduced the LVEDV [295-299]. The contrast may be due to a reduced sympathetic neurohormonal response associated with pacing induced HR increases as opposed to a rise in systemic activity and greater positive inotropy with exercise, in turn improving cardiac performance [300]. Early work on exercise in healthy humans has shown dramatic reductions in diastolic filling time, for example a reduction from 502 to 173 ms as the HR increased from 73 to 167 bpm via exercise [301]. It has been shown in multiple early pacing studies with healthy participants that HR increases by pacing alone is associated with reductions in LVEDV and SV [302-304]. Similar findings have been found in animals [305]. This suggests that exercise has a ventricular filling effect that not only compensates for isolated HR increases such as that found by pacing but is associated with increases in SV through higher LVEDV.

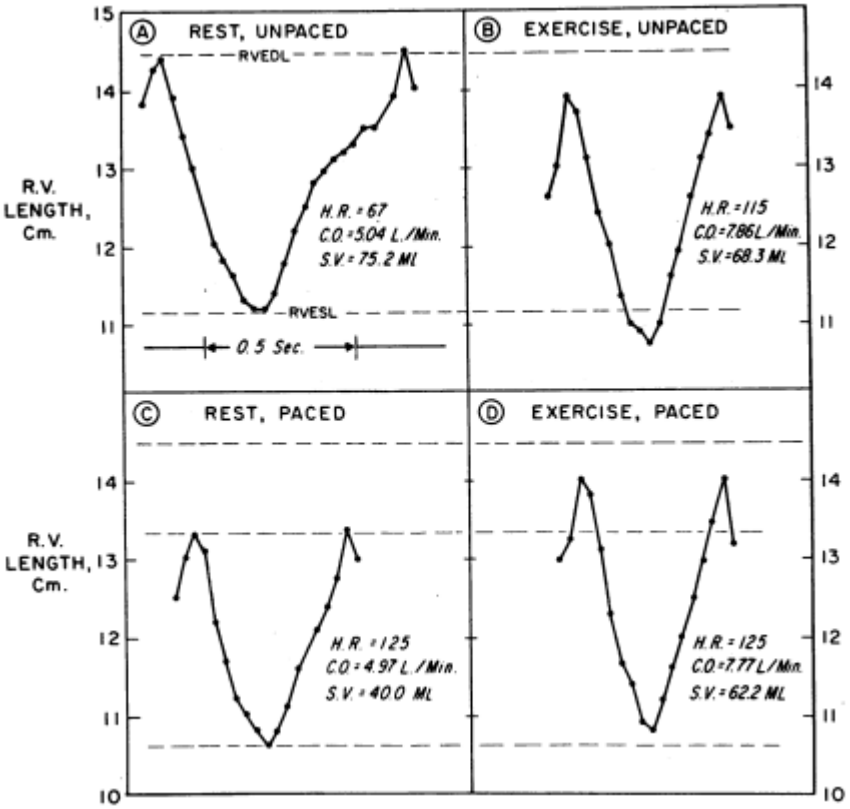


Figure 20 – Historical studies observing reduced ventricular length in healthy individuals with pacing as opposed to exercise. Adapted from Sonnenblick et al [303].

- LVEF – There is an inverse relationship between increased HR and the LVEF. As LVSV = LVEDV – LVESV, the reducing LVEDV associated with reduced diastolic filling time alongside a relatively static LVESV gives an overall largely linear reduction in LVEF. Notably, LVEF is consistently higher with CRT active. CRT is associated with significant increases in LVEF following implantation. This finding has been found in CHF cohorts with a pre-implant LVEF <35% and in those >35% [306]. Specifically, it is likely that BiV pacing is able to normalise aortic valve closure (rather than delayed as found in LBBB) resulting in improved ventricular filling [307]. The reduced diastolic filling time and earlier initiation of systole has been observed previously when increasing HR via atrial pacing and helps to explain decreasing LVEF [293]. Indeed, small cohort studies suggests that sympathetic activity associated with exercise may have a greater role than an increase in preload [297]. A state of denervation or sympathetic overdrive as present in HF can dampen the haemodynamic changes to SV traditionally associated with exercise [308]. Similar findings of reductions in ventricular dimensions and SV are also seen in the human foetus with HR increase via auditory stimulation [309].
- LVCO – As the HR is exquisitely controlled in this study, it would be expected that as HR increases, a concordant increase in CO would be observed as CO = HR X SV. However, in our CHF cohort, increasing HR caused CO to increase and then drop after 100 bpm whereas CRT on extended peak CO to 125 bpm. This is interesting as CO has been shown to significantly increase with higher HR during exercise in healthy and older participants[310, 311]. Specifically, both HR and SV increase at lower exercise levels with HR subsequently continuing to increase (whilst SV peaks) during higher exercise levels [262]. The SV increases with exercise are largely associated with increased ventricular filling and contractility. These finds are partly due to exercise producing additional demands on the cardiovascular system which would not be the case with pacing related HR increase.
- SBP – This parameter appears static with increasing HR in CHF patients, however activating CRT gives an upward shift of approximately 10mmHg that

is persistent across the HR. This finding agrees with early work by Mertens et al [312] that showed increasing the HR by atrial pacing did not result in an increase in SBP whereas exercise produces the expected rise which is likely via SV augmentation as a result of increased metabolic demands on the body. BP rises with BiV pacing has been shown before when compared with RA pacing, however our work suggests more clearly a lack of response to SBP with increasing HR [313].

- LV contractility – Contractility appears to be static in CHF patients. This is a finding that has been shown earlier by Gierula et al [272]. Our contractility levels are also relatively similar to the previous work. Notably the baseline LVEF in both studies are similar despite our cohort being younger. It is interesting to see that CRT on causes an increase in contractility at the higher HR from 125 bpm onwards which is persistent. Therefore we have found that the CHR seems to become extended when CRT active.

In summary, the cardiac response of different HR in CHF patients with CRT active and disabled is made much clearer by focusing on parameter change from baseline. Whilst LVEDV appears relatively similar, LVESV is dramatically lowered as HR increases with CRT on vs off. Whilst SBP was not found to be significantly different between CRT on and off, BiV pacing looks to give an overall boost across the HR measurements. LVEF reduced with increasing HR, however it was consistently higher with CRT on and was significantly different at the higher HR. LVCO appears to have a parabolic response at the studied HR range with a higher peak and shallower plateau when CRT is on with statistically significant differences in response at the higher HR. Interestingly, the response to LV contractility is consistently higher as the HR increases, with statistically significant differences found intermittently. This pattern in particular suggests that a higher sample size may have produced more significant results across the range of HR. Overall with many of the significant differences in parameters found at the higher HR in the context of plateau or slight decline, the assumption would be that BiV pacing is mitigating much of the decline in function that would otherwise occur. It would be useful to ascertain how this improvement would compare to control patients with preserved LV function,

thus helping to identify if this improvement is a consequence of improved or normalised LV contraction.

Our results are similar to an inotropy focused study investigating a relationship with survival conducted by DeVecchi et al [314]. Patients with a CRT device were switched from CRT on and off and underwent echocardiography whilst being paced at their baseline (or 70 bpm), 100 and 120 bpm. They also showed a reduction in ventricular dimensions with increasing HR that was coupled with less dramatic decreases in SV with CRT active. Notably, contractility measured by LV elastase was relatively static whereas CRT appeared to trend upward at similar HR to my study. My findings also largely agree with invasive studies identifying improvements in contractility with BiV pacing and increasing HR when compared with LV and RV pacing alone [315, 316]. These studies along with our work suggest that the contractility benefits associated with active CRT may be due to reduced LV delays. LV pacing alone is associated with reduced filling time and higher delays in longitudinal contraction compared with BiV pacing despite haemodynamically performing similarly [317]. Indeed, this resulted with longer aortic pre-ejection delays. Additionally, interventricular dyssynchrony is reduced with BiV pacing. Leclercq et al [318] showed in dogs that mechanical dyssynchrony correction took priority over electrical dyssynchrony in terms of haemodynamics (aortic pulse pressure and $dP/dt_{max}$). It is likely that a similar situation is present in humans. BiV pacing achieves coordinated contraction through intramyocardial conduction despite this pathway being often significantly slower in CHF patients [319]. The delays are also present in non-ischaemic hearts (both epicardial and endocardial conduction velocities are altered) [320]. This is notable as it enables mechanical synchrony to be often feasible and an area for further study as cardiac regions generally shorten at similar times [318]. Furthermore, Ukkonen et al [321] have shown via PET scanning that BiV pacing seems to improve cardiac function without increasing LV oxidative metabolism. This is of critical importance as it is one of the key advantages of device therapy over traditional positive inotropes (and associated lack of improved long-term survival) such as milrinone or dobutamine [322-324].

Assessing contractility via end systolic index as conducted in the present study is not load dependent. This is particularly relevant as the traditional marker of contractility LV $dP/dt_{max}$ is load dependent and CHF patients are known to have a dynamic fluid

status and variable preload [263]. Furthermore, traditional markers such as LVEF are highly load dependent leading to reduced reproducibility in this cohort [325]. The cardiac functionality improvements noted by my findings also bear some similarities to the work by Steendijk et al [326]. This group invasively studied the haemodynamic response to pacing in 22 CHF patients and repeated the study 6 months post CRT implantation with BiV pacing active. Similarly to my work, they describe a bell-shaped curve in improving CO that was higher and prolonged when CRT was active when compared to pre implantation. LVEF also trended downwards at higher HR which reduced decreases with BiV pacing. Contractility was also relatively flat though was improved slightly with BiV pacing active. The improvements noticed were more profound than what was observed in my acute study which likely represents a combination of BiV pacing and reverse ventricular remodelling which can be observed. Reverse LV remodelling changes can be identified as early as 1 month [327, 328]. Further improvements are often noted at 6 months which are maintained in the majority of patients at 1 year [329, 330]. Despite this, our findings found a reduction in LVESV acutely with CRT active of 5% at 100 bpm whilst Steendijk's group showed a reduction of 42.5% at 100 bpm. This difference is likely explained by the fact that my study focuses on patients that have a CRT device in situ and comparing the acute difference between CRT on and off whilst Steendijk's findings highlights the effect of a 6 month period of novel BiV pacing in which beneficial cardiac re-modelling is taking place via CRT and the subsequent difference between CRT and pre-CRT performance. Similarly, when considering CO, our group displayed an improvement of 17.18% at 100 bpm when comparing CRT active against disabled. Steendijk's group found an improvement 22.02% in over the 6 months follow up after CRT implantation. This is remarkable as it suggests that the majority of the improvement in LVCO at paced HR is obtained acutely through the intrinsic action of the BiV pacing. Unfortunately, it is not feasible to compare contractility directly between the two studies due to the variation in methodology. It is interesting to compare the pattern of response (figure 20). My data shows that CRT off produces a relatively flat FFR response to increasing HR with a noticeable improvement at higher HR with CRT active. Steendijk's cohort found greater contractility from baseline and a subsequent flat response to FFR with increasing HR pre and post CRT implant. The primary explanation for the upward shift in contractility is the beneficial reverse remodelling that occurs following CRT

implantation as described earlier. The slight trend to a right shifted FFR with CRT active that is not found in Steendijk's data could be explained by the modern imaging techniques used in my study which employs state of the art 3.0T CMR. Furthermore, it is possible that in my study with pharmacologically optimised patients receiving modern therapies, that the level of neurohormonal disruption was less than present in Steendijk's group. Notably, only 10/22 patients were taking BB compared to 100% in my study cohort. This is a critical point as the effects of betablockers are believed to partially halt the positive feedback loop that occurs when the heart rate goes above the CHR. Indeed, our contractility improvements agree with the findings by Vollmann et al [315] who also found a positive FFR at the higher paced HR with BiV pacing when compared with LV or RV pacing. Whilst direct comparisons are not possible due to the different study designs, it gives a notion of delineating the possible direct effects of CRT function from longer term beneficial reverse remodelling processes.

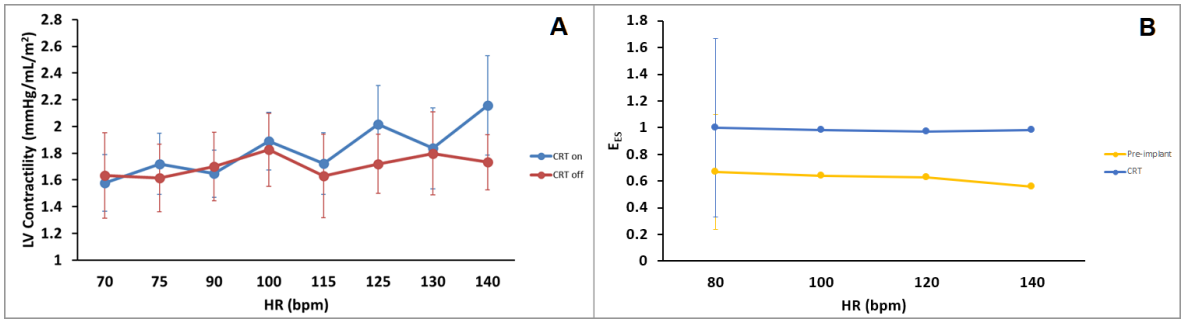



Figure 21 - Comparing contractility change with increasing HR in this study (A) against Steendijk's group (B). Adapted from Steendijk et al [326].

Note that error bars were only possible to be created in panel B from the baseline data supplied.

An interesting consideration is the neurohormonal effect of BiV pacing on the patient. BiV pacing is associated with reductions in sympathetic activity, specifically sympathetic nerve activity when compared with RA and RV pacing [313, 331]. The changes longer term (3 months), seem to be less consistent with some studies indicating a lack of improvement when assessing plasma catecholamines despite beneficial changes to ventricular remodelling present [332]. Other studies have shown improvements in muscle sympathetic nerve activity (2-6 months) post CRT implantation [333, 334]. Cha et al [335] conducted a unique study in which CHF patients had cardiac pre-sympathetic function assessed via iodine 123

metaiodobenzylguanidine scintigraphy. This method can assess sympathetic nerve activity in a number of ways. It identified reduced sympathetic activity after CRT implantation and appears to reverse the sympathetic overdrive that occurs in CHF patients. The majority of these studies suggest that CRT likely produces a reduction in sympathetic activity in CHF patients after months of CRT. The interesting question would be to assess if this effect is due to direct improvement to the sympathetic nervous system or more likely as a consequence of improved cardiac function through the mechanical correction of electrical dyssynchrony. A study by Ståhlberg et al [336] neatly ties this concept together with my own findings. In approximately 10 CHF patients, they found that the MSNA reduced linearly when increasing the HR from 50 to 70 and then to 90 bpm. Importantly the CO also increased with the HR. This is notable as the same pattern is noted in my findings and it could be projected similarly that with a plateau and subsequent reduction in CO that would be expected at the higher HR, the MSNA would return to a neutral point and potentially increase further.

## 7.8 Limitations

A larger sample size would have been useful in some of the parameters to delineate a trend from statistical difference. However, this is the largest CRT cohort to date to have been studied with CMR whilst observing the cardiac response to augmenting HR. It would have been useful to assess sympathetic activity with increasing HR as a possible factor to the increased CO and upwards trend in FFR with CRT active. This would have been difficult to achieve due to the lack of robust non-invasive measures of sympathetic activity that becomes further limited in the MRI setting. Furthermore, measures such as HR variability as a surrogate measure would not have been valid due to the process of HR augmentation.

Patients placed into CRT off meant switching the programming to AOO or DOO as required. AOO pacing was prioritised, however some patients required DOO pacing (5/17 patients) due to intrinsic AV conduction deficits or presence of AF. Whilst pacing at the RV rather than the RA may be expected to produce a difference in conduction pattern, the acute effect on RV dimensions and function have been shown to be largely limited [337, 338]. Sub-analysis in my dataset did not reveal a

significant difference between AOO and DOO pacing nor in patients with an ischaemic aetiology.

## 7.9 Conclusions

This work has shown for the first time that scanning patients with MR-conditional CRT-D devices and active biventricular pacing at different heart rates is possible using 3.0T CMR. I have found an abnormal FFR in patients with HFrEF that seems to be improved with CRT. Finally, a paced HR of 100 bpm produced peak LVCO in this cohort, after which performance continued to drop to below baseline. Further study is required to compare the changes found in CHF patients against controls.

# Chapter 8 – Comparing cardiac response in CHF and non-HF patients

## 8.1 Background

Once we completed scanning the CRT patients, it became important to explore the cardiac response to pacing in non-HF patients. This is particularly relevant as our results suggest a normalisation effect of BiV pacing in CHF patients. Furthermore, with our success in CMR with BiV pacing, I wanted to confirm that it is also viable to scan participants with a non-CRT CIED using the same scanning protocol. Studies in healthy animals have shown that chronotropy and inotropy contribute to myocardial perfusion in approximately equal parts [339]. Increasing the HR via pacing in patients with transplanted hearts showed a reduction in ventricular dimensions in a similar manner found in my studied cohort, however the degree of relative reduction is unclear [293]. Notably, there is a lack investigation into the FFR in older participants which would more closely represent the CHF population. It is possible that the FFR is affected by age thus it would be interesting to compare the FFR and cardiac mechanics of CHF patients with older participants who have a CIED implanted that allows for HR programming in the CMR setting.

## 8.2 Methodology

Control participants were recruited from outpatient cardiology clinics at Leeds General infirmary, Leeds, UK. An approved patient information sheet was given to the patient to ensure informed consent. A full explanation of the rationale, purpose and structure of the study was also given prior to recruitment.

Inclusion criteria:

- Patient over the age of 18
- Implanted with a 3.0T MR-conditional dual chamber pacemaker device
- CIED in situ for greater than 3 months

Exclusion criteria:

- Previous diagnosis of heart failure
- Baseline LVEF < 45%,
- History of uncontrolled arrhythmias
- Acute myocardial infarction or cerebrovascular event within 1 month
- Patient is unable to lie flat
- Patient is unable to tolerate the CMR environment

Participants underwent an identical pre-scanning protocol (6.2 Methodology) to ensure that their device and leads, thus their pacing package was compatible with the 3.0T MRI scanner. In order to scan control patients in a 3.0T scanner, the Abbott Assurity MRI pacemaker (models - PM 1272, PM 2272) was chosen due to the prevalence of this device in our local population and ability to manipulate HR in a similar manner to the CRT devices (Chapter 7). As the manufacturer of the dual chamber devices fitted in the control cohort was different to the manufacturer of the CRT devices, I ensured that technical staff from Abbott (the manufacturer) were on site during our first few scanning sessions. On arrival at the department, control participants underwent the same pre-scan protocol as the CRT cohort involving a medical history, examination and safety questionnaire. Once in the control room, the control group had a pre-scan device interrogation and then completed a similar programming and scanning protocol as the CRT patients. Visual, audio and physiological monitoring (including ECG) was present in all patients. Participants had a post scan device interrogation via manufacturers programmer followed by a period of observation and debrief.

## 8.3 Results

| | Atrial impedance | RV impedance | Battery voltage |
|---|---|---|---|
| **% change from pre-scan** | 4.39 | -1.11 | -0.04 |

Table 7 - Change in lead impedance and battery voltage following CMR in the control cohort with dual chamber pacemakers.

There were limited changes in device parameters following scan. There were no significant clinical symptoms during scanning prompting the termination of scanning, nor the formation of arrhythmias or significant changes in SBP.

| | CRT cohort | Control cohort | p-value |
|---|---|---|---|
| **N (male %)** | 17 (76.4%) | 13 (76.9%) | 0.97 |
| **Age** | 65.1±12.1 | 76.9±6.4 | <0.01 |
| **Height (cm)** | 167.9±10.4 | 166.3±9.7 | 0.68 |
| **Weight (kg)** | 87.1±13.8 | 84.8±14.8 | 0.25 |
| **BMI** | 31.2±6.5 | 28.8±3.4 | 0.24 |
| **Systolic BP** | 127.1±22.4 | 144.9±17.3 | 0.02 |
| **NYHA** | | | |
| **I** | 3 | | |
| **II** | 10 | | |
| **III** | 4 | | |
| **Ischaemic aetiology (%)** | 9 (52.9%) | 3 (23.1%) | 0.10 |
| **Dilated aetiology (%)** | 5 (29.4%) | 0 (0%) | 0.03 |

| | | | |
|---|---|---|---|
| **AF (%)** | 4 (23.5%) | 4 (30.8%) | 0.67 |
| **Baseline LVEF** | 33.7±11.1% | 53.4±8.9% | <0.01 |
| **ACEi or ARB use (%)** | 14 (82.4%) | 8 (61.5%) | 0.21 |
| **ARNI use (%)** | 1 (5.9%) | 0 (0%) | 0.21 |
| **Betablocker use (%)** | 17 (100%) | 4 (30.8%) | <0.01 |
| **MRA use (%)** | 14 (82.4%) | 1 (7.7%) | <0.01 |
| **Loop diuretic use (%)** | 11 (64.7%) | 5 (38.5%) | 0.16 |
| **Baseline HR** | 66.7±14.4 | 71.5±8.8 | 0.30 |
| **CHR (bpm)** | 125 | 100 | 0.01 |
| **Baseline LV contractility (SBP/LVESVI)** | 1.74±0.79 | 3.30±0.87 | <0.01 |
| **LV contractility at CHR (SBP/LVESVI)** | 2.01±1.16 | 4.01±1.06 | <0.01 |

Table 8 - Demographics of CRT and Control cohorts

The most notable difference between these cohorts is that the control group were older. Statistical analysis did not find a identify a correlation between the CHR and age in my studied cohorts (r=0.22, p=0.24). As this study employs state of the art 3.0T CMR, the qualifying device packages were limited. Furthermore, the mean age group for implanting dual chamber pacemakers is 76 in the UK with most RCT data present for patients between 73-80 [340]. With this in mind, prioritisation was given to non-HF participants with a suitable baseline LVEF in keeping with the described inclusion/exclusion criteria. In retrospect this was a wise decision as issues were encountered during this period of study. Firstly, the novelty and breadth of this study required a significant number of professionals present during scanning to ensure high quality and safety standards were met. When combined with the second issue of the COVID-19 pandemic, a large sample size of highly matched participants was

not possible, especially with the study cohort representing a vulnerable group that required shielding to minimise health risks. I am grateful that we managed to scan a reasonable number of patients in both cohorts, enabling interesting and meaningful analysis to take place.

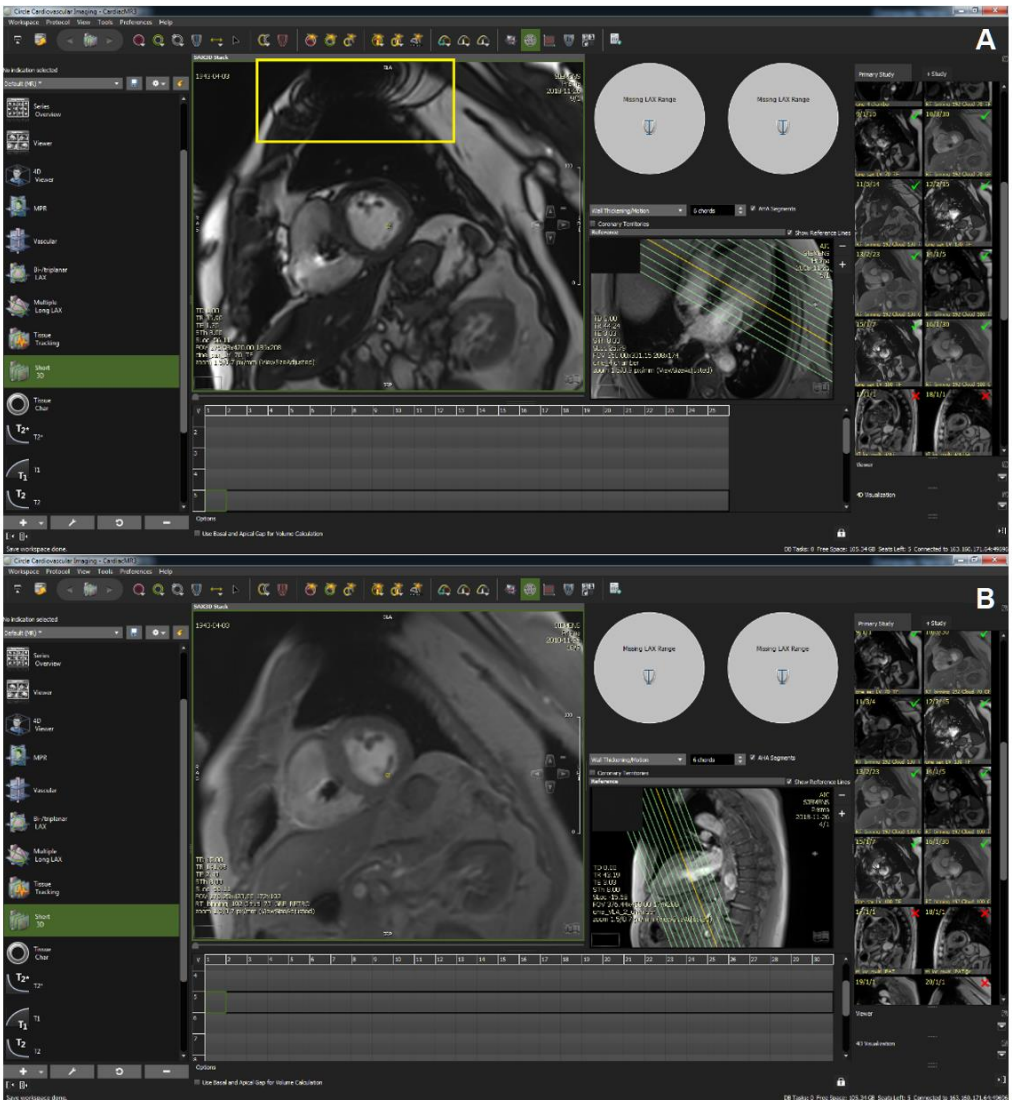



Figure 22 - SSFP (A) and GRE (B) CMR scans of a 3.0T MR-conditional dual chamber pacemaker. Susceptibility artefacts (yellow box) and poorly defined cardiac borders were immediately apparent with the SSFP scan.

A SSFP scan was trialled once more as a different CIED and thus form factor was being scanned. As observed in the CRT cohort, there were multiple artefacts produced (primarily susceptibility artefacts) alongside frequent poorly defined cardiac

borders in the image which impacted image analysis. GRE scans proved to be superior in terms of artefact formation as found earlier.

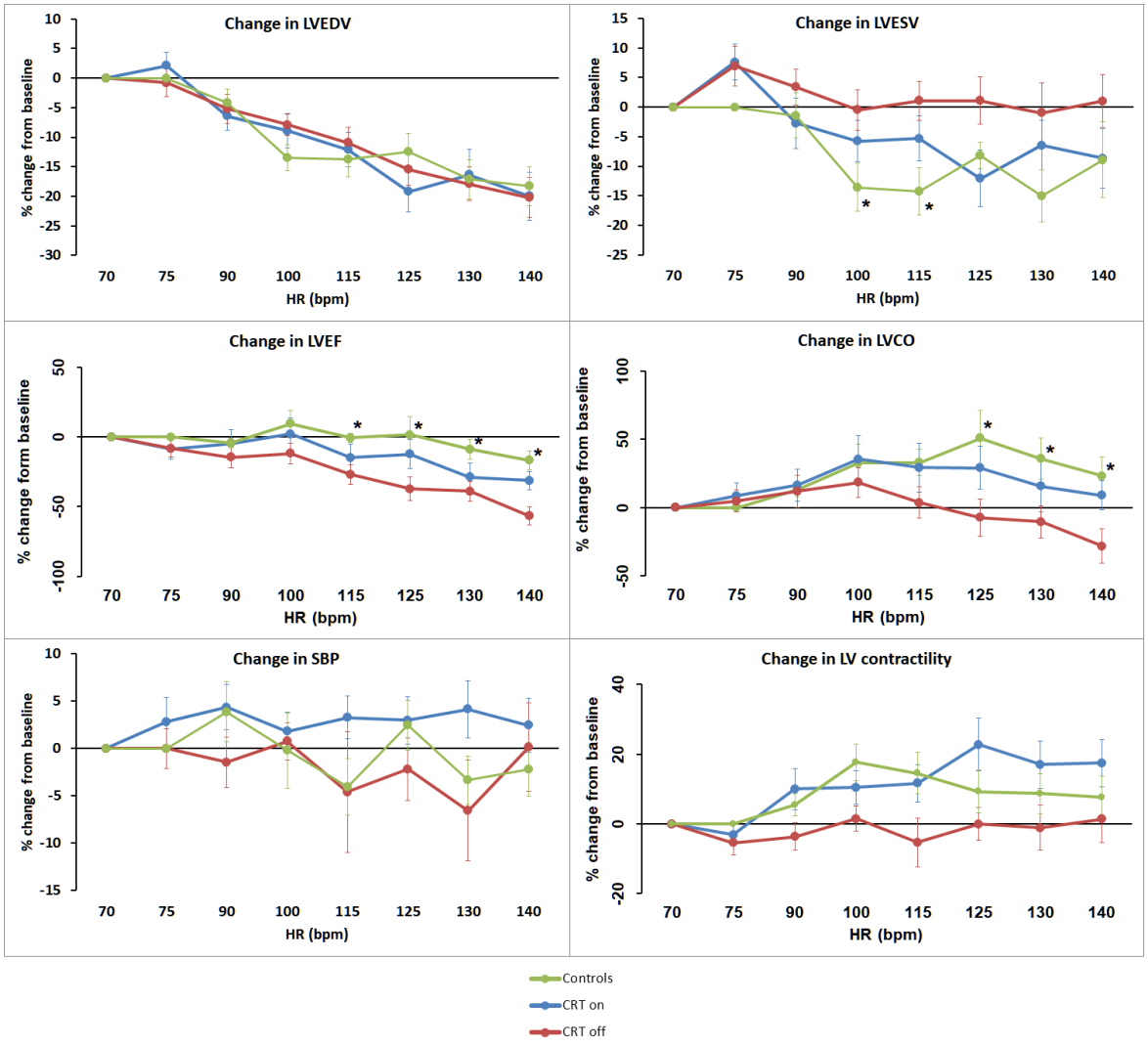



Figure 23 - Comparing cardiac response to increasing HR via atrial pacing in controls and CRT patients. *p<0.05 between Controls and CRT off. Note there was no significant difference detected between Controls and CRT on.

## 8.4 Discussion

It is reassuring that we were successfully able to conduct a similar device programming and scanning protocol as utilised with CRT devices. This approach was not associated with any clinically significant device parameter change, physiological or symptom based consequence. This is largely to be expected as the programming was more comparable to routine MRI scanning for a MR-conditional

CIED patients. This gives me more confidence in not only the safety of this technique but also the versatility of this scanning protocol which seems to be feasible across device types and manufacturers.

Control participants displayed a similar decrease in LVEDV to CRT patients with increasing HR, a finding supported by previous work in non-HF patients [293]. Furthermore, control participants have a reduction in LVESV that appears more in line with CHF patients when CRT is active. This suggests that BiV pacing is creating a similar contraction at systole to what is achieved by individuals without HF. Interestingly, there is no obvious difference in SBP between controls and CRT activity. I believe this is due to a combination of factors causing controls to rest in between these two groups. A possible explanation for the control group having a lower rise in SBP than patients with CRT active could the due to LV pacing giving a more responsive cardiac response at higher HR. The notion of superior performance with LV pacing at higher HR requires further study as it could suggest benefits of implantation in a larger cohort than current indicated.

Increasing HR had a largely similar effect in both CRT patients and control participants to varying degrees. Control participants maintained their LVEF longer (primarily through greater reductions in LVESV) as HR increased than CRT patients, resulting in a higher LVEF at all points. This manifests in the control group producing the highest increase in LVCO of the 3 groups at the higher HR. Both controls and the CRT active cohort showed a positive response to increasing HR. This suggests that experimentally it is possible for both CHF patients and controls to increase CO beyond their basal requirements via pacing in a similar manner to medications such as dobutamine. Indeed even in exercise, the relationship between CO and oxygen consumption is not at a linear ratio of 1 in controls with CHF patients known to have greater inefficiency [341]. Interestingly, both groups have a CHR within our HR range suggesting that negative inotropic factors are present. Furthermore the CHR in the controls was 100 bpm compared with 125 bpm for CRT on patients. Hasenfuss et al [237] identified that there was a significant correlation between frequency at which peak twitch tension was reached and levels of SERCA. As peak twitch tension is similar to the concept of CHR, there could be value in not only comparing SERCA levels against the CHR but considering if the CHR is indeed determined by SERCA activity. This could be achieved by obtaining biopsy samples from CHF patients to

identify SERCA levels at the point of CRT implantation and then conducting an echocardiography based methodology as utilised by Gierula et al [272] with a subsequent CMR based protocol as utilised in this study once the device has been situ for > 3 months.

One factor that could be relevant to my dataset which may potentially explain the lower CHR in the control group is that the average age was 65.1 and 76.9 in the CRT and control cohorts respectively. Notably, increasing age was not associated with a change in the CHR in my dataset. Ageing is likely to be a factor in causing contractility issues at higher HR that BiV pacing via active CRT could be mitigating for. Ageing has shown to cause a downward shift in FFR in skeletal muscle [342]. Both ageing and CHF are associated with reductions in Type II fibre area within skeletal muscle. Notably, this change in muscle distribution is independently connected with a leftward shift in FFR [343]. This is validated further in animal studies which have found FFR to become left shifted in older subjects [344]. Ageing is a complicated variable to assess with regards to performance and disease. A study by Herraiz-Martínez et al [345] examined right atrial myocytes in 80 non-HF patients according to three age groups; <55 years, 55-74 years and >75 years old. They found an age dependent decrease in calcium handling, specifically, a decrease in L-type calcium channel, free calcium, reduced SERCA and slower transportation of calcium. The changes in calcium handling that are found in ageing and those associated with CHF per se seem almost identical. Notably, ageing is known to be a strong risk factor for CHF and the prevalence of HF increases from 1-2% amongst adults aged 45-54 to >10% in those >75 years old. CHF generally represents a common outcome for most cardiovascular diseases such as IHD or HTN which result in ventricular remodelling and the development of reduced exercise capacity via ventricular dysfunction [346]. Moreover, age is an important risk factor for hospitalisation and mortality in CHF [347]. My belief is that there is significant overlap in the syndromes of CHF and ageing. This explains the multiple commonalities such as calcium handling, breathlessness, deconditioning and infection [348, 349]. Indeed it would be near impossible to conduct a study on CHF in patients <40 and if possible, would likely represent a different set of haemodynamic or performance parameters to what the cardiology community would consider as CHF. Our results suggest that the FFR response is depressed and left shifted not only by CHF but

also by age as this is the only plausible variable that is significantly different between the two groups. An interesting extrapolation of this point would be the reminder that parameters such as the FFR, CO and even LVEF are likely to be regressive with increasing age. This concept not only has impact in disease progression but also on a practical level in areas such as device programming. My results suggest that monitoring of cardiac mechanics could have a beneficial impact on tailored programming which takes into account factors such as CO and the FFR. Ageing and CHF is an area that has received limited study with regards to cardiac mechanics and haemodynamics. We look forward to further study that may delineate or indeed the merge these two entities more accurately.

Overall, these results show that both control and CHF patients are susceptible to reduced LVEDV with increasing HR that is believed to be due to decreased diastolic filling time. The functional LV in patients with active CRT and control patients seem to produce a protective effect on performance with higher HR resulting in a superior LVEF and LVCO. The superior ventricular response to HR produces an upshifted FFR in both controls and CRT on when compared with CRT off. It would be interesting to explore these findings in future work to see if the improved performance at higher HR is associated with increases in functional capacity. The fact that the LV contractility curves between controls and CRT on bear such as resemblance is reassuring and for CRT on to have a higher CHR is suggestive of additional benefits of BiV and encourages the further study of CRT pacing in older cohorts of patients.

## 8.5 Limitations

This analysis is limited by the sample size which ideally would have been larger to smoothen some of the variance noted in some of the parameters. The sample size was limited by importance placed on a similar methodology as conducted in the CRT cohort and the viability of scanning patients in the context of the outbreak of COVID-19. Despite this, significant differences were noted and my work represents the only study investigating the effect of augmenting HR in control patients with a focus on FFR and common cardiac mechanical parameters. A larger sample size would have also enabled investigation into more than one device and CIED manufacturer to ensure that the methods and results are not vendor specific. It would also have been

useful to follow up device parameter changes over the longer term to confirm a lack of significant issues downstream of scanning.

## 8.6 Investigation of Strain

In order to assess LV contractility further we utilised strain analysis which has an increasingly important role in assessing ventricular contractile function. Strain analysis, otherwise referred to as myocardial deformation analysis quantifies tissue movement at a frame-by-frame level from diastole to systole using imaging modalities such as echocardiography or CMR [350, 351]. It has advantages over markers such as LVEF as it can be segregated into regions and different movement types. Additionally, it is less load dependant or affected by artefacts or observer variance. We are fortunate in this study to be able to utilise high quality feature tracking (FT) which is generally able to assess myocardial deformation in 3 different axes; radial, circumferential and longitudinal (figure 23) [352]. Radial strain (RS) is the measure of contraction towards the centre of the ventricle and depicted as a more positive value the more the LV thickens in systole. Circumferential strain (CS) is the analysis of shortening across the perimeter based on the transverse plane. This is generally a negative value, with the more negative values translating to greater shortening. Longitudinal strain (LS) is the contraction of longitudinal cardiac fibres from the base to apex and is often depicted as a negative value. One of the primary advantages of FT is that it does not require any further MRI scanning or contrast that would be expected with alternative MRI techniques such as myocardial tagging or strain encoding [353]. CMR FT uses a “block matching” [354] method which follows the cardiac cycle and tracks features of interest around the myocardial borders along each frame. The technique provides a rapid assessment of ventricular strain without significant compromise to accuracy and performs well when compared

with echocardiography [355-357].

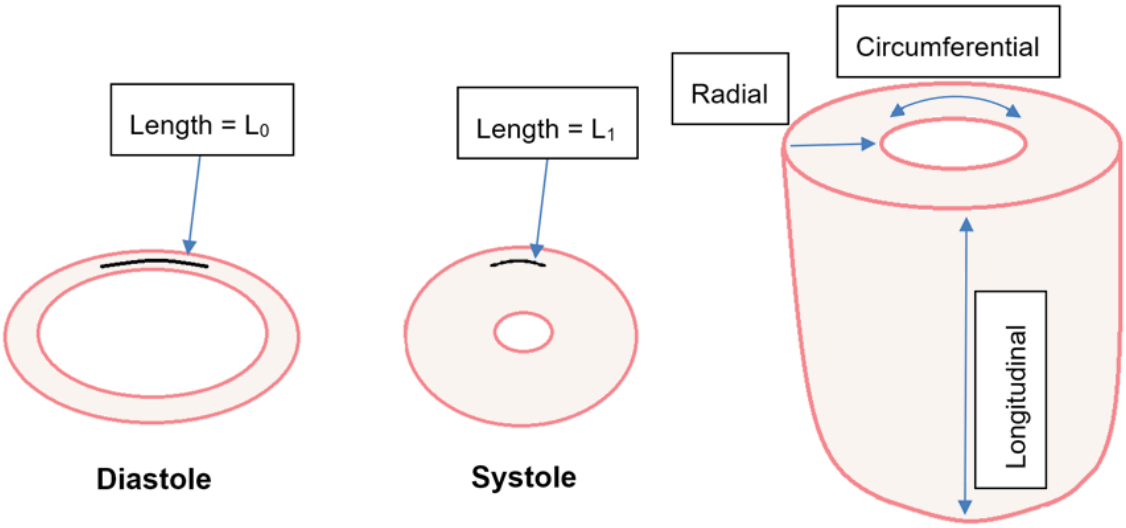



Figure 24 - Determinants of strain and the 3 axes in which strain is routinely calculated.

Strain is calculated by the following equation:

$$\text{Strain} = (L_1 - L_0) / L_0$$

Global RS and CS analysis was possible in all of the scans conducted across the two patient groups, CRT and controls. Unfortunately, LS analysis would have required additional scanning to be performed for the required views and so was not possible to include in this analysis. Following iterative learning from educational resources, my PhD supervisor PS and experienced colleagues, I completed analysis of RS and CS in my dataset. Subsequent moderation was completed by PS and a senior cardiologist trained in image analysis. Strain analysis was obtained using the same MRI software package, Circle Cardiovascular Imaging (cmr42, Circle Cardiovascular Imaging Inc, Calgary, Alberta, Canada). Importantly, this software package compares favourably across vendor options and has reassuring reproducibility [358-360]. Specifically, the LV endocardial and epicardial borders were manually contoured at the mid ventricular slice. Strain is then calculated via automated computation of the total slices available for the relevant scan. Contouring for strain analysis was then conducted for all patients (CRT and control cohorts) at

each assessed HR.

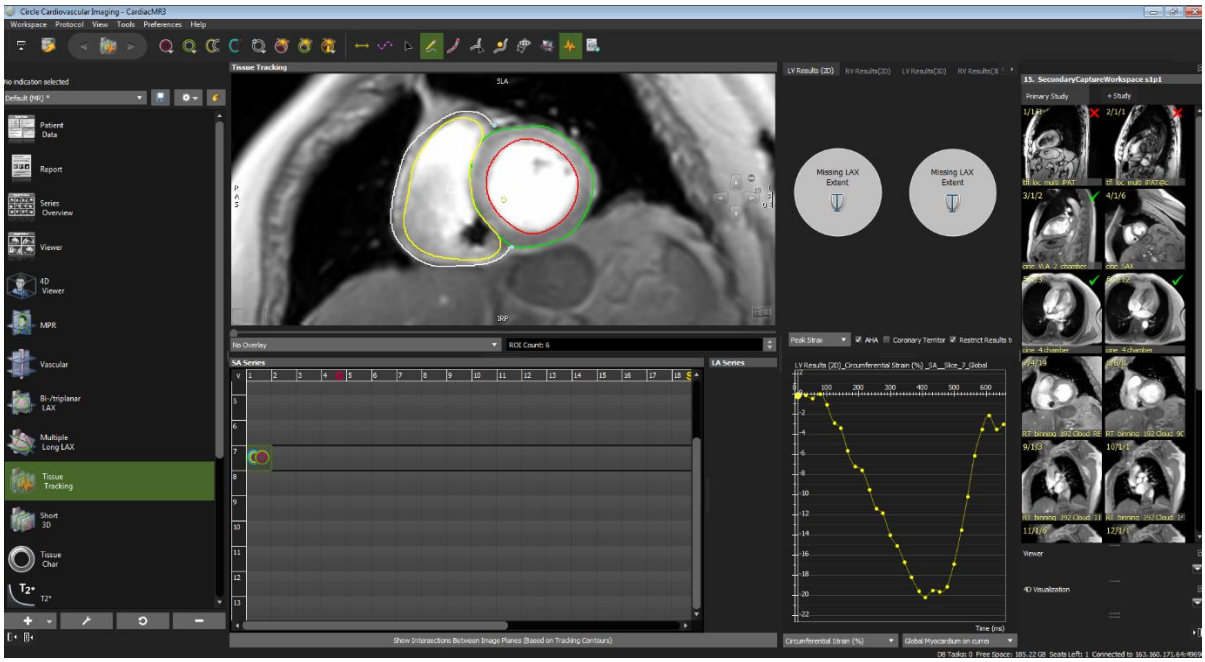



Figure 25 - Conducting strain analysis following CMR. The LV endocardial (red) and (green) epicardial contours are manually defined.

| | CRT | Control | p-value |
|---|---|---|---|
| N (male %) | 17 (76.4%) | 13 (76.9%) | 0.97 |
| Age | 65.1±12.1 | 76.9±6.4 | <0.01 |
| BMI | 31.2±6.5 | 28.8±3.4 | 0.24 |
| Baseline LVEF | 33.7±11.1% | 53.4±8.9% | <0.01 |
| Baseline RS | 13.2±6.6 | 30.4±9.7 | <0.01 |
| Baseline CS | -9.16±3.9 | -17.8±3.8 | <0.01 |

Table 9 - Baseline characteristics for CRT and control patients.

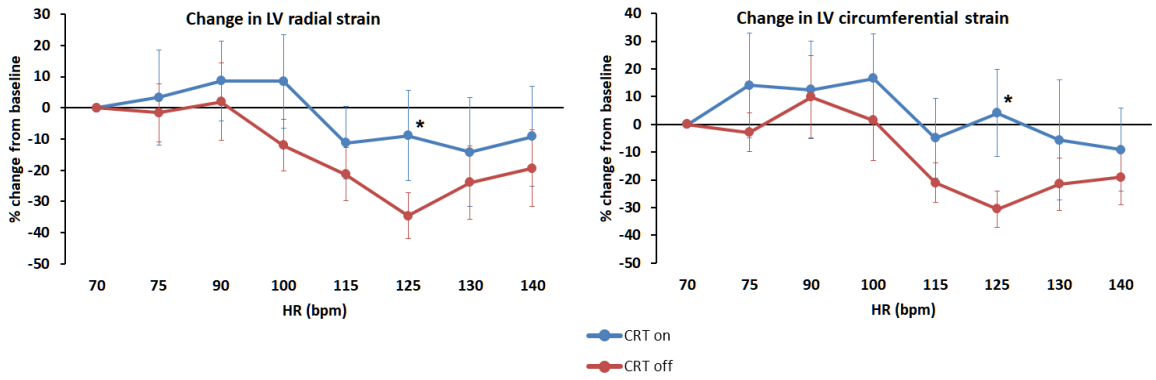



Figure 26 - Changes in RS (left) and CS (right) with increasing HR when comparing CRT on vs off. *p<0.05 between CRT on and off.

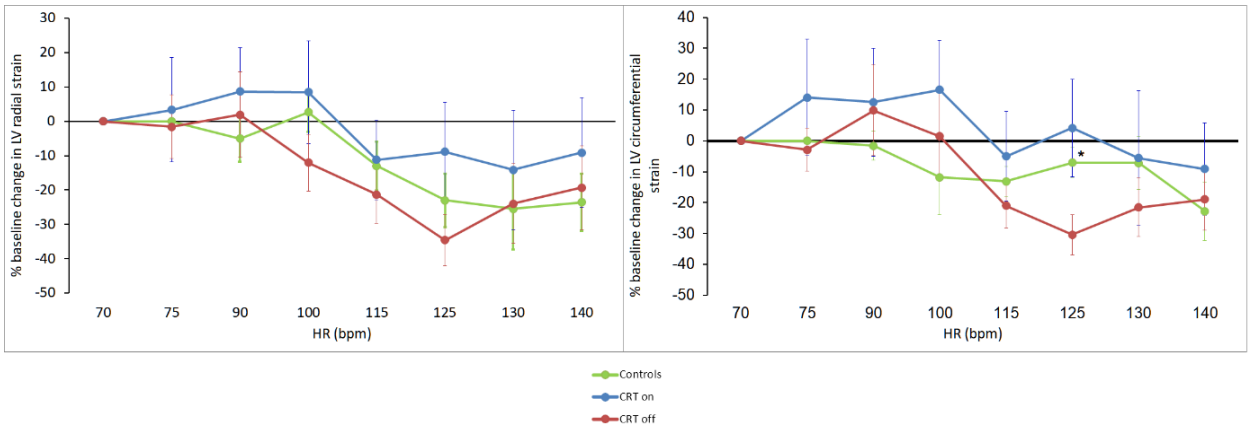



Figure 27 - Changes in RS (left) and CS (right) with increasing HR when comparing controls vs CRT patients. *p<0.05 between Controls and CRT off. Notably there were no significant differences found between Controls and CRT on.

Comparing my control data (table 9) with “normal value” data (figure 27), it is reassuring to see that my values compare favourably in both RS and CS, albeit on the lower range of normal in all cases. The range that is apparent in these measures makes it more valuable to compare change from baseline as conducted earlier.

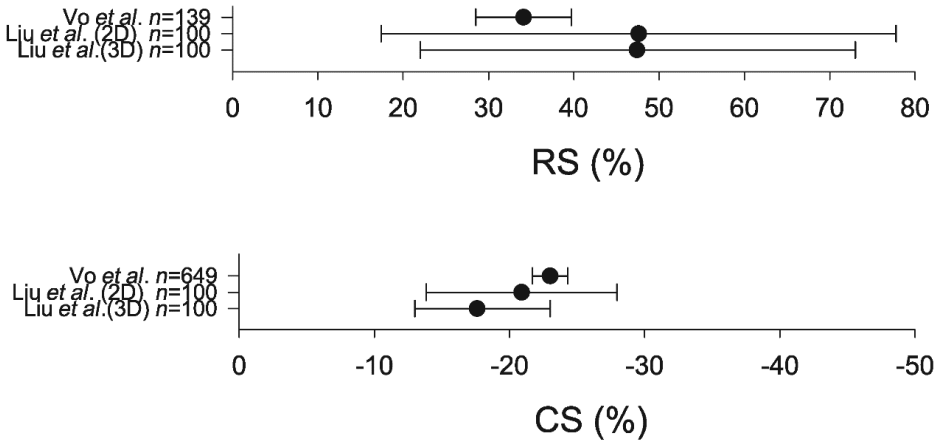



Figure 28 - Comparing global RS and CS values in healthy individuals using CMR feature tracking. Adapted from Amzulescu et al [354].

This is the first dataset to describe the effect of increasing HR on strain in CRT and control participants. The baseline RS and CS is much lower in CRT than in controls. This has been noted in earlier studies using both echocardiography and alternative

CMR methods [361, 362]. It is notable that LV strain (both RS and CS) appears higher when CRT is on compared to off throughout the entire HR sequence, reaching significance at 125 bpm when RS and CS seems to be dipped maximally. It seems unlikely that strain values improve after this point, rather that appears to plateaus after having reached a limit in minimal strain.

There is a relatively clear strain pattern with increasing HR in CRT off for both RS and CS. CRT off seems to generate a small increase in strain that drops quickly after 90 bpm. The trough that is found at 125 bpm in the CRT off cohort is likely to be more of a plateau due to the minimal changes found at 125bpm in any of the other many parameters assessed in this cohort in addition to the minor changes noticed at the neighbouring HR of 115 and 130 bpm. CRT on follows a similar pattern to CRT off whilst being shifted upwards throughout in terms of both RS and CS. This suggests that the addition of BiV pacing improves ventricular shortening radially and circumferentially without altering the behaviour or response at higher HR. This pattern is similar to what was obtained in my dataset for LVEF. Zhang et al [363] showed that patients improve their RS and CS significantly following 3 months from CRT implantation (37.0% and 40.9% respectively). Over a longer period of 1 year, improvements in strain persist suggesting that the superior performance is maintained by ongoing CRT [364]. My findings of an approximate 10% improvement across the HRs between CRT on and off in strain amongst well optimised patients shows that a significant portion of the improvements noted in studies could lie within the acute action of CRT in addition to the longer term beneficial reverse remodelling changes associated with CRT.

It is fascinating to compare the strain results found in CRT patients against controls. Controls have a better response to increased HR in terms of strain decrease than CHF patients with CRT disabled with a significant difference observed at 125 bpm. However cardiac strain is not as responsive in controls at higher HR when compared against CRT on. A similar pattern was obtained in the LV contractility results across the 3 groups suggesting that BiV pacing may be offering additional contractility improvements at higher paced HR in older patients. The concordance across the parameters is reassuring as the strain work is conceptually akin to LV contractility and in this case appears to validate my findings further. There does not seem to be a great difference in cardiac performance in terms of the strain method assessed (RS

or CS). This suggests that either pacing based increases in HR produces a similar contractile pattern regardless of if the patient has CHF or is a control. An alternative explanation as eluded to earlier is that older patients mimic some of the contractile patterns found in CHF patients. My results correlate well with the findings made in early work done by Weidemann et al [365] who studied the effect of HR increase on SV and strain in the porcine heart. They observed a general decrease in baseline strain as HR increased with atrial pacing whereas dobutamine infusion caused a parabola effect over the HR range. It is notable that the use of esmolol, a cardioselective BB caused a dramatic drop off from baseline. This pattern was not noticed in our cohort which suggests that the presence of BB is not likely to be a major contributor to the results observed and rather more defined by pacing and sympathetic activity.

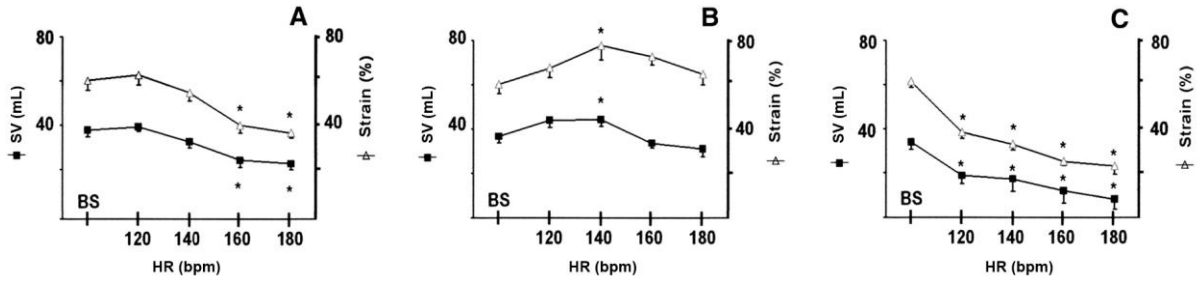



Figure 29 – Similar patterns of strain were obtained in earlier work exploring the effect of HR change via atrial pacing (A), dobutamine infusion (B) and esmolol infusion with subsequent atrial pacing (C) using porcine hearts. Dobutamine is a alpha and beta receptor agonist that reduces vascular resistance unlike Esmolol ( cardioselective BB). Adapted from Weidemann et al [365]. BS – Baseline.

However other studies have failed to find a significant change in strain with increasing HR despite showing a downwards trend [366]. This may be relevant as RV pacing is associated with worsening strain and dyssynchrony generally across the range of measures in animal studies [367, 368]. Thus, my results which show improved cardiac response with CRT on could be explained by the partial normalisation effect of BiV pacing.

I believe my strain results require further investigation, particularly with regards to the effect of ageing and sympathetic activity which are expected to be determinants of strain values. Strain has recently been shown to have value in identifying HFpEF patients with a higher level of certainty than traditional measures such as LVEF

[369]. As RS represents the entire myocardium, it has been associated with concentricity in CHF patients [369]. Concentricity is defined by the LV mass divided by the LVEDV and so is associated with remodelling and general function. Deterioration in the rate of CS is also believed to be predictive of ventricular remodelling, thus healthy CS should partially mitigate ventricular enlargement associated with CHF progression [370]. Strain is being investigated for utility in patients with CRT devices and has been helpful in locating ideal LV lead positioning including areas to avoid lead placement due to presence of scar [88, 371]. As the results of my research suggest improved strain performance in patients with active CRT as well as greater preservation at higher HR, it could be of significant value to explore this further in a larger cohort with exercise included to compare the level of normalisation that occurs against controls when CRT is functioning.

## 8.7 Limitations of strain analysis

The primary limitation is the sample size of the controls and CRT patients. Strain analysis is improving dramatically, however myocardial deformation analysis remains with a non-insignificant variability rate that suggests large sample sizes are needed. It is likely that the presence of the CIED slightly impacted analysis, potentially increasing variability further. It would have been useful to analyse the changes that occur in LS; however this was not felt to be viable in this study due to the majority of scans completed before this measure was considered. There are newer techniques such as hyperelastic warping that could have been utilised in this cohort to rapidly assess strain in a semi-automated fashion, however this was not a technique our team has experienced in conducting which is important in the context of the observer variability rate [362]. Additionally, it is becoming apparent that strain values alter between layers of cardiac tissue. For example, CS appears to reduce when transitioning from endocardial to epicardial layers regardless of the pathology present in the heart [369]. It is therefore not unreasonable to take a global assessment of strain as utilised in this study. Finally, strain is likely to require sex-specific reference values as men generally have higher strain values when compared with women [369, 372]. This is an area of ongoing study and due to the

lack of uptake of this principle thus far, it was felt to be inappropriate to separate this modest cohort sample further.

## 8.8 Investigation of the RV

One the advantages of CMR as an imaging modality is the ability to analyse ventricular dimensions and function of the RV [3]. RV impairment is often caused by LVSD via increased LV end-diastolic pressure raising pulmonary artery pressure and RV afterload or pulmonary disease causing a similar cycle of events starting from the pulmonary circulation [373]. The increased pressure on the right heart in either situation generally leads to RV dilation and tricuspid regurgitation, eventually resulting in RV failure. Furthermore, RV function is recognised as a predictor of mortality and hospitalisation in patients with CHF [374, 375]. In most circumstances RV function is measured using echocardiography, however due to the difficulty in imaging this structure and the inherent assumptions that have to made with the 2D technique usually employed, the variability is markedly high [376]. This has positioned CMR as one of the few methods of measuring RV dimensions accurately, non-invasively and without ionising radiation, making it the gold standard for assessment [3, 377, 378]. Despite this, RV analysis is difficult due to the irregular shape of the ventricle, contraction pattern and the lack of study in this area [379, 380]. Even with CMR, analysis of the RV must be done with care. The geometry is complex and as with the LV, areas of trabeculation in the RV should be considered with a consistent decision made with regards to the inclusion or exclusion of trabeculations which can significantly alter the analysed dimension size [381].

I carried out RV contouring at the same time as LV contouring albeit at a slower pace with more iterative learning and moderation from senior colleagues than required for LV dimension assessment. RV contouring and analysis was done using Circle (cmr42, Circle Cardiovascular Imaging Inc, Calgary, Alberta, Canada).

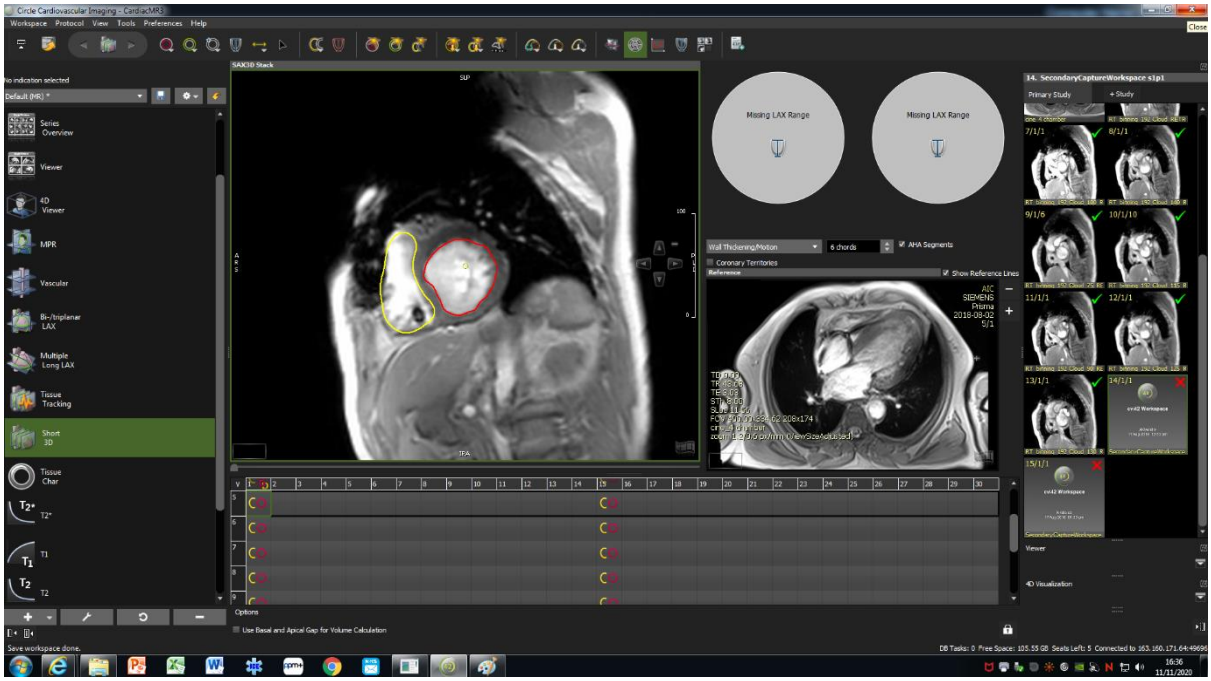


Figure 30 - Ventricular dimension assessment enabling analysis of LV (red) and RV (yellow).

| | CRT | Control | p-value |
|---|---|---|---|
| **N (male %)** | 17 (76.4%) | 13 (76.9%) | 0.97 |
| **Age** | 65.1±12.1 | 76.9±6.4 | <0.01 |
| **BMI** | 31.2±6.5 | 28.8±3.4 | 0.24 |
| **Baseline RVEF** | 28.7±10.9% | 37.8±10.3% | <0.01 |
| **Baseline RV RS** | 19.4±10.6 | 18.6±9.2 | 0.82 |
| **Baseline RV CS** | -10.9±4.7 | -10.9±4.9 | 0.99 |

Table 10 - Baseline characteristics for CRT and control patients.

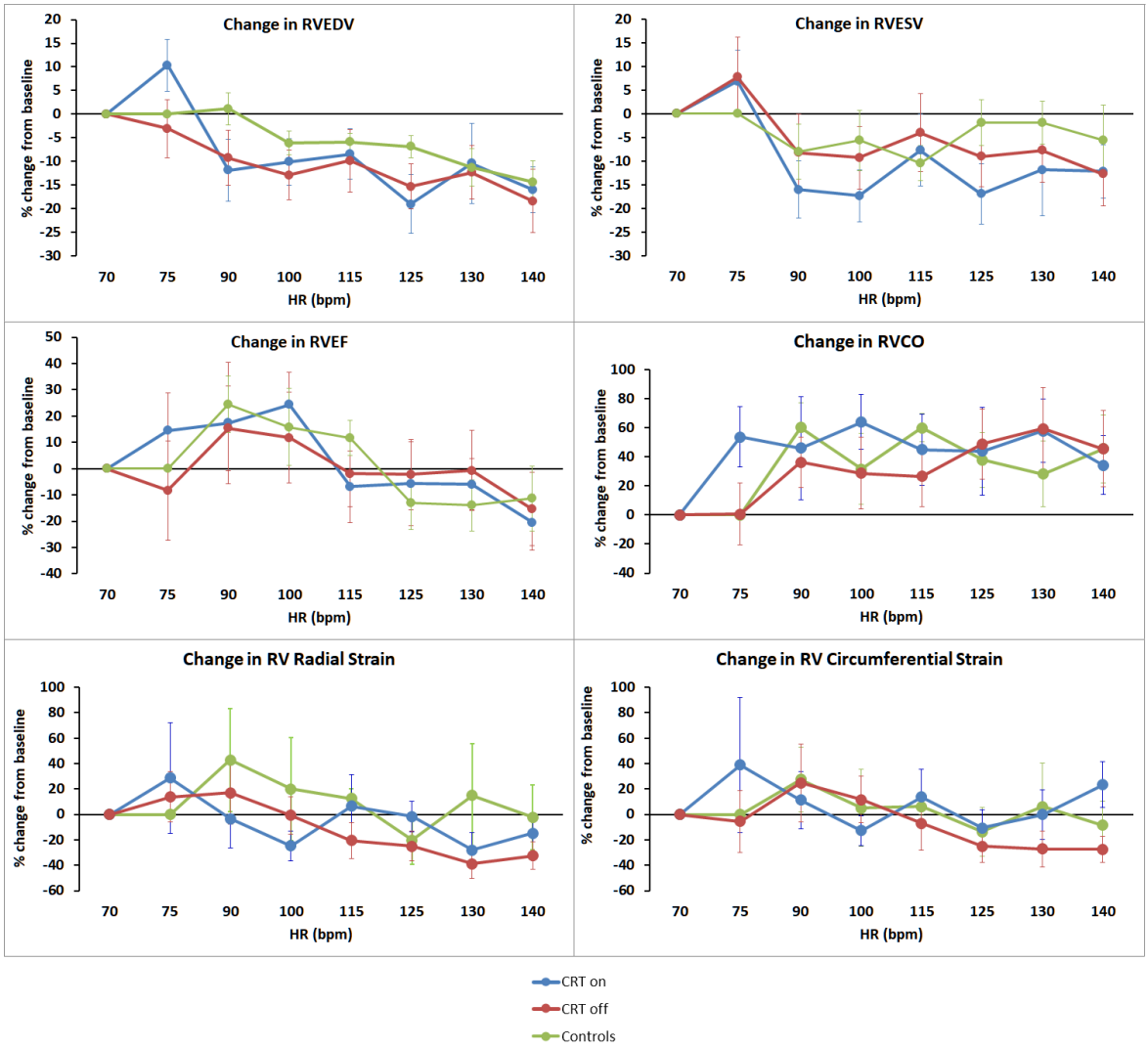



Figure 31 - Comparing cardiac response to increasing HR in controls and CRT patients. Note there was no significant difference detected between the groups.

As there is a high level of overlap in the error bars, it seems most appropriate to discuss the trends noticed in these parameters as opposed to specific regions with respect to the RV. As the HR increases with pacing, RVEDV reduced almost immediately in both CRT on and off whereas controls only start dropping after 90 bpm. The gradient of decline is similar across the groups. As with the LV, it is likely that this is related to reduced ventricular diastolic filling time leading to a steady reduction in RVEDV [382]. The RVESV appears to reduce from baseline to 90 bpm after which increasing HR does not change dimensions significantly. It is interesting to note that BiV pacing gives a greater reduction in RVESV than when CRT is disabled which may explain the improvements noted in RVEF and RVCO in CRT on at the lower HR compared with off and seemingly matched by the controls. This

suggests that the improved functionality of the LV improves RV function. At the higher HR, RVCO is relatively similar in response across the 3 groups. RS and CS appear to show similar patterns in all 3 groups, with a negative trend as HR increases, with a notable delayed peak in the controlled groups at 90 bpm rather than closer to baseline with CHF patients. This is interesting as RV strain assessment is increasingly positioned as a marker of general RV function [383]. With many of the parameters merging at the higher HR, one interpretation would be that much of the benefits of a “normally” contracting LV are at the lower HR with higher HR via pacing going past physiological capacity in this cohort. This notion is further supported by the fact that nearly all the parameters have gone past their physiological peak by 140bpm. The common factor in these 3 cohorts are that all are receiving a paced rhythm to the RV and are of an older age group.

RV analysis is a growing area and is showing increasing utility in prognostication [384]. The error bars found in my research and previous studies investigating the RV with its higher observer variability suggests that these results should be taken with care. It is likely a higher sample size would be needed in order to make a stronger conclusion on RV response to HR increase in CHF patients especially. Importantly, recent work by Erley et al [385] has validated a concern held in the cardiac imaging community, being that different strain imaging techniques should not be used interchangeably to monitor or compare RV strain. Despite this, it is exciting to look into RV function, especially as it was obtained in the same scanning protocol conducted for LV analysis. The finding that BiV pacing seems to improve RV function is not new [386]. Donal et al [337] found that RV peak velocity increased with BiV pacing over RV pacing alone. RV strain has also shown to improve in approximately two thirds of patients who were implanted with a CRT device which was concordant with being a CRT responder, thus suggesting that the improvements in RV are associated with the improvements in LV contractility and LV reverse remodelling [387]. However, a number of studies have not found significant changes in RV function post CRT implantation. Burri et al [388] utilised radionuclide angiography at baseline, acutely after CRT implantation and at 6 months follow up. They found that there was no change in RVEF when switching from RA pacing to CRT pacing acutely, however a significant increase of 1.8% was noted at follow up.

There are likely to be a number of reasons for the variable improvement of RV function post CRT. The methodology of assessment being primarily echocardiography focused makes RV assessment, especially around function difficult due to the complex anatomy and contractility pattern of the RV. Additionally, CRT studies have had a trend to split CHF patients by groups such as responder and non-responder. Whilst there is merit in this approach, the variability of what is defined as a responder (such as LV dimensions or NYHA class change), generally low sample sizes and a lack of complete or supplementary data has made assessing the effect of CRT on RV function difficult to assess objectively. I suspect the LV in terms of CRT which still remains unclear in many respects has taken priority and RV function remains a low secondary interest to conduct appropriately powered studies to investigate this area. However, there are number of reasons why CRT should lead to improvements in RV function in CHF patients with conduction deficit. One mechanism of improvement is the normalisation of mitral regurgitation which in turn would be associated with reduced left atrial pressure and left ventricular end-diastolic pressure [389]. This seems to be likely due to the more coordinated activation (mechanically) of the papillary muscle giving reduced regurgitation and importantly this benefit is noticed immediately post CRT implantation [390]. Le Tourneau et al [391] found that patients with corrected mitral regurgitation and existing RVF had the greatest improvements after surgical correction and concluded that RV function is relatively dependent on LV ventricular remodelling and septal function. The explanation for the majority of patients who improve RV function following CRT is likely related to beneficial LV reverse remodelling. Indeed as RVF is often secondary to LVF via increased pulmonary pressure to mitigate pulmonary oedema or reduced coronary perfusion, it is reasonable to consider improvements in LV function should at least dampen if not partially reverse this sequence [392, 393]. My finding that these improvements do not persist at the higher HR suggest that ageing could be a factor in these cohorts. Ageing is associated with increased myofiber stiffness and at a clinical level is directly proportional to reduced RV function in healthy individuals [394, 395]. Interestingly, conducting myofiber *in vitro* and *in vivo* studies suggest that skeletal muscle fibres undergo cytoskeletal disorganisation with ageing, a phenomenon that leads to myofiber collapse and increased stiffness [396]. Indeed it is likely that the increased stiffness found in aged myofibers is related to the reduced regenerative capacity of these fibres themselves [397]. My research also suggests

that the RV should be treated separately to the LV due to the variance in response across HR when compared to the LV. Bristow et al [244] conducted a fascinating study in 1992 in which ventricular tissue was analysed from 3 patient cohorts: non-failing organ donors, patients with end stage BiV failure and those with isolated RVF secondary to primarily pulmonary hypertension. Total β (both $\beta_1$ and $\beta_2$) receptor density was reduced in both the LV and RV of congestive CHF patients when compared with controls; however the isolated RVF patients only had reduced receptor density in the RV. Binding affinity of the β receptor sites was not majorly different across the different groups. This suggests that there is a surprising level of selectiveness or localisation to the neurohormonal response with the LV and RV responding differently based on the underlying pathology.

These results emphasise the value of further study into the RV mechanistically and in terms of response to CRT. It is known that the LV and RV are significantly different to each other not only in terms of anatomy and contractility pattern but also potentially in terms of inotropic response [398]. My findings particularly around the methodology and safety suggest value in utilising CMR to explore the RV both mechanistically and in response to interventions such as device therapy.

## 8.9 Limitations of RV analysis

The main limitation around the RV assessment in this dataset is the sample size. RV assessment is certainly more complex and is associated with a higher inter and intraobserver variability [399]. This issue is likely exaggerated with regards to RV strain [400]. Technologies such as CMR is expected to limit the variability however, it remains an unclear area especially when complicated by the presence of a CIED. Notably, my research protocol was not focused on RV function which meant the aetiology and method of investigation was not as thorough as would be ideal for a RV study (such as exploring pulmonary circulation). This also meant that RV function was not considered as part of participant eligibility. Future studies that investigate RV in a more focused manner will benefit from larger sample sizes and stricter inclusion and exclusion criteria.

## 8.10 Investigation of Exercise

Based on my findings that HR increases via pacing generally reduces ventricular dimensions amongst both CRT and control patients whilst LV contractility is static when CRT is disabled, I was curious to explore the effect of exercise. Exercise should result in an increase in sympathetic activity that would be expected to shift FFR upwards [365]. This effect is also interesting to consider in the context of the sympathetic overload present in CHF patients. Exercise induced increases in HR have been associated with limited change in LVEDV in either athletes or CHF patients, with a significant improvement in LVEF found in healthy individuals (largely through reduced LVESV) [294]. The aim of my research into exercise was to compare the cardiac changes observed in the context of exercise induced HR increases in participants with CHF and those who are healthy. As this had not been conducted by our team before, this work was positioned as foundational to assess for feasibility.

I was keen to utilise CMR as it is the gold standard for ventricular assessment, however this makes exercise difficult due to the fact participants generally need to be supine and the risk of ferromagnetic materials present in most standard equipment. Additionally, ECG gating issues arise with high variation in HR whilst movement gives rise to artefact generation and difficulty in identifying important ECG signs such as ST elevation due to the MRI magnetohydrodynamic effect. The fact that our patient cohort have CIED heightens the issues particularly around safety and image quality post acquisition. Maximal exercise would not be appropriate based on the patient cohort and equipment requirements. I have had previous success in HR increases via supine leg raising in CHF patients who are undergoing catheterisation [401]. My supervisor, PS suggested the use of resistance bands (figure 31) with leg raising that would both standardise the exercise intervention as well as achieving various intensity of exercises (instead of duration based) through various resistances. Resistance bands placed around the legs are an inexpensive method of sub-maximal methods of HR increase via exercise that mitigates upper body movement and is safe in the MRI environment [402]. We confirmed that it is possible to raise HR relatively quickly with these bands via leg raising with myself as the test.

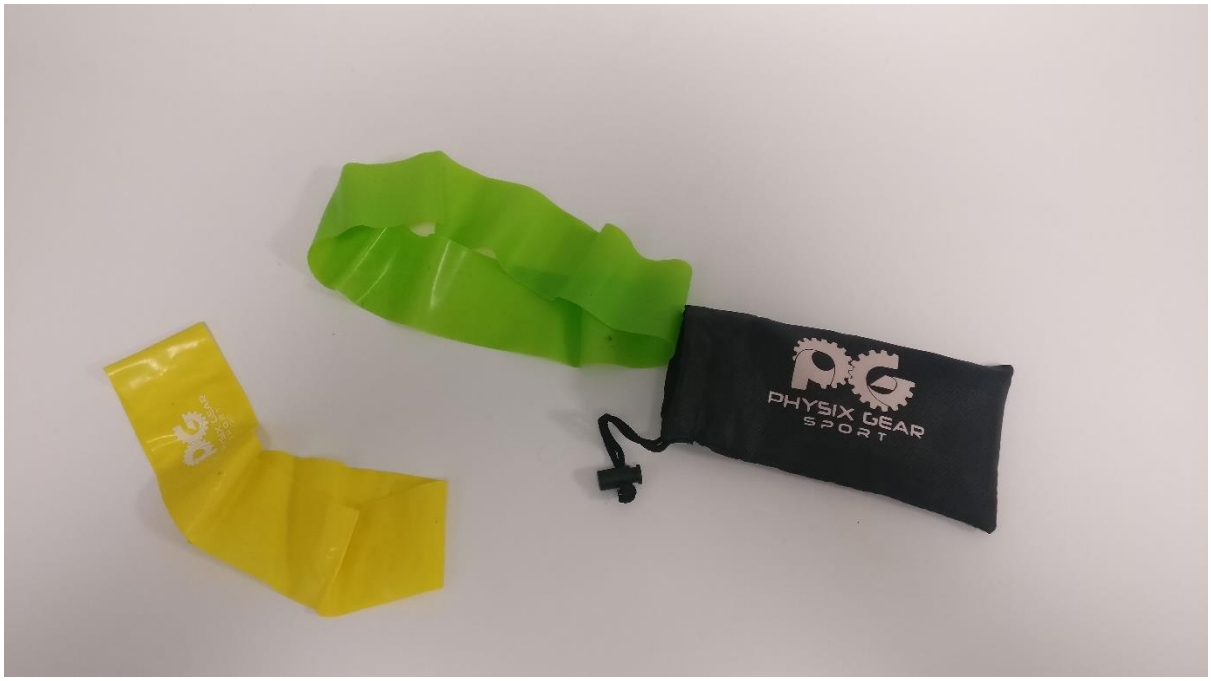



Figure 32 - Resistance bands made of thermoplastic rubber that have various resistances.

Subsequently it was necessary to validate the ability of the bands to increase HR in the MRI setting. I recruited two healthy medical students to assess this, excluding any chronic medical diseases or issues around exercise performance. Once informed consent was obtained and a complete safety check was undertaken as per normal MRI protocol, we conducted the same CMR scanning sequence as utilised in the LV analysis of CRT and control patients (7.2 & 8.2 Methodology). As a team, we discussed scanning CRT patients with exercise. One important consideration to be made is that pacemakers once in the MRI environment lose their ability to reliably sense native electrical activity in the heart. This made the notion of performing exercise in patients with pacemakers performing ventricular pacing whilst in an MRI environment unpalatable following discussion with our scanning team (cardiologist, MRI radiographer and cardiac physiologist). One of the primary concerns is the risk of exercise induced tachycardia giving propensity for R-on-T and possible cardiac arrest [403, 404]. We decided that it would be viable to scan CRT patients who had already been recruited into our series of studies whilst keeping CRT disabled for the exercise period. The required personnel in addition to the entrance of COVID-19 stopped us conducting more than 4 scans in total (table 2). It was reassuring to

obtain high quality scans in both healthy participants and those with CHF and a CRT implanted (figure 33).

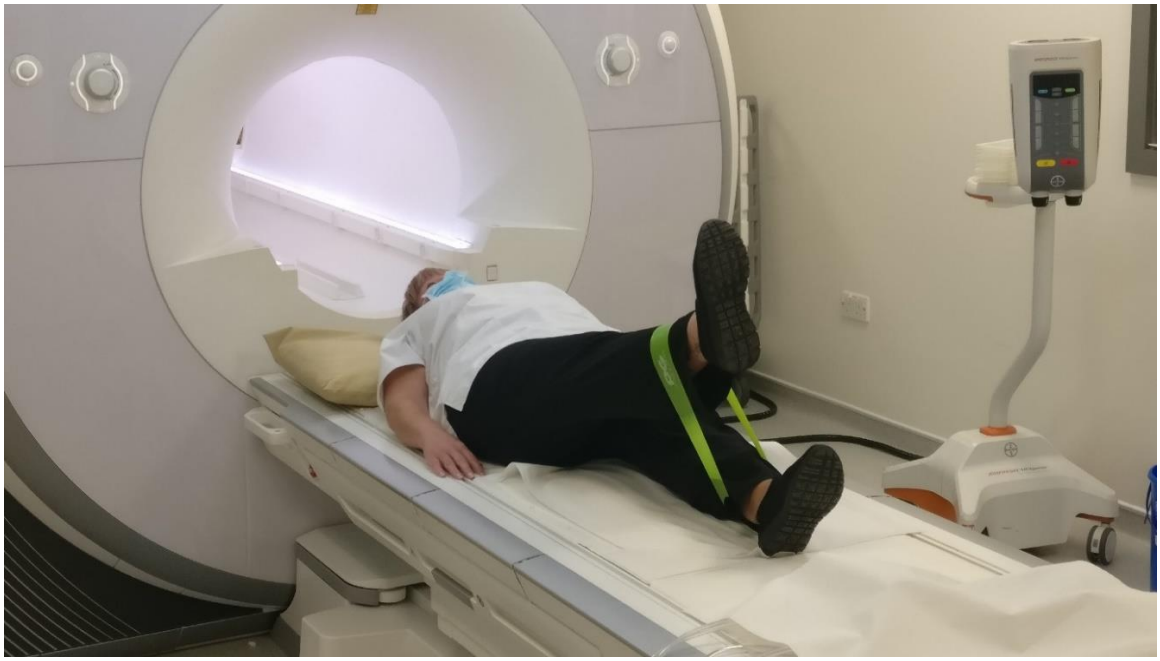


Figure 33 - Example of using the resistance bands in the MRI scanning environment.

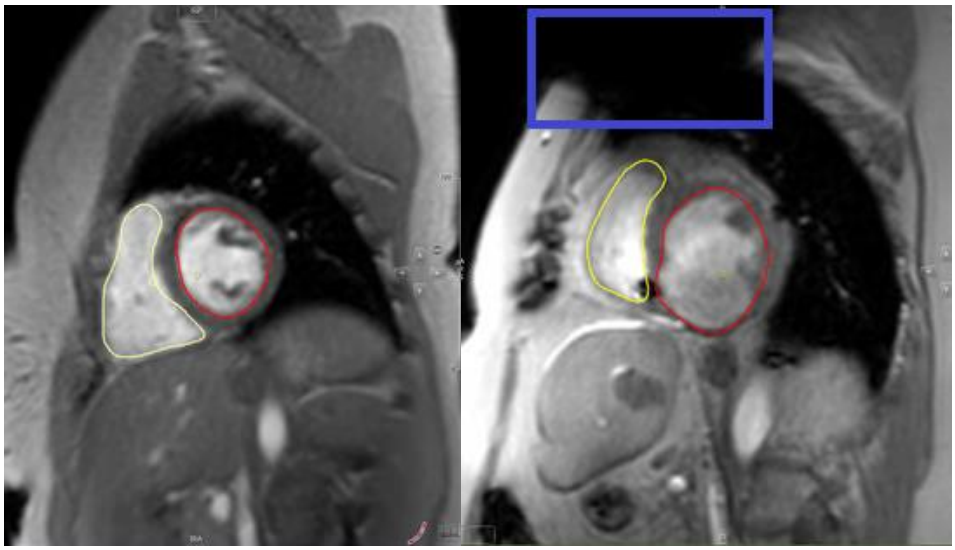


Figure 34 – CMR images using a GRE sequence to produce analysable slices of the heart during light resistance exercises in a healthy (left) and CHF (right) participant. The LV (red) and RV (yellow) have been contoured with an artefact noted (blue) as a result of the CRT device.

| | Healthy | CRT |
|---|---|---|
| **N (% male)** | 2 (50%) | 2 (50%) |
| **Age** | 23.5±0.7 | 68.5±3.5 |
| **Baseline HR** | 69.0±7.1 | 59±8.5 |

Table 11 - Demographic details of the healthy and CRT cohort who underwent exercise CMR. CRT – Cardiac resynchronisation therapy, HR – Heart rate.

| | | Healthy | CRT | p-value |
|---|---|---|---|---|
| **HR** | LR | 33.19% | 24.60% | 0.66 |
| | MR | 47.55% | 40.71% | 0.81 |
| **SBP** | LR | 8.02% | 5.07% | 0.75 |
| | MR | 10.86% | 14.18% | 0.81 |
| **LVEDV** | LR | 2.79% | 0.34% | 0.81 |
| | MR | 4.76% | 3.50% | 0.91 |
| **LVESV** | LR | 12.45% | 2.48% | 0.59 |
| | MR | 21.30% | 20.08% | 0.94 |
| **LVEF** | LR | -6.66% | -6.02% | 0.98 |
| | MR | -5.18% | -50.01% | 0.17 |
| **LVCO** | LR | 19.90% | 20.98% | 0.98 |
| | MR | 33.83% | -31.81% | 0.25 |
| **LV contractility** | LR | 29.24% | 3.59% | 0.59 |
| | MR | 29.00% | -6.09% | 0.45 |
| **RS** | LR | 65.81% | -2.64% | 0.26 |
| | MR | 44.03% | -15.35% | 0.25 |
| **CS** | LR | 42.33% | 6.40% | 0.44 |
| | MR | 39.56% | -4.48% | 0.34 |

Table 12 – Comparing percentage change from rest to exercise in CRT and healthy participants. LR – Low resistance, MR – Moderate resistance.

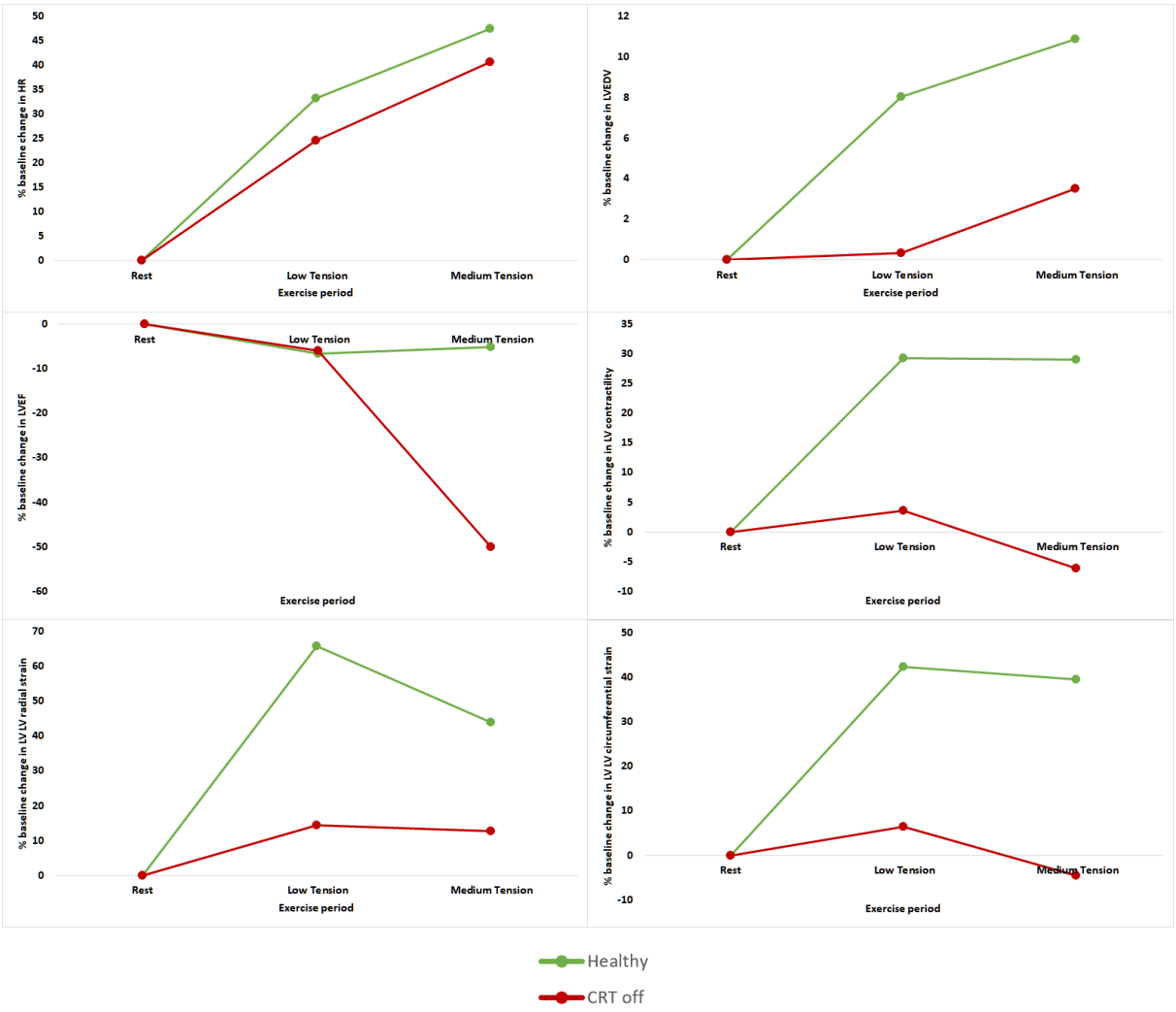



Figure 35 - Comparing % change from baseline in common parameters during various exercise at various low and medium resistance in CRT and healthy participants.

Most notably even with some parameters displaying a large difference at different exercise states between CRT and healthy participants, the p-values were never found to be significant between the two cohorts due to the low sample size. Despite this, it is reassuring to see that our proof-of-concept analysis does suggest that exercise bands are useful alongside leg raising to increase HR, SBP and CO in both healthy and CHF patients. This simple exercise is in line with previous work finding that stretches and repeated movements can produce significant and rapid increases in HR [405]. As HR is increased via exercise, LVEDV is increased in both my healthy and CHF patient cohorts. Exercise with moderate resistance appears to have collapsed LVEF and LVCO in CHF patients which is likely due to the non-beneficial increases in HR with a lower increase observed in healthy individuals. LV

contractility looks to be slightly increased in light exercise in CHF patients before reducing to below baseline which suggests that the higher tension caused performance to go beyond the CHR.  In both the healthy and CHF cohort, the light tension bands were enough for participants to reach the CHR with a more dramatic drop found in CHF patients. RS and CS have both remained relatively static or marginally increased in CHF patients with exercise whereas dramatically increased in healthy individuals.

These results, albeit in the context of a low sample size do suggest that exercise induced HR produces a different cardiac response when compared with pacing induced HR changes. This is likely due to the sympathetic effect of exercise, leading to increases across the board of parameters observed. Our results in the healthy cohort agree with previous work into exercise haemodynamics in non-HF patients in which modest improvements in CO and EF are observed [262, 297, 308]. O'Driscoll et al [406] showed that isometric squats in non-HF patients increased CO, LVEF, SV, RS and CS. Our findings are similar in terms of producing an upward and right shift in strain with increasing HR via exercise as found with an infusion of dobutamine [365]. The blunted response to exercise in CHF patients has been noted in previous studies and is likely related to the neurohormonal dysregulation present in this cohort [407, 408]. We look forward to future studies that investigate the effect of exercise in CHF patients with CRT devices via CMR. This is expected to be an area of significant interest. Software and programming around CRT is increasingly sophisticated with tailored programming showing improvements to cardiac function [272]. Hopefully solutions around higher pacing rates whilst exercising can be navigated in CMR through safety assessments. This would enable greater appreciation of pacing on cardiac mechanics during activity which may be one of the key areas in improving functional capacity post CRT implantation.

## 8.11 Limitations of exercise analysis

A sample size of 4 means that meaningful analysis of the findings is not possible. Increasing the sample size was not possible here due to issues with patient enrolment and the COVID-19 pandemic. However as a proof of concept, the findings are promising. It was also not possible to perform exercise in patients whilst

ventricular pacing was active due to the concerns of serious arrhythmia formation. This is a significant limitation with respect to CMR that requires further thorough safety focused research studies. If resolved it would allow the assessment of the change in CO during different levels of exercise and HR giving greater insight into mechanical response of the heart.

## 8.12 Observer variability of analysed parameters

One of the strengths of CMR is the comparatively low inter and intraobserver variation in measurements. Inter-observer variation in CMR for ventricular dimensions and general function is around 4% with our specialist unit at Leeds benchmarked as <5% [409]. RV measurements are known to be less consistent due to the more conical and irregular shape in addition to the complex contraction pattern [410]. Interobserver variability is noted to be approximately 9% for RV based dimension analysis with our unit believed to have a variability rate of 10% [399, 411]. However, many of the techniques conducted in this study are novel or have received limited study. Indeed, my research is one of the few to have investigated RV in CRT devices and is unique in exploring HR augmentation via pacing with CMR imaging. Whilst my training in MRI analysis was organised in a teaching environment with early educational training and moderation by experts, it remains valuable to explore inter and intraobserver variation in my dataset.

Interobserver variability was conducted by a senior cardiology registrar and academic trained in CMR analysis. A scan list of random anonymised participants of the study was generated in order for 20% of the patients scanned to be moderated in terms of LV and RV dimensions in addition to LV and RV strain (RS & CS). Intraobserver variability involved myself re-contouring 20% of patients scanned. This was randomly selected and conducted in a blinded fashion >3 months after the original scan and analysis took place. Statistical analysis was conducted using GraphPad Prism version 7.04 for Windows (GraphPad Software, San Diego CA, USA). Bland-Altman analysis was utilised with results presented as % difference to aid comparison between inter and intraobserver variability. 95% upper and lower confidence intervals are indicated by blue dashed lines with the bias line shown as a red dashed line with label.

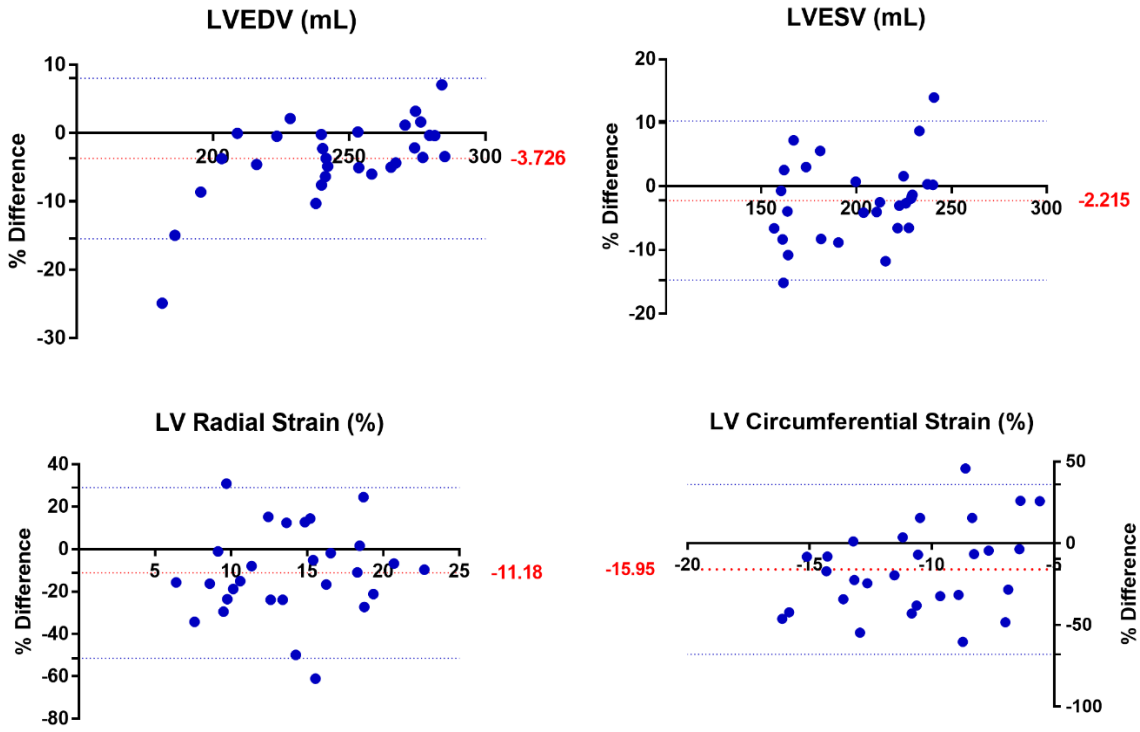



Figure 36 - Bland-Altman chart of interobserver variability with regards to LV assessment of dimensions and strain.

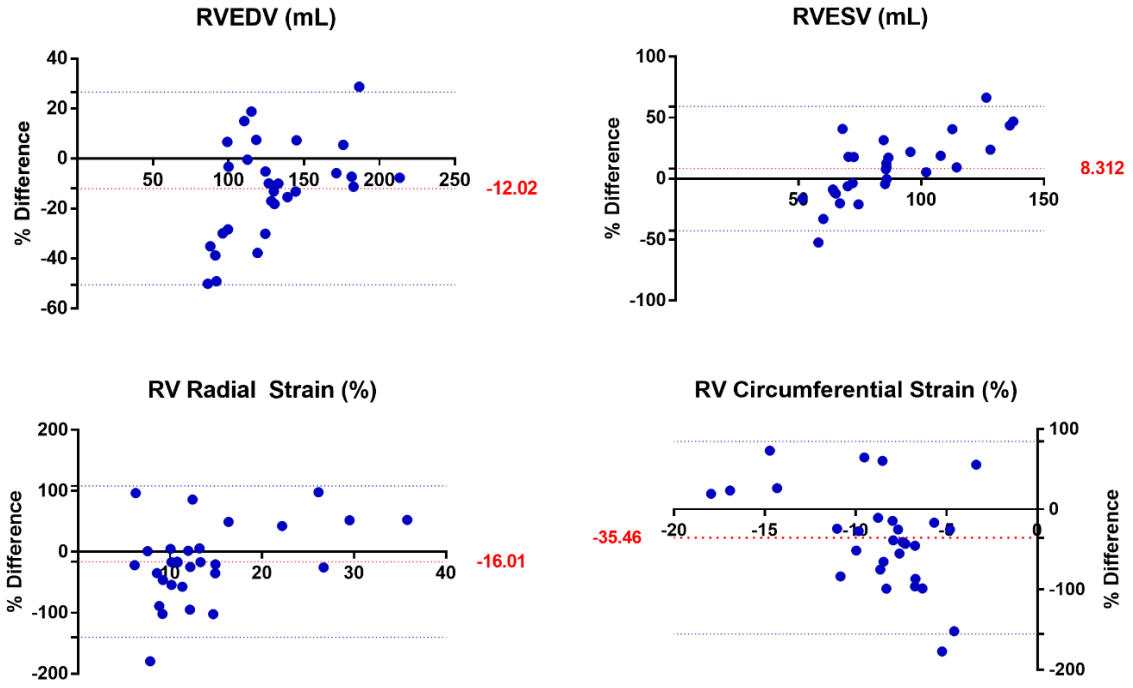



Figure 37 - Bland-Altman chart of interobserver variability with regards to RV assessment of dimensions and strain.

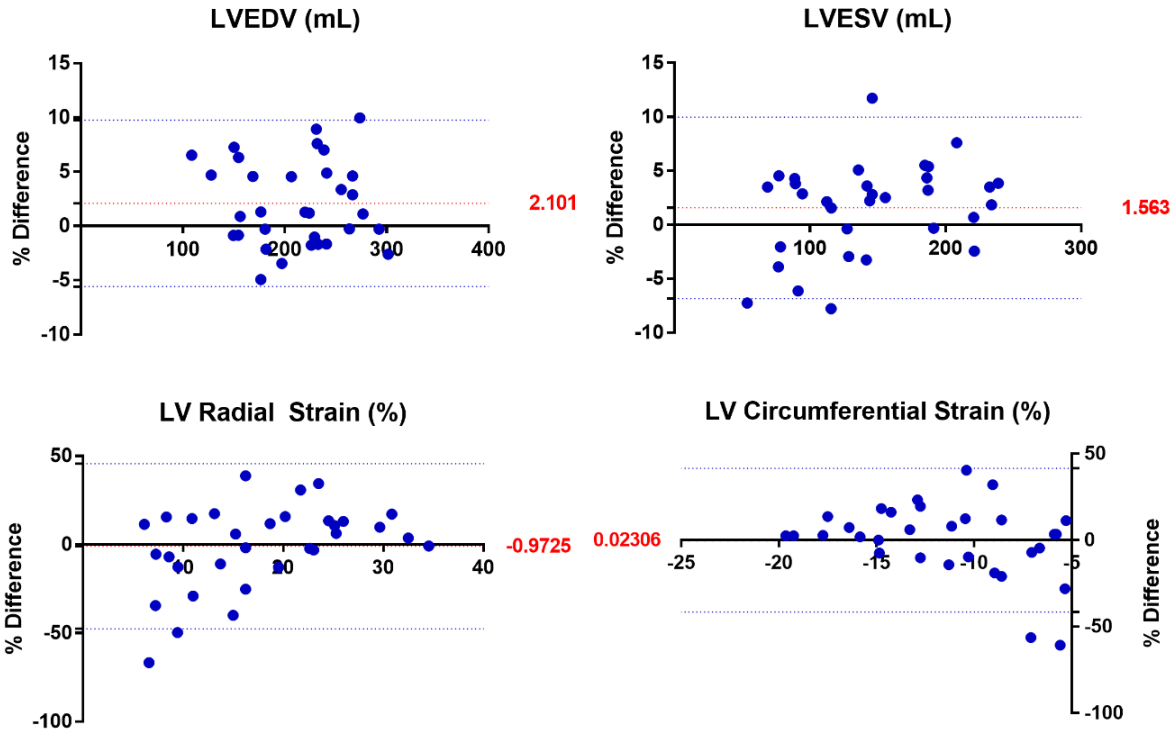



Figure 38 - Bland-Altman chart of intraobserver variability with regards to LV assessment of dimensions and strain.

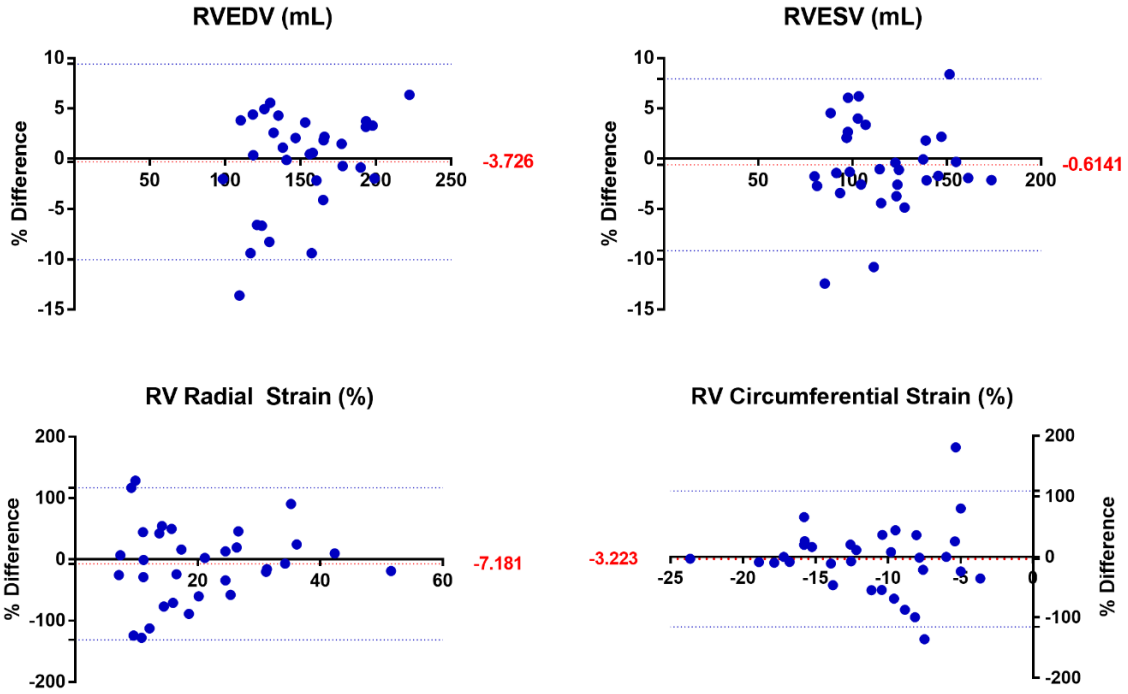



Figure 39 - Bland-Altman chart of intraobserver variability with regards to RV assessment of dimensions and strain.

Bland-Altman analysis traditionally compares two sets of measurements and generally should be assessed informally with a focus on the overall picture as well as the context of the measurements. Overall there does not seem to be much inter-observer difference with respect to LV dimension assessment. This is important as it is the cornerstone of my research despite the complicating factor of the CIED. Specifically, the level of variation identified is in keeping with the 5% that is followed for LV dimension assessment. The interobserver variation strain was much higher at 11% and 16% for LV RS and CS respectively. When compared with the standard 5-16% variability for LV strain analysis with feature tracking, my values are quite reasonable [412-414].The intraobserver variability for LV dimensions and strain are also reassuring and are likely a reflection of the training received and number of contours done (in excess of 10000) as part of this study. The interobserver variability for RV dimensions is quite similar to the published standards which is encouraging for further work in this area. However, RV strain displayed more variation in my dataset than previously published [400, 415]. This is presumably due to the inclusion of a CIED and the HR augmentation. The combination of the higher areas of artefact due to the CIED with varying and specifically higher HR could be causing issues on the feature tracking software. The HR changes could also have been occasionally problematic for the ECG triggering required for image acquisition, however if this was a major issue it would have been expected in other parameters such as simple LV dimension assessment which does not seem to be the case. Additionally, it is possible that the software vendor used (cmr42, Circle Cardiovascular Imaging Inc, Calgary, Alberta, Canada) may have reduced accuracy on the automated feature tracking mode utilised. This is not borne out in the literature and this potential issue was mitigated by routine procedure with FT by reviewing the cine slice by slice and frame by frame to ensure appropriate tracking throughout [416]. It is reassuring to see that the intraobserver variability for both RV dimensions and strain was tighter and within reasonable limits.

One observation that can be made from the Bland-Altman plots with respect to strain analysis is that there appears much more variation at the lower strain values for both inter and intraobserver assessment. This pattern has a relatively convincing funnel

shape in almost all of the strain plots. There are a few possible explanations for this finding. It could be that in periods of ECG mis-triggering in the context of HR augmentation or CIED related artefact generation, there is subsequent reduced strain change. This hypothesis is countered by the fact that the funnel pattern is not present in the LV or RV dimension plots which, if mis-triggering or artefact generation was the issue, would be expected to be similarly present. A second possible explanation could be that the vendor specific FT software is not as capable of consistent analysis at lower strain values present in disease patients such as CHF. CHF patients likely present more complexity (such as segmental variation) and higher intra and interobserver variability values than found in healthy individuals. A third explanation is that CMR FT whilst highly convenient and generally robust has been shown to have greater variation in obtaining strain values than other techniques such as CMR tagging or even echocardiography [354]. However, it is one of the newer techniques and is likely to continue to improve due to the sheer flexibility it offers and few associated issues around acquisition when compared with nearly all other techniques currently available. Indeed, my study findings despite the complicating factors fared reasonably well overall, particularly with regards to LV assessment. It is known that training reduces observer variability as does experience [414, 417]. A fourth possible explanation is that having the y-axis as % difference could give the appearance of a larger distance at areas of high readings. I repeated the analysis in all studied parameters for both interobserver and intraobserver measures using another standard variable, absolute difference. This did not dramatically alter the funnel appearance found in the strain parameters (figure 39) nor made any obvious changes to the other measures. Changing the Y-axis to absolute difference did not obviously change the results obtained. This suggests that the variance observed is more related to the MRI analysis process.

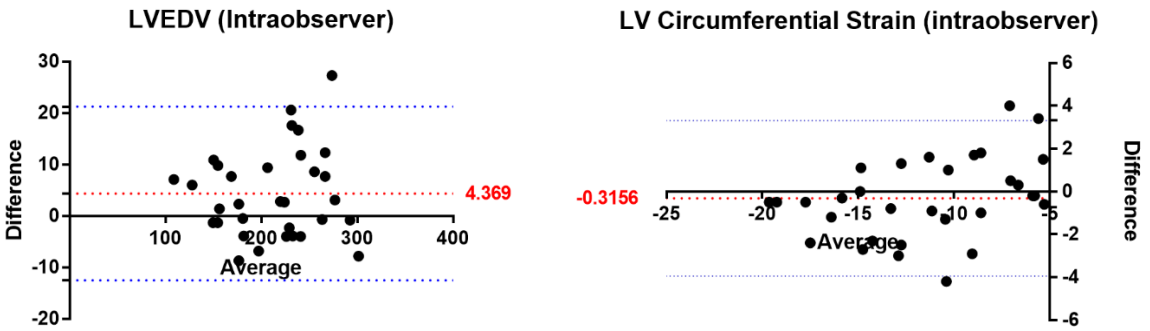



Figure 40 - Bland-Altman chart of intraobserver variability using absolute difference instead of % difference as utilised earlier.

This change did not change the appearance significantly. The confidence intervals (blue dashed line) and percentage bias (red dashed line with red text) are presented for each parameter.

## 8.13 Conclusions

CHF patients appear to have a dampened cardiac response to increased HR when compared with controls. Active CRT is associated with a partial normalisation effect in the majority of parameters assessed in the context of increasing HR however the changes were non-significant in this cohort. It is reassuring that strain analysis complimented the FFR response observed. Assessment of the RV in the CRT and control cohorts suggests that LV pacing is providing a beneficial effect to the RV that may go beyond what is found in older controls. Our pilot data from healthy and CRT patients gives confidence to the use of leg raising with resistance elastic bands as a method of increasing HR via exercise in the MRI setting. Variability analysis investigating interobserver and intraobserver variance shows that this body of research around the LV and RV largely falls in line with accepted variation associated with MRI analysis despite the presence of a CIED and HR augmentation. Further work is required to expand these findings through larger patient cohorts and explore the myocardial origins through non-invasive imaging and cellular studies.

# Chapter 9 - MRS in a porcine phantom with implanted CRT leads

## 9.1 Introduction

$^{31}$P-MRS analysis is able to investigate cardiac metabolism and has found CHF patients to have reduced energy capacity in cardiac and skeletal muscle [179, 187, 204]. For the purpose of assessing the effect of varying HR on cardiac energetics, $^{31}$P-MRS is the best choice as it enables evaluation of metabolites such as ATP and PCr, thus obtaining the PCr/ATP. My findings thus far have shown that CRT provides improvements to cardiac performance in response to HR augmentation. Interestingly, this is in the context of CRT reducing metabolic burden to the heart through improved efficiency and energy reserve [286]. I wanted to explore the viability of $^{31}$P-MRS in patients with a CRT implanted as it would be fascinating to observe the variation in cardiac energetics in terms of active and disabled CRT and HR augmentation. The first step to achieve this is a phantom model for $^{31}$P-MRS to ensure that analysis is possible. Specifically as MRS has not yet been performed in CHF patients with implanted CRT devices, it is important to check that MRS would be viable in assessing energetics without significant interference from the CRT device or leads. If the interference or artefact generation is unduly high or unable to be mitigated, it could mean that MRS would not be viable in patients (due to lack of appropriate ventricular signal capture). Unfortunately there are no known phantom models for CRT and MRS.

A phantom model in this case needed to have a few characteristics. We required a heart in a medium similar to blood, with a CRT device and leads placed in anatomically correct areas of the heart. All the components for the phantom model should be safe for MRI scanning. The container for the model should enable the relatively accurate positioning of the device in the context of the heart (importantly appreciating the space between the CIED to the patient's heart). A porcine heart seems most appropriate cardiac model for the purpose of the phantom. Porcine hearts are frequently chosen as the cardiac model of choice due to their anatomical and physiological similarities to humans [418-421]. Porcine hearts are also relatively accessible and affordable.

## 9.2 MRS methodology

I was fortunate at my institute to not only have relevant expertise but also key components that were made available for this work. Specifically, we received a “Not for Human Use” version of the actual CIED that are used in clinical medicine from Medtronic, who are a global leader in pacemaker design and manufacture. In fact I was given the same device and leads implanted in the CRT cohort of this study (table 13).

| Component name | Description |
|---|---|
| **DTMB2QQ Amplia MRI Quad CRT-D SureScan** | 3.0T MRI-Conditional CRT-D |
| **6947M Sprint Quattro Secure** | RV lead |
| **4298 Attain Performa** | LV lead |
| **4074 CapSure Sense** | RA lead |

Table 13 - CIED components (Medtronic) that were utilised for creating the CRT phantom model.

After making contact with a large local abattoir (John Penny & Sons, Leeds, UK, I was fortunate to collect fresh pigs’ hearts (<5 minutes from extraction) directly from the abattoir for this project. Furthermore, I am extremely grateful to receive guidance and assistance from Dr Nadira Yuldasheva who is an expert in animal anatomy and was able to aid in the preparation steps. Additionally, my supervisor JS was a major source of knowledge for creating the phantom model. The majority of the protocol follows standard procedure for animal heart fixation [422]. I conducted the following protocol for producing the porcine CRT phantom model at Light Laboratories, University of Leeds, UK:

- Obtained porcine heart from abattoir.
- Stored heart in a professional grade thermal insulated Thermo future box® packed with a mixture of ice and Thermafreeze® (cooling crystals) for transportation to the University.

- Irrigated the heart with large volumes of distilled water at room temperature to maximise perfusion, remove thrombi and reduce thrombus formation.
- Dissected vasculature to 2-3 cm.
- Placed heart into autoclaved container (bucket) with 4% paraformaldehyde (PFA) solution in PBS for 1 minute. The container was surrounded with ice and distilled water.
- Washed heart with 1% PFA and stored for fixation over 5 days.
- Washed heart with PBS X3.
- CRT device is suspended within phantom container (device approximately 8cm above the heart). The heart is placed on the bottom of the container with the RA, LV and RV leads implanted.
- Poured 2.5% agarose (Iberose high specification agarose for electrophoresis) in 0.9% saline and kept warm at ~30˚.
- Stored for cooling and setting for a minimum of 4 hours.

This methodology whilst relatively standard, had two obvious differences to most other similar studies. We initially opted for 2.5% agarose instead of 1 or 1.5 due to the human sized heart and CRT device that should be kept stationary in multiple positions. Furthermore, this study required a significant volume of agarose in 0.9 saline to be made up, approximately 6L. This is orders of magnitude larger than most laboratory work and I was fortunate to be allocated separate laboratory space to conduct this protocol in a timely manner. Once the agarose process was started, timing was critical to ensure a smooth pouring of large volumes of agarose. This was important for three reasons. First, care had to be taken to pour in a smooth continuous fashion to minimise bubble formation which would cause decreased image quality after MRI scanning. Secondly, timing was critical to ensure that the agarose was poured with minimal delays so that 6L volume solidified as a single column (rather than layered). Thirdly, care was needed during the agarose stage to ensure that the CRT device and leads remained in the anatomically accurate positions.

All MRS was conducted using the same 3.0T Siemens Prisma scanner housed at the advanced imaging centre at Leeds General Infirmary as described in earlier

chapters. Imaging was conducted with myself, an MRI radiographer, medical physicist and my supervisor JS present. A standard $^{31}P$ transmit/receive surface coil as used for clinical studies was utilised. Positioning of the phantom was confirmed with a survey scan. The RF field and receiver sensitivities were analysed using the departmental purpose-built cuboidal phantom housing a $2cm^3$ cube of $KH_2PO_4$(aq) surrounded by 500mL of saline. Shimming was conducted with Siemens standard software. The porcine phantom model was placed horizontally with the coil placed over it at the isocentre of the magnet [423]. $^{31}P$-MRSI with 3D chemical shift imaging (CSI) sequences were employed with voxels placed in the mid-ventricular septum. This generated a series 32x32 CSI grid at the mid-ventricular slice. Analysis was conducted using tailored (inhouse) software utilising Matlab version R2012a (MathWorks, Natick, Massachusetts) with the kind assistance of David Broadbent, a medical physicist at the Advanced Imaging Centre. This approach allowed the assessment of voxels around areas of interest across the myocardium.

***Phantom model attempt 1***

The first attempt of the porcine model produced appropriate survey scans of the phantom model which confirmed anatomically correct positioning of the CRT device and leads in relation to the porcine heart. However, $^{31}P$-MRS failed to obtain the expected discrete spectra required for analysis. From reviewing the scan, it was believed that the higher contractions of agarose was interfering in the signal acquisition. After discussing the methodology with my supervisor JS, we decided to reattempt the phantom model whilst reducing the agarose concentration closer to more standard levels at 1%.

Figure 41 - First attempt at phantom model with 2.5% agarose.

***Phantom model attempt 2***

The same protocol for creating the phantom model was conducted as previously. However, this time the agarose concentration was reduced to 1% to balance the need for physiological similarity and potential signal interference with stability for the positioning of the CIED and heart.

Unfortunately as with attempt 1, the MRS spectra signal was neither discrete or of an adequate quality to obtain reliable data. However, it was reassuring to find that 1% agarose was strong enough to hold the CIED and porcine heart in place.

***Phantom model attempt 3***

The same protocol as conducted with attempt 2 was followed, but this time we opted to use gadolinium solution (Omniscan™0.5mmol/ml) to enhance image acquisition further. Gadolinium shortens relaxation time at both T1 and T2 giving a hyperintense and hypointense signal respectively. Specifically, the tissue undergoes interstitial and intravascular enhancement [424, 425]. A concentration of 0.5 millimolars of gadolinium was added to the 1% agarose in 0.9% saline solution. I am pleased to

report that this attempt was successful in obtaining discrete and high-quality spectra following MRS-P in the phantom model. This was a breakthrough moment for the team. However, on analysis there was poor delineation of the porcine heart and contained surface (giving poor appreciation of the cardiac borders) as the heart was resting directly on the container.

***Phantom model attempt 4***

My supervisor, JS recommended that we repeat the process but this time, an agarose layer could be created at the bottom of the container to keep the glass container separate from the porcine heart. Attempt 4 was conducted with the same methodology as attempt 3. An additional step was made just prior to the agarose step at which point a 3 cm agarose layer was set onto the base of the phantom container. After partial setting (approximately 30 minutes), the porcine heart was laid down on the agarose layer with the remainder of the agarose used to fill the container as per protocol. This attempt was a complete success in terms of stability, image acquisition and the obtained spectra. A full analysis was completed as shown below.

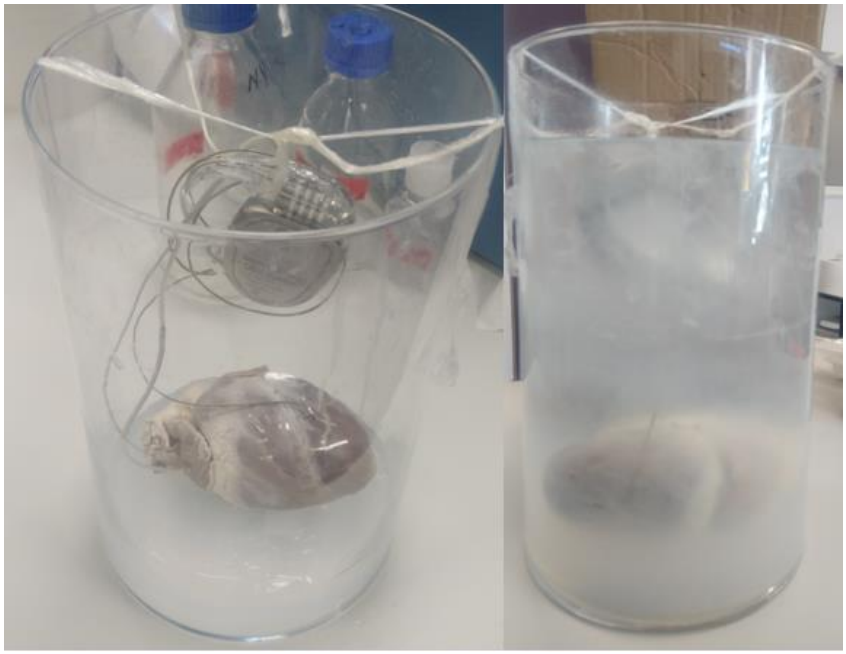


Figure 42 - Phantom model attempt 4 in which the porcine heart is placed on top of the agarose layer with leads inserted and CRT device suspended above (left).

The container is then filled slowly with the agarose solution and left to set, note the reduced turbidity of this model (right).

Figure 43 - Porcine phantom model being broken down post scanning.


Figure 44 - The phantom model (red arrow) placed in the clinical 3.0T scanner a standard Siemens flexible body coil for MRI T1 and T2 sequences.


Figure 45 - Porcine phantom model being scanned in the 3.0T Siemens Prisma MRI scanner.

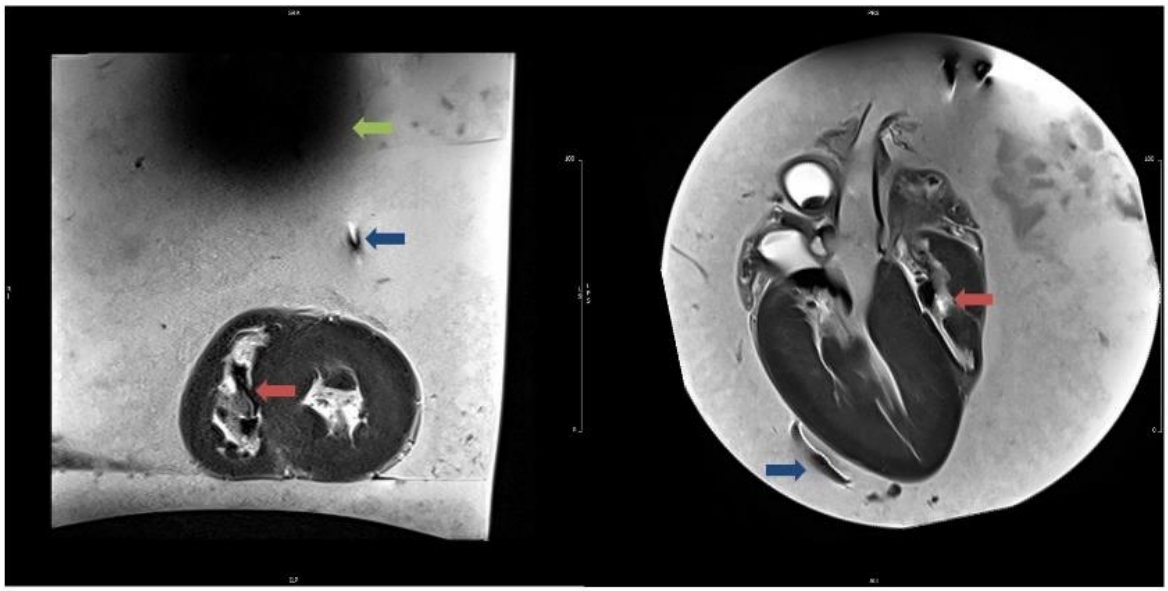



Figure 46 - T2 weighted turbo spin echo short axis (left) and long axis (right) view of phantom model. The LV lead (blue arrow) and RV lead (red arrow) artefacts are visible. Notably, there is a large area of void artefact caused by the pacemaker generator (green arrow).

Figure 47 - Interrogating porcine phantom with CRT active using a standard programmer.

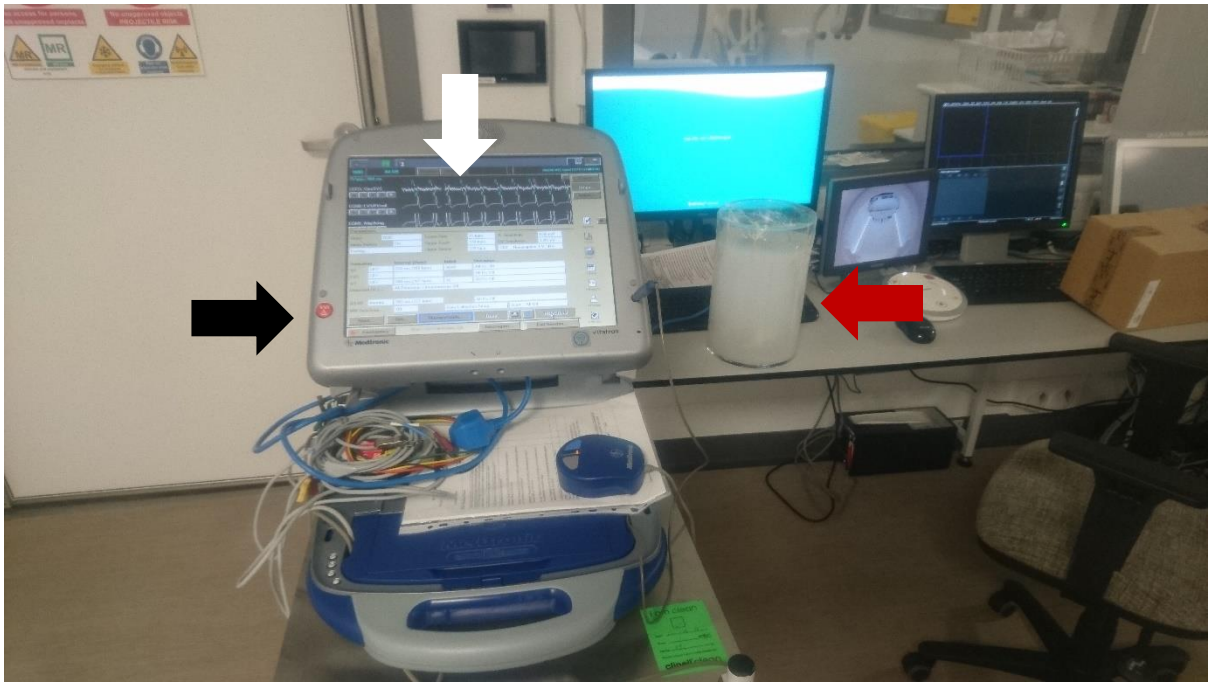


Figure 48 - Successful linking and interrogation of the CRT embedded into porcine phantom model (red arrow) using a standard programmer (black arrow). The results of the live readings (white arrow) and interrogation were within expected ranges for this device.

## 9.3 Results

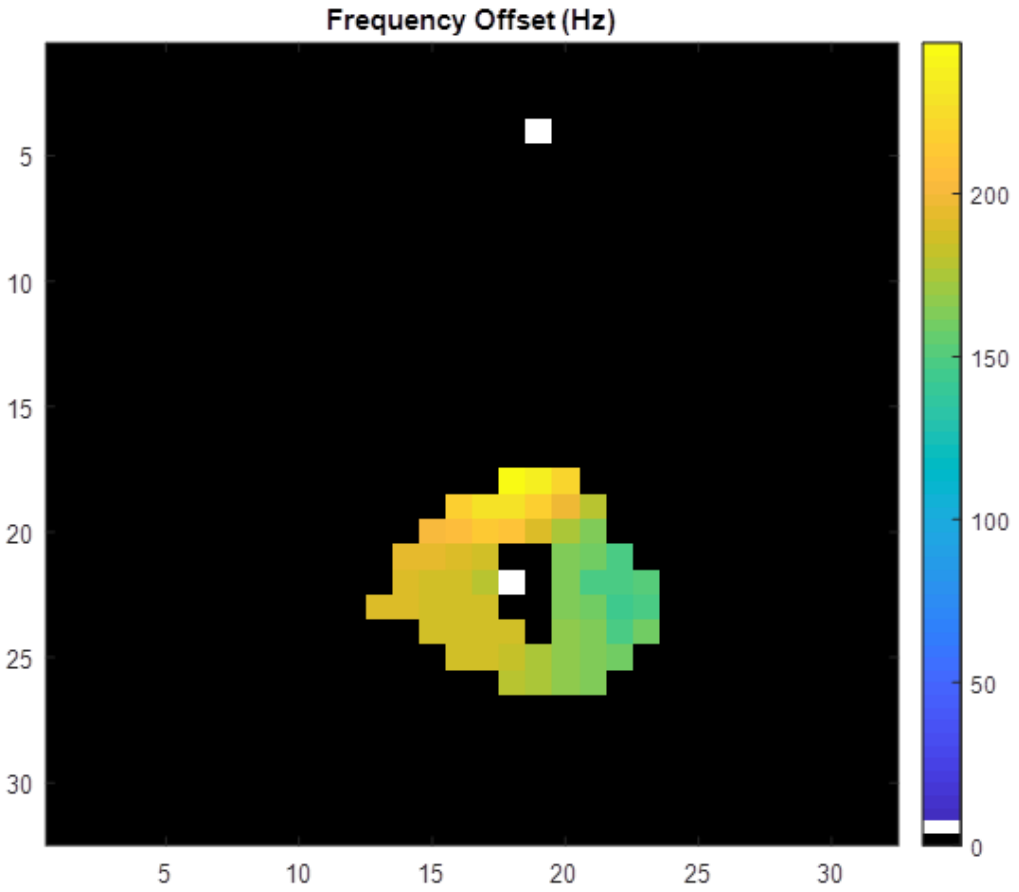



Figure 49 - CSI of frequency offset variance of porcine myocardium with CRT device (top white voxel) and implanted lead (bottom white voxel).

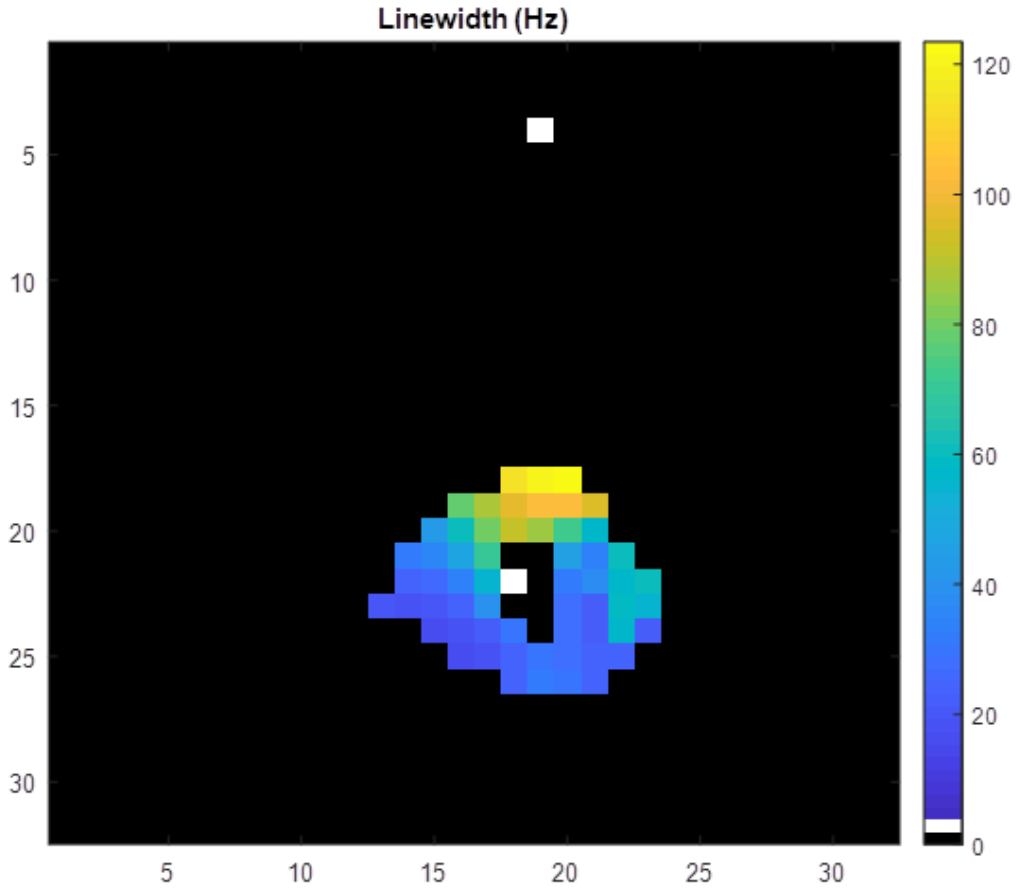



Figure 50 – CSI of linewidth variance of porcine myocardium with CRT device (top white voxel) and implanted lead (bottom white voxel)

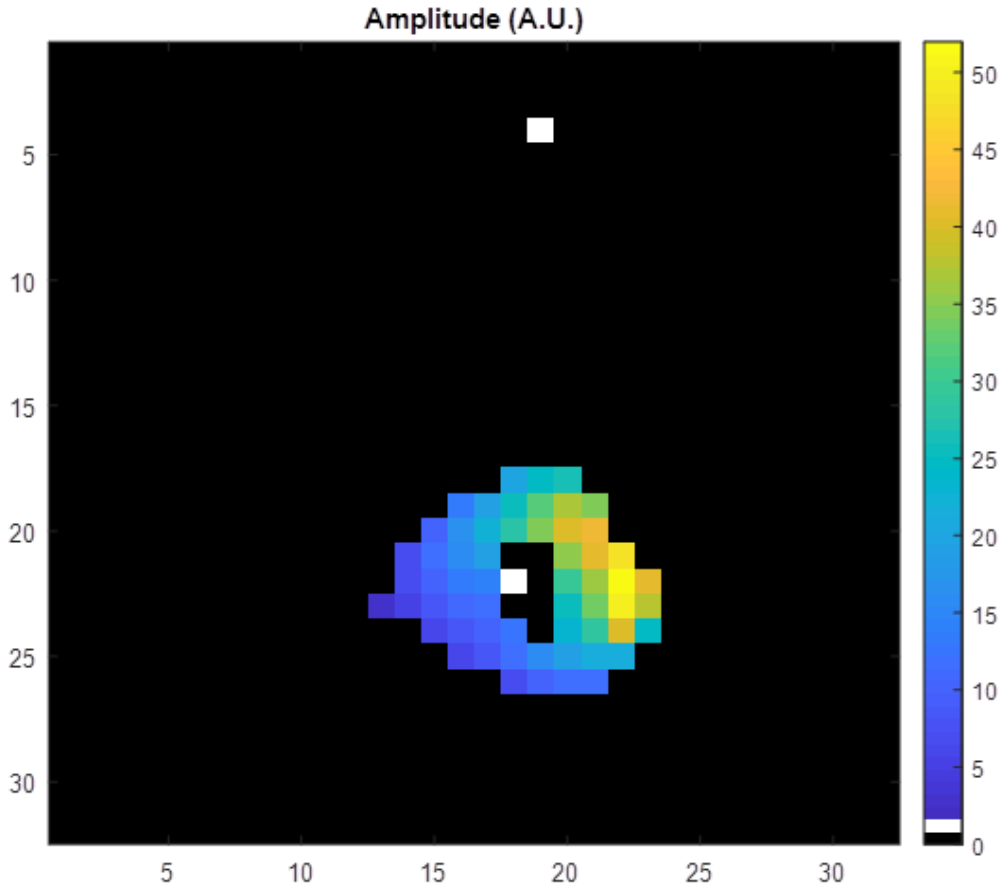
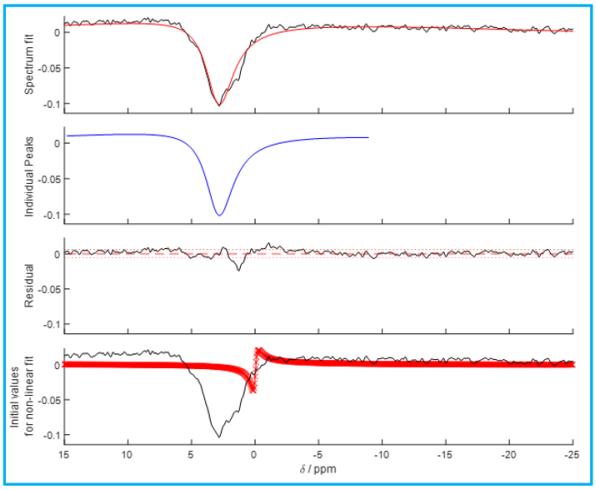
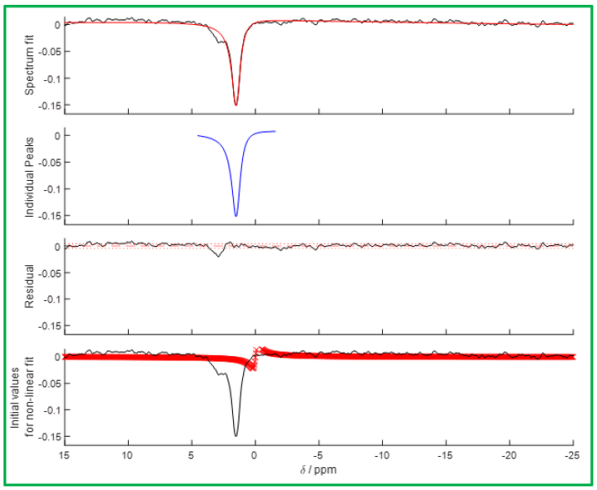



Figure 51 - CSI of amplitude variance of porcine myocardium with CRT device (top white voxel) and implanted lead (bottom white voxel)

Frequency offset is the change in frequency across the voxels at the Larmor frequency of the metabolites. A perfect shim would manifest in similar frequencies across the analysed voxels. Linewidth is the width at half the maximal peak of the spread of Larmor frequencies from the metabolites during MRS and is formed during T2* relaxation [426]. Therefore, linewidth shows the frequency variation within each voxel and is a measure of data quality. The amplitude is described in arbitrary units (au) and follows the standard definition of the maximal strength of vibration. It is a combination of the coil sensitivity profile (a measure of signal noise) and the linewidth, thus the area under the peak. This is primarily determined by the number of spins in the voxel. Increased linewidth causes the peak height to be reduced (as the peak gets wider) whilst the amplitude (the area) remains the same

These results (figures 48-50) show the spectra (single peak) across the myocardium of the porcine phantom model with the implanted CRT device and leads. It is apparent that there are limited changes found in myocardium close to the leads. Both frequency offset and linewidth showed few changes, however there is a noticeable shift focused on the superior aspect, i.e. the area closest to the CRT device. Indeed, the finding that the linewidth largely varies towards the pacemaker instead of the leads implies that the shim is mainly affected by the pacemaker pulse generator. Amplitude variance was relatively low throughout the myocardium, however is in a different direction to linewidth indicating that the primary factor is the imaging coil rather than the pacemaker components. Thus, the positioning of the $^{31}P$ coil and subsequent sensitivity is the key component to factor rather than intrinsic issues with scanning the CRT device.

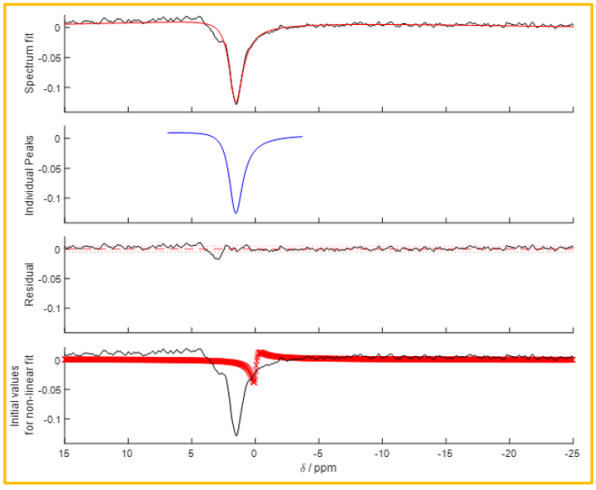



Figure 52 - Spectra analysis at various voxels within the myocardium of the porcine heart.

The voxel or landmark view of the myocardium (top left) shows positioning of the voxels at various points in relation to the lead ranging from superior (top right/blue), inferior (bottom left/green) and adjacent (bottom right/orange). Colour coded to ease appreciation of respective voxel locations.

The direct spectra analysis at various locations (figure 51) gives a more detailed insight into the previous matrix results and highlights the aforementioned trends. The voxel on the superior aspect (blue) stands out as the most different and this is likely due to its proximity to the CRT device itself (rather than the leads) producing artefact that alters expected readings. Specifically, the smoothened spectrum fit is quite similar across the majority of the voxels with a relative discrete narrow peak found on the individual peaks. The residual parameter which shows the spectra with the principal peak subtracted is relatively stable throughout. The initial values for non-linear fit (non-corrected) is helpful to assess for over correction. These results show relative consistency across the range of assessed areas with the minor variance largely explained by the proximity to the CRT device (with a smaller change adjacent to the lead).

## 9.4 Discussion and limitations

These results are reassuring with analysis overall being appearing to be minimally affected by the presence of the CRT device and leads. The consistency of the results suggests MRS being viable in the clinical setting in terms of scanning CHF patients. This foundational work has further credibility in the fact that it is has utilised not only a pig's heart but also a functioning CRT device that is commonly implanted model in CHF patients. Indeed the device interrogation checks (figure 47) confirmed that the device was functioning normally, thus unlikely to present an issue when scanning patients. Whilst these results are better than expected there are two major differences in this phantom model when compared with the real-world setting. Firstly, instead of a largely saline solution, the patient will have blood which has a different set of issues such as artefacts from flowing blood which can be mitigated by spatial presaturation protocols [427]. Another problem is that in patients, hearts would be

pumping which when combined with the CIED could produce problematic susceptibility artefacts. However, as $^{31}$P-MRS has been conducted in patients with a focus on cardiac function, I believe this would not be an insurmountable problem if at all. The pig heart has been shown as a robust choice in MRI studies due to its size and can prepared in an *ex vivo* fashion whilst beating [428]. A beating *ex vivo* preparation would have been technically challenging in our institute, especially whilst coordinating the placement of the CRT device and leads. This could be an experiment for the future though I suspect efforts focused on scanning CHF patients with CRT devices directly would be of greater value based on my findings.

It was hoped that this work would lead onto MRS in CHF patients with CRT devices implanted. Unfortunately a series of problems arose that could not be solved. Principally whilst we have thus far achieved reassuring results and feasibility in scanning CIEDs in 3.0T MRI, $^{31}$P-MRS has not been formally assessed by the device manufacturers for safety. The theoretical risk here is that the local transmitting surface coil would be resting in proximity to the CIED and would cause more RF related heating to the CIED than standard imaging or $^{1}$H-MRS. Specifically as the majority of device manufacturers have only confirmed safety for an active CIED whilst using the integrated coil (which is often sufficient for $^{1}$H-MRS) or commonly utilised coils (such as head or knee), the use of a different coil such as that required for $^{31}$P-MRS would be beyond the tested circumstances. Additionally, the frequency of $^{31}$P-MRS is 49MHz compared with 126MHz in standard $^{1}$H-MRS leading to a longer wavelength. To assess this properly, real-world testing, modelling or simulation ideally should take place. This is quite an extended series of testing to assess limits and variability which in turn incurs significant financial costs. As a team we investigated this further and received a quote of approximately €60-100k for RF safety and €125-200k for full MRI safety certification with this method. We discussed the possibility of safety testing with the device manufacturers; however this discussion was fruitless due to the time and financial cost associated with this research direction. As a panel (cardiologists, medical physics, MR radiographer, cardiac physiologists and academics) we went through all the options of progressing with MRS in patients and following multiple meetings and advice obtained internationally, the decision was made not to proceed with MRS in patients until further safety work was conducted. This decision mainly rested on our work being a

research study and not clinical thus the risks were felt to outweigh the benefits to both the patient and research group.

## 9.5 Conclusions

The presence of a CRT device and leads in the anatomically correct areas are not expected to be an absolute barrier to MRS in terms of read out analysis in patients with MR-conditional CRT devices implanted. Further safety testing is required before a clinical MRS assessment can be conducted in humans due to potential issues around heating and damage to either human tissue or the CIED itself.

# Chapter 10 – Conclusions

## 10.1 General discussion

I feel privileged to have conducted a number of pioneering experiments. To my knowledge, this work is the first internationally to have investigated cardiac response to active CRT in CHF patients and HR augmentation with the use of CMR. Furthermore, we have investigated strain and RV function in the context of CRT at a higher resolution than ever before. Finally, my work represents the only known investigation into CRT via MRS. This resulted in reaching the limits of primary research in the clinical setting by requiring device safety testing that is generally conducted by the manufacturers to proceed further.

My research identifies what appears to be a safe methodology for scanning patients via CMR with CRT active and augmentation of the HR through pacing. This methodology was not associated with any significant deviations from baseline pacemaker values post scan and notably none of the patients experienced any significant side effects. Importantly, the quality of images obtained after image enhancement techniques that ranged from appropriate positioning to the scanning technique employed enabled adequate MRI analysis. This is a milestone event and should give confidence to other centres internationally to explore cardiac mechanisms in response to CRT activity, utilising the fidelity that CMR offers. Maintaining BiV pacing whilst scanning was only possible due to the experienced team members of this project consisting of a cardiologist, MRI radiographer, cardiac physiologist, medical physicist and assistance as required from the device manufacturers. Further studies are required to prove safety in a larger cohort, but certainly these findings are reassuring. It is hoped that in the near future it becomes standard procedure to scan CRT patients with BiV pacing, thus similar to their native programming rather than switching the device to RV pacing which is associated with reduced CO and worsening of cardiac function long term [429].

We have found that BiV pacing results in contractility benefits at increased HR. Many studies have shown the survival benefit of CRT pacing in patients with CHF [102]. CRT is also associated with improvements in exercise capacity, reverse remodelling and LVEF [430, 431]. It is difficult to interpret my findings of increased performance

with CRT active as the inotropic improvements acutely of BiV over RV pacing obtained with CRT active have not been found to be predictive of HF related rehospitalisation or death [314]. It is likely that CRT acts as a mechanical corrector for the dyssynchrony that is present in the implanted cohort of CHF patients. Early studies validate this concept by showing that BiV pacing conferred improvements in cardiac mechanics such as SV without placing additional oxidative metabolic requirements on the myocardial tissue [95, 321]. This should not be underestimated. Cardiac tissue in patients with CHF are likely to be energy starved based on physiological and MRS investigations [192, 432]. Further study is needed to investigate the effect improved contractile function could have on factors intrinsic to CHF such as altered SERCA levels and energetics. The shallower FFR slopes in response to increasing HR found in my cohort of CHF patients likely reflect the higher sympathetic activity required to reach adequate CO in HF patients [238]. This relationship can explain some of the benefits of BB by stopping the FFR peaking, thus mitigating the sympathetic overdrive that occurs through the positive feedback loop associated with CHF in failing to reach required CO. The same rationale can be applied to CRT devices which are able to mechanically increase CO and LV contractility and are similarly associated with reductions in sympathetic activity post implantation [331].

We have identified a a HR window (100 bpm in this cohort) beyond which further increases via pacing worsens CO in CRT patients. This finding could explain why previous studies that have raised HR have failed to increase exercise capacity [433]. The bell-shaped curve that is observed in my research supports previous findings by Steendijk et al [326] which showed a similar pattern in CO, ventricular dimensions and LVEF via pacing induced HR increases as found in my work. Notably, a similar peak point of 100 bpm in CO was noted suggesting that despite the vast changes in medical optimisation therapy, core physiological changes associated with CHF may be the determining factor. This could be a significant finding and further work into FFR and cardiac response is likely to lead to important discoveries that appreciate CHF as a syndrome. My results also suggest that active CRT gives a partial normalisation effect towards a positive FFR as found in controls. This is valuable information as CRT is a practical solution in many CHF patients with conduction delay. Indeed, the improvement is not too dissimilar from early work by Mulieri et al

[434] who used Forskolin to reduce FFR reductions in CHF patients. Forskolin is an adenylate cyclase activator that has been shown to almost completely reverse the FFR shift and tension blunting found in failing hearts. This is believed to be through the effect of the drug increasing cyclic adenosine monophosphate (cAMP). However, this drug is not utilised in clinical practice which may be due to its side effect profile and narrow of therapeutic range [435]. The fact that CRT appears to give a similar mechanical response whilst being well tolerated is appealing and merits further investigation in a larger cohort.

Assessing controls and CHF patients in terms of response to HR seems to produce variable response. It is possible that this technique could be valuable in identifying contractility and cardiac health in general. Our work has shown a difference in LVCO, contractility and strain with the use of CRT and in controls when compared to when CRT is disabled. Importantly this imaging protocol at 3.0T CMR is likely to be feasible in the majority of patients with modern CRT or dual chamber pacemakers implanted. Future studies that couple these profiles with traditional endpoints such as functional capacity, quality of life and mortality could reveal the FFR response to changing HR as a powerful examination tool for risk stratification and response to intervention. I believe it could even be more useful than the current utilisation of LV reverse remodelling which seems to be reported in a variety of fashions and does not take into account the variation in HR that would be expected in active patients.

My results imply that in some areas such as strain and LV contractility, BiV pacing is superior to physiological LV contraction in control participants at higher HR. Whilst there is an age difference in favour of the CRT cohort, the fact that at higher HR there is superior contraction in a CHF patient suggests that CRT may be helpful in a wider group of patients than currently implanted. Indeed, it supports the notion that that cardiac mechanics in response to HR are likely to be dynamic and regressive with age. This finding should be followed up with studies that focus on endpoints such as exercise capacity, breathlessness and quality of life scores in older patients. Similarly, BiV as opposed to RV only pacing appears to increase RV function in CHF patients that are suitable for CRT implantation for which there is limited study in this area. This is potentially significant as RVF has been shown to be a predictor of poor outcomes in patients, specifically as a cohort with a low response to CRT [436]. My research highlights the RV as a poorly understood component of the heart. At the

higher HR there was a convergence across the majority of parameters assessed such as RVCO, RVEF and RV dimensions across the 3 cohorts. Whilst this is partially explained by commonality of mechanism (RV pacing), it may relate to the concept of chamber specific effects which focuses on the failing LV producing a different neurohormonal feedback loop when compared to the failing RV despite CHF being a syndrome with systemic effects [244]. Further research is required here with my work indicating CMR as a reasonable imaging modality for subsequent investigation.

We have shown that exercise CMR appears to be safe and viable in patients with CRT devices using inexpensive techniques such as leg raise with resistance bands. It is early but reassuring to see increases in HR, SBP and CO in both healthy individuals and older patients with CHF through such simple techniques. Future research could utilise this and investigate the effect of exercise induced HR increases on cardiac mechanics such as FFR in paced patients. It is likely that preliminary safety work to create accepted working practices and avoid risks such as hazardous arrhythmia formation will be required to achieve this goal.

MRS has not been utilised in the context of CRT devices before. Through multiple porcine phantom models, we have found that $^{31}$P-MRS in CHF patients with implanted compatible CRT devices is expected to be viable, or more accurately not likely to be limited by image acquisition issues. There are technical and safety challenges remaining in order to achieve MRS analysis in patients with implanted devices which revolve around the safety assessment for heating and damage risk to human tissue and the device itself. This will require an arduous battery of tests that likely need to be conducted by device manufacturers. However, my research highlights the feasibility and potential value of $^{31}$P-MRS in CHF patients which hopefully entices manufacturers and other research groups to pursue this further. The ability to evaluate metabolite changes with regards to ATP and changes in energetics such as PCr/ATP would be valuable in assessing not only the benefits of CRT but may be one of the missing links in patient selection and device optimisation.

Despite much of this work being novel with the use of state-of-the-art technology, it was reassuring to find that the variability analysis across the board of measurements studied were largely within the standards for MRI reporting. Notably this largely applied for both LV and RV analysis despite HR augmentation via MR-conditional

CIED. This gives confidence to not only utilise many of the findings within this thesis further but also for research groups to implement some of the imaging techniques utilised which may well lead to significant discoveries around cardiac mechanics and pacing.

## 10.2 Future work

CRT is a largely effective device therapy that remains with a significant non-responder rate [3]. This is likely in relation to the lack of mechanistic work conducted on this technology and the CHF population [286]. It would be valuable to explore the effects of exercise on the FFR and cardiac mechanics in patients with implanted CRT. This would be the next step in clarifying the cardiac response to HR increase via the two main modalities present in patients (exercise and pacing). Exercise would be expected to result in a right and upward shift in the FFR, however as CHF is syndrome of reduced cardiac function, sympathetic overdrive and peripheral manifestations, it is likely that the response is complex. I believe it would also be of value to conduct cellular studies on muscle samples from CHF patients, specifically focusing on calcium handling and SERCA and comparing this with FFR and exercise performance in well optimised patients. This work could be helpful at the point of HF workup as a marker of disease progression and likely benefit decision making around intervention, indeed even guide ideal CIED programming.

I remain in contact with major device manufacturers with the aim of progressing safety testing of MRS. Hopefully this will enable assessment of patients with implanted CIED as my work suggests significant value in exploring the effects of CRT on energetics. This approach could lead to improvements in device functionality and fine tuning. My results have identified CMR in general as both a robust and versatile imaging modality enabling the assessment of multiple performance markers, especially with regards to RV function and LV response to HR. This merits further investigation into the concept of personalised care with the use of MRI as a key technology, for example in the role of patient assessment for expected response to CRT implantation and programming modes.

## 10.3 Final conclusion

3.0T CMR appears to be a viable and versatile imaging modality for assessing cardiac function in response to active CRT and HR augmentation. BiV pacing offers improved mechanical function and FFR with a partial normalisation effect when compared with CRT off and controls. $^{31}$P-MRS is expected to be a useful tool for the analysis of energetics in CRT patients once further safety testing is completed.

# Appendix 1 – CMR settings utilised for scanning patients using GRE sequence

| | |
|---|---|
| FOV ($mm^2$) | 450 |
| FOV phase (%) | 89.6 |
| Slices | 13 |
| Slice thickness (mm) | 8 |
| Flip angle (degrees) | 12 |
| TE (ms) | 2.36 |
| TR (ms) | 139.72 |

FOV – Field of view, TE – Echo time, TR – Repetition time

# Appendix 2 – Favourable opinion from REC for conducting HR augmentation in CHF patients with implanted CRT devices

NHS
Health Research Authority
South Central - Berkshire B Research Ethics Committee
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 0207 104 8059

**Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval**

30 November 2017

Dr Klaus Witte
Senior Lecturer in Cardiology
University of Leeds
LIGHT building
c
LS2 9JT

Dear Dr Witte

| | |
|---|---|
| **Study title:** | **Using an MRI scan to explore the Bowditch phenomenon in chronic heart failure** |
| **REC reference:** | **17/SC/0612** |
| **EudraCT number:** | |
| **IRAS project ID:** | **231889** |

Thank you for your letter of 28 November 2017 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 HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

A Research Ethics Committee established by the Health Research Authority

**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.

**Conditions of the favourable opinion**

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

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

*Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).*

*Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk 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 management permissions from host organisations*

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

**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).**

**Ethical review of research sites**

NHS sites

The favourable opinion applies to all NHS sites listed in the application, 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).

**Approved documents**

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

| *Document* | *Version* | *Date* |
|---|---|---|
| Covering letter on headed paper [Covering letter] | | 27 November 2017 |
| Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Liability insurance] | | 21 September 2017 |
| GP/consultant information sheets or letters [GP letter (Tracked)] | 1.1 | 27 November 2017 |
| Instructions for use of medical device [Manual Percepta] | | |
| Instructions for use of medical device [Manual Amplia] | | |
| IRAS Application Form [IRAS_Form_28112017] | | 28 November 2017 |
| IRAS Checklist XML [Checklist_29112017] | | 29 November 2017 |
| Letters of invitation to participant [Invitation letter (Tracked)] | 1.1 | 27 November 2017 |
| MHRA Notice of No Objection Letter (Medical Devices) and relevant correspondence [MHRA advice] | | 09 October 2017 |
| Other [WITTE GCP] | | 27 November 2017 |
| Participant consent form [Consent form] | 1.1 | 27 November 2017 |
| Participant information sheet (PIS) [PIS Non-CHF (Tracked)] | 1.1 | 27 November 2017 |
| Participant information sheet (PIS) [PIS CHF (Tracked)] | 1.1 | 27 November 2017 |
| Research protocol or project proposal [Protocol] | 1.0 | 26 June 2017 |
| Summary CV for Chief Investigator (CI) [KW CV] | | 08 November 2017 |

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

**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 procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

**HRA Training**

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

| **17/SC/0612** | **Please quote this number on all correspondence** |
|---|---|

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

Yours sincerely

pp.

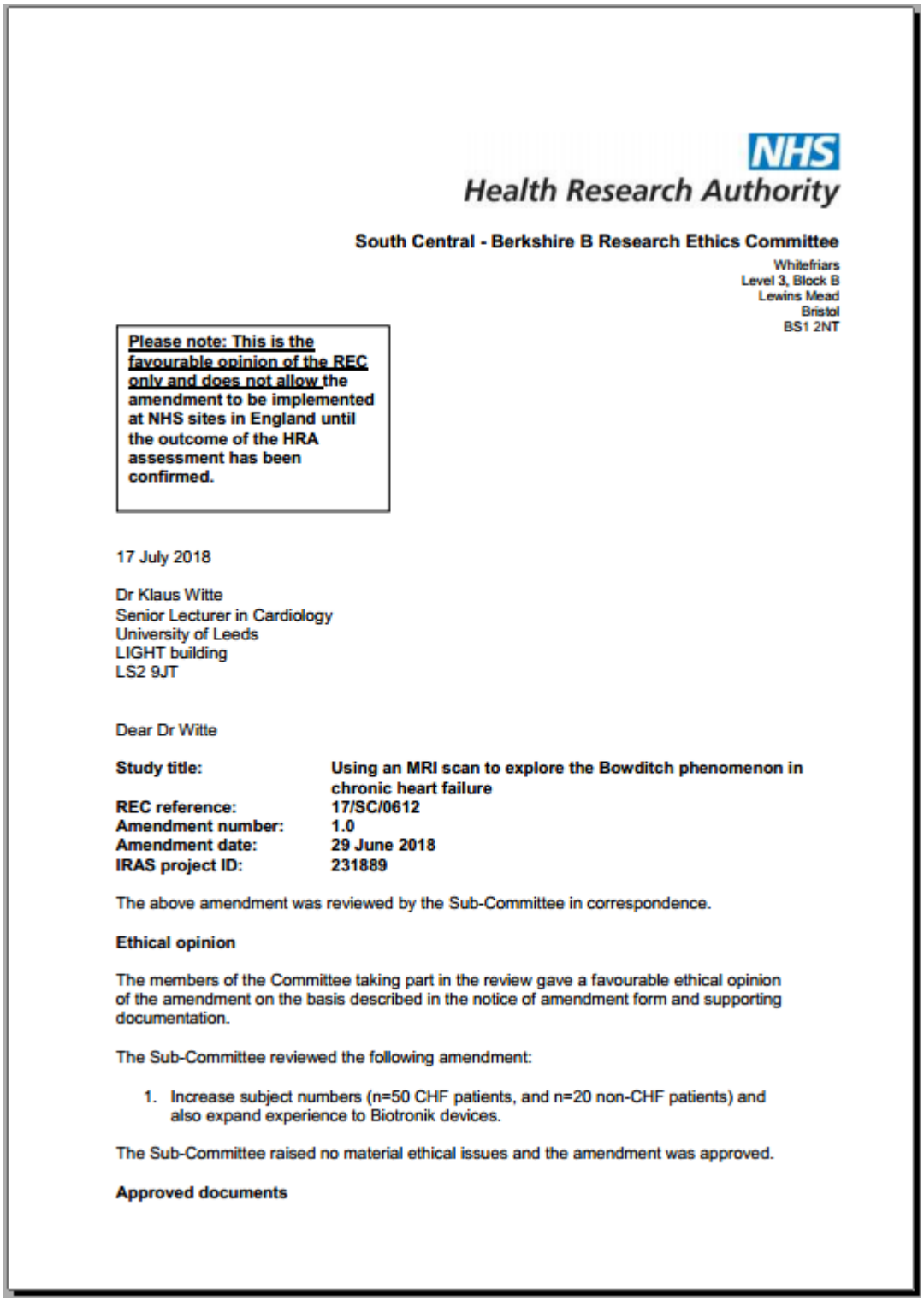
**Dr John Sheridan**
**Chair**

Email:nrescommittee.southcentral-berkshireb@nhs.net

*Enclosures:* "After ethical review – guidance for researchers"

*Copy to:* *NHS Research Ethics Officer*
*Mrs Amanda Burd, LTHT R+I*

# Appendix 3 – Favourable opnion received from REC for Ammendment 1 allowing FFR exploration in control participants



NHS
Health Research Authority

**South Central - Berkshire B Research Ethics Committee**

Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

**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.**

17 July 2018

Dr Klaus Witte
Senior Lecturer in Cardiology
University of Leeds
LIGHT building
LS2 9JT

Dear Dr Witte

| | |
|---|---|
| **Study title:** | **Using an MRI scan to explore the Bowditch phenomenon in chronic heart failure** |
| **REC reference:** | **17/SC/0612** |
| **Amendment number:** | **1.0** |
| **Amendment date:** | **29 June 2018** |
| **IRAS project ID:** | **231889** |

The above amendment was reviewed by the Sub-Committee in correspondence.

**Ethical opinion**

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.

The Sub-Committee reviewed the following amendment:

1. Increase subject numbers (n=50 CHF patients, and n=20 non-CHF patients) and also expand experience to Biotronik devices.

The Sub-Committee raised no material ethical issues and the amendment was approved.

**Approved documents**

The documents reviewed and approved at the meeting were:

| *Document* | *Version* | *Date* |
|---|---|---|
| Covering letter on headed paper [Covering letter 29th June 2018 Amendment 1 231889] | | 29 June 2018 |
| Notice of Substantial Amendment (CTIMP) [AmendmentForm_ReadyForSubmission June 29th 2018] | 1.0 | 29 June 2018 |
| Other [Function-Manual_Enitra-6-8_en_429316-B_2017-11-16..pdf] | | 16 November 2017 |
| Other [Bowditch in CRT using MRI V1.1 29th June 2018] | 1.1 | 29 June 2018 |

**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**

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

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/

**17/SC/0612: Please quote this number on all correspondence**

Yours sincerely

pp. LRoberts.

**Dr John Sheridan**
**Chair**

E-mail: nrescommittee.southcentral-berkshireb@nhs.net

*Copy to:* *Mrs Amanda Burd, LTHT R+I*
*NHS Research Ethics Officer*

**South Central - Berkshire B Research Ethics Committee**

**Attendance at Sub-Committee of the REC meeting via correspondence**

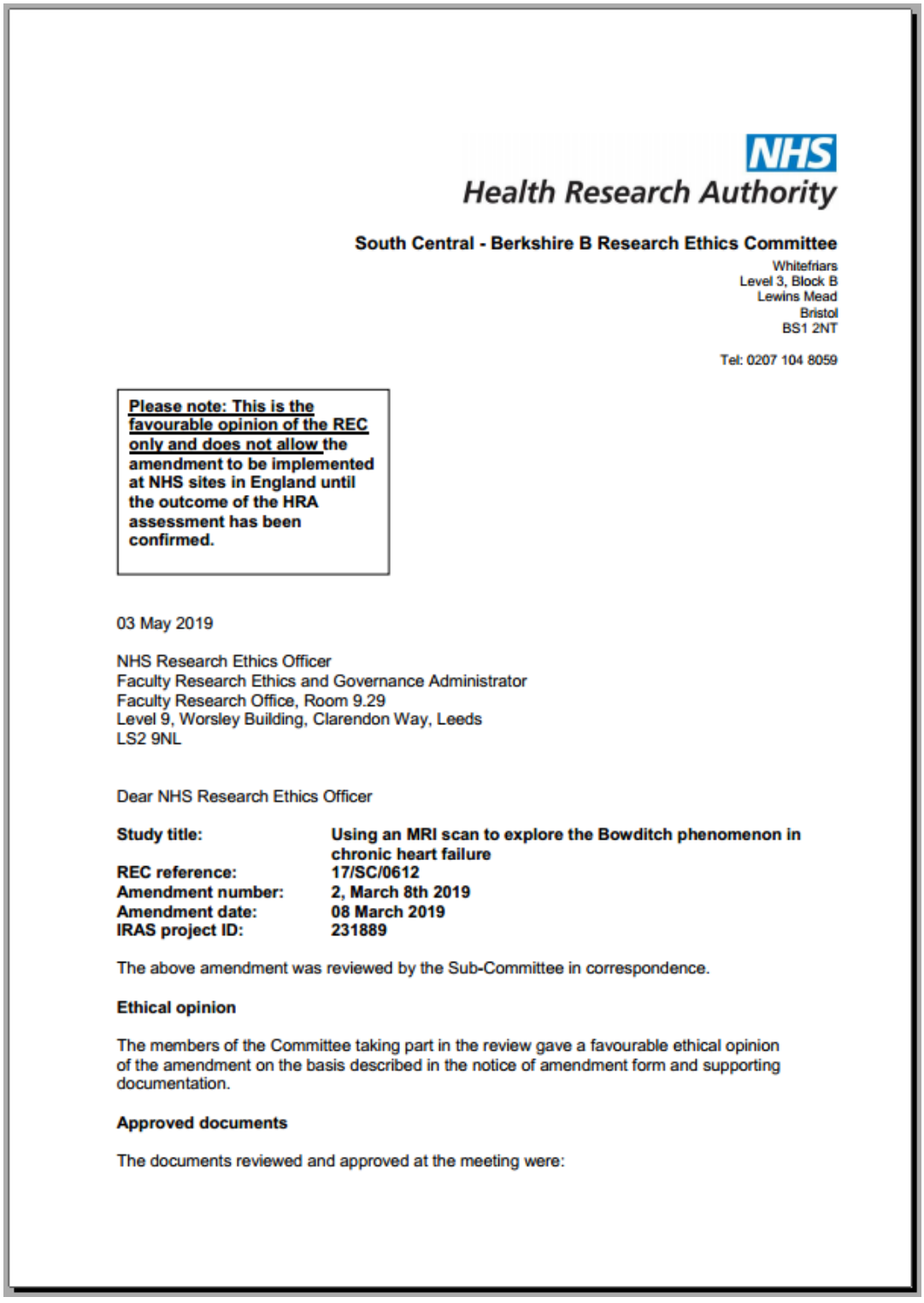
**Committee Members:**

| *Name* | *Profession* | *Present* | *Notes* |
|---|---|---|---|
| Mrs Sue Harrison | Retired Managing Director of a Trade Association | Yes | |
| Dr John Sheridan | Consultant Toxicologist and Chemist | Yes | |

**Also in attendance:**

| *Name* | *Position (or reason for attending)* |
|---|---|
| Miss Charlotte Ferris | REC Manager |

# Appendix 4



NHS
Health Research Authority

**South Central - Berkshire B Research Ethics Committee**

Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Tel: 0207 104 8059

**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.**

03 May 2019

NHS Research Ethics Officer
Faculty Research Ethics and Governance Administrator
Faculty Research Office, Room 9.29
Level 9, Worsley Building, Clarendon Way, Leeds
LS2 9NL

Dear NHS Research Ethics Officer

| | |
|---|---|
| **Study title:** | **Using an MRI scan to explore the Bowditch phenomenon in chronic heart failure** |
| **REC reference:** | **17/SC/0612** |
| **Amendment number:** | **2, March 8th 2019** |
| **Amendment date:** | **08 March 2019** |
| **IRAS project ID:** | **231889** |

The above amendment was reviewed by the Sub-Committee in correspondence.

**Ethical opinion**

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* |
|---|---|---|
| Covering letter on headed paper [ Covering letter 8th March 2019 Amendment 2 231889] | | 08 March 2019 |
| Notice of Substantial Amendment (CTIMP) [ AmendmentForm_ReadyForSubmission ] | 2, March 8th 2019 | 08 March 2019 |
| Participant consent form [ Consent form 8th March 2019, V1.2] | 1.2 | 08 March 2019 |
| Participant information sheet (PIS) [ Patient information CHF v1.2 8th March 2019 - MRICONT.] | 1.2 | 08 March 2019 |
| Participant information sheet (PIS) [ Patient information non CHF v1.2 8th March 2019 - MRICONT] | 1.2 | 08 March 2019 |
| Research protocol or project proposal [ Bowditch in CRT using MRI V1.3 8th March 2019] | 1.3 | 08 March 2019 |

**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**

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

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.

**HRA Learning**

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

| **17/SC/0612:** | **Please quote this number on all correspondence** |
|---|---|

Yours sincerely

PP
**Mr John Inman**
**Alternate Vice-Chair**

**South Central - Berkshire B Research Ethics Committee**

**Attendance at Sub-Committee of the REC meeting in Correspondence.**

**Committee Members:**

| *Name* | *Profession* | *Present* | *Notes* |
|---|---|---|---|
| Mrs Sue Harrison | Retired Managing Director of a Trade Association | Yes | |
| Mr John Inman | Retired Pharmacist | Yes | *Meeting Chair* |

# References


1. NICE. Chronic heart failure in adults: Diagnosis and management. 2018.

2. Jones NR, Roalfe AK, Adoki I, Hobbs FR, Taylor CJ. Survival of patients with chronic heart failure in the community: A systematic review and meta-analysis. European journal of heart failure. 2019;21(11):1306-25.

3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, 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):891-975.

4. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 accf/aha guideline for the management of heart failure: Executive summary: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. Circulation. 2013;128(16):1810-52.

5. van Empel VPM, Bertrand ATA, Hofstra L, Crijns HJ, Doevendans PA, De Windt LJ. Myocyte apoptosis in heart failure. Cardiovascular Research. 2005;67(1):21-9.

6. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. Nature reviews Cardiology. 2017;14(1):30-8.

7. Braunwald E. Heart failure. JACC Heart Fail. 2013;1(1):1-20.

8. Shah AM, Mann DL. In search of new therapeutic targets and strategies for heart failure: Recent advances in basic science. Lancet. 2011;378(9792):704-12.

9. Felker GM, Shaw LK, O'Connor CM. A standardized definition of ischemic cardiomyopathy for use in clinical research. J Am Coll Cardiol. 2002;39(2):210-8.

10. Braunwald E, Rutherford JD. Reversible ischemic left ventricular dysfunction: Evidence for the "hibernating myocardium". J Am Coll Cardiol. 1986;8(6):1467-70.

11. Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. New England Journal of Medicine. 2016;374(16):1511-20.

12. Chew DS, Heikki H, Schmidt G, Kavanagh KM, Dommasch M, Bloch Thomsen PE, et al. Change in left ventricular ejection fraction following first myocardial infarction and outcome. JACC: Clinical Electrophysiology. 2018;4(5):672-82.

13. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, et al. Lifetime risk for developing congestive heart failure: The framingham heart study. Circulation. 2002;106(24):3068-72.

14. Boron WF, Boulpaep EL. Medical physiology e-book: Elsevier Health Sciences; 2016.

15. Colledge NR, Walker BR, Ralston S, Davidson S. Davidson's principles and practice of medicine. 2010:544.

16. Petersen S, Rayner M, Wolstenholme J. Coronary heart disease statistics: Heart failure supplement. London: British Heart Foundation. 2002.

17. Cowie MR, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V, et al. Incidence and aetiology of heart failure; a population-based study. Eur Heart J. 1999;20(6):421-8.

18. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, et al. Quantifying the heart failure epidemic: Prevalence, incidence rate, lifetime risk and prognosis of heart failure the rotterdam study. Eur Heart J. 2004;25(18):1614-9.

19. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail. 2001;3(3):315-22.

20. Hobbs FD, Kenkre JE, Roalfe AK, Davis RC, Hare R, Davies MK. Impact of heart failure and left ventricular systolic dysfunction on quality of life: A cross-sectional study comparing common chronic cardiac and medical disorders and a representative adult population. Eur Heart J. 2002;23(23):1867-76.

21. Taylor CJ, Ryan R, Nichols L, Gale N, Hobbs FDR, Marshall T. Survival following a diagnosis of heart failure in primary care. Family Practice. 2017;34(2):161-8.

22. NICE. Chronic heart failure in adults: Management. 2010.

23. Stewart S, Horowitz JD. Home-based intervention in congestive heart failure: Long-term implications on readmission and survival. Circulation. 2002;105(24):2861-6.

24. Oh JK. Echocardiography in heart failure: Beyond diagnosis. European Journal of Echocardiography. 2007;8(1):4-14.

25. Oudejans I, Mosterd A, Bloemen JA, Valk MJ, van Velzen E, Wielders JP, et al. Clinical evaluation of geriatric outpatients with suspected heart failure: Value of symptoms, signs, and additional tests. Eur J Heart Fail. 2011;13(5):518-27.

26. Mant J, Doust J, Roalfe A, Barton P, Cowie MR, Glasziou P, et al. Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care. Health Technol Assess. 2009;13(32):1-207, iii.

27. Greupner J, Zimmermann E, Grohmann A, Dubel HP, Althoff TF, Borges AC, et al. Head-to-head comparison of left ventricular function assessment with 64-row computed tomography, biplane left cineventriculography, and both 2- and 3-dimensional transthoracic echocardiography: Comparison with magnetic resonance imaging as the reference standard. J Am Coll Cardiol. 2012;59(21):1897-907.

28. Peterzan MA, Rider OJ, Anderson LJ. The role of cardiovascular magnetic resonance imaging in heart failure. Cardiac Failure Review. 2016;2(2):115-22.

29. Adigopula S, Grapsa J. Advances in imaging and heart failure: Where are we heading? Cardiac failure review. 2018;4(2):73-7.

30. Erdei T, Smiseth OA, Marino P, Fraser AG. A systematic review of diastolic stress tests in heart failure with preserved ejection fraction, with proposals from the eu-fp7 media study group. Eur J Heart Fail. 2014;16(12):1345-61.

31. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2d speckle tracking echocardiography: Consensus document of the eacvi/ase/industry task force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging. 2015;16(1):1-11.

32. Kirkpatrick JN, Vannan MA, Narula J, Lang RM. Echocardiography in heart failure: Applications, utility, and new horizons. Journal of the American College of Cardiology. 2007;50(5):381-96.

33. Boogers MJ, Fukushima K, Bengel FM, Bax JJ. The role of nuclear imaging in the failing heart: Myocardial blood flow, sympathetic innervation, and future applications. Heart Failure Reviews. 2011;16(4):411-23.

34. Bengel FM, Higuchi T, Javadi MS, Lautamäki R. Cardiac positron emission tomography. Journal of the American College of Cardiology. 2009;54(1):1-15.

35. Moss AJ, Williams MC, Newby DE, Nicol ED. The updated nice guidelines: Cardiac ct as the first-line test for coronary artery disease. Current Cardiovascular Imaging Reports. 2017;10(5):15.

36. Koshy AO, Gallivan ER, McGinlay M, Straw S, Drozd M, Toms AG, et al. Prioritizing symptom management in the treatment of chronic heart failure. ESC Heart Failure. 2020;7(5):2193-207.

37. Effect of metoprolol cr/xl in chronic heart failure: Metoprolol cr/xl randomised intervention trial in congestive heart failure (merit-hf). Lancet. 1999;353(9169):2001-7.

38. Effects of enalapril on mortality in severe congestive heart failure. Results of the cooperative north scandinavian enalapril survival study (consensus). N Engl J Med. 1987;316(23):1429-35.

39. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. N Engl J Med. 1999;341(10):709-17.

40. Wilcox J, Yancy CW. Stopping medication for heart failure with improved ejection fraction. The Lancet. 2019;393(10166):8-10.

41. Cruden NL, Fox KA, Ludlam CA, Johnston NR, Newby DE. Neutral endopeptidase inhibition augments vascular actions of bradykinin in patients treated with angiotensin-converting enzyme inhibition. Hypertension. 2004;44(6):913-8.

42. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. Atlas study group. Circulation. 1999;100(23):2312-8.

43. Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril cardiac evaluation (trace) study group. N Engl J Med. 1995;333(25):1670-6.

44. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of candesartan in patients with chronic heart failure and reduced left-

ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: The charm-alternative trial. Lancet. 2003;362(9386):772-6.

45. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001;345(23):1667-75.

46. Information UM. When can a combination of angiotensin converting enzyme inhibitors with angiotensin ii receptor antagonists be used in patients with heart failure? UKMi, 2014.

47. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. New England Journal of Medicine. 2014;371(11):993-1004.

48. King JB, Bress AP, Reese AD, Munger MA. Neprilysin inhibition in heart failure with reduced ejection fraction: A clinical review. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2015;35(9):823-37.

49. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Butler J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. J Am Coll Cardiol. 2009;54(19):1747-62.

50. Chatterjee S, Biondi-Zoccai G, Abbate A, D'Ascenzo F, Castagno D, Van Tassell B, et al. Benefits of β blockers in patients with heart failure and reduced ejection fraction: Network meta-analysis. BMJ : British Medical Journal. 2013;346.

51. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the carvedilol or metoprolol european trial (comet): Randomised controlled trial. Lancet. 2003;362(9377):7-13.

52. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344(22):1651-8.

53. Krum H, Bigger JT, Jr., Goldsmith RL, Packer M. Effect of long-term digoxin therapy on autonomic function in patients with chronic heart failure. J Am Coll Cardiol. 1995;25(2):289-94.

54. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. N Engl J Med. 2002;347(18):1403-11.

55. Slatton ML, Irani WN, Hall SA, Marcoux LG, Page RL, Grayburn PA, et al. Does digoxin provide additional hemodynamic and autonomic benefit at higher doses in patients with mild to moderate heart failure and normal sinus rhythm? J Am Coll Cardiol. 1997;29(6):1206-13.

56. Group TDI. The effect of digoxin on mortality and morbidity in patients with heart failure. New England Journal of Medicine. 1997;336(8):525-33.

57. Ouyang AJ, Lv YN, Zhong HL, Wen JH, Wei XH, Peng HW, et al. Meta-analysis of digoxin use and risk of mortality in patients with atrial fibrillation. Am J Cardiol. 2015;115(7):901-6.

58. Vamos M, Erath JW, Hohnloser SH. Digoxin-associated mortality: A systematic review and meta-analysis of the literature. Eur Heart J. 2015;36(28):1831-8.

59. Washam JB, Stevens SR, Lokhnygina Y, Halperin JL, Breithardt G, Singer DE, et al. Digoxin use in patients with atrial fibrillation and adverse cardiovascular outcomes: A retrospective analysis of the rivaroxaban once daily oral direct factor xa inhibition compared with vitamin k antagonism for prevention of stroke and embolism trial in atrial fibrillation (rocket af). The Lancet. 2015;385(9985):2363-70.

60. Bohm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, et al. Heart rate as a risk factor in chronic heart failure (shift): The association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet. 2010;376(9744):886-94.

61. Duarte JD, Cooper-DeHoff RM. Mechanisms for blood pressure lowering and metabolic effects of thiazide and thiazide-like diuretics. Expert Rev Cardiovasc Ther. 2010;8(6):793-802.

62. Faris R, Flather MD, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. Cochrane Database Syst Rev. 2006(1):Cd003838.

63. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. New England Journal of Medicine. 1999;341(10):709-17.

64. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352(3):225-37.

65. Torp-Pedersen C, Moller M, Bloch-Thomsen PE, Kober L, Sandoe E, Egstrup K, et al. Dofetilide in patients with congestive heart failure and left ventricular dysfunction. Danish investigations of arrhythmia and mortality on dofetilide study group. N Engl J Med. 1999;341(12):857-65.

66. Group TSR. A randomized trial of intensive versus standard blood-pressure control. New England Journal of Medicine. 2015;373(22):2103-16.

67. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358(18):1887-98.

68. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: A combined analysis of three trials. Lancet. 2006;368(9535):581-8.

69. Windecker S, Stortecky S, Stefanini GG, daCosta BR, Rutjes AW, Di Nisio M, et al. Revascularisation versus medical treatment in patients with stable coronary artery disease: Network meta-analysis. BMJ : British Medical Journal. 2014;348.

70. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Jr., Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The save investigators. N Engl J Med. 1992;327(10):669-77.

71. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: The capricorn randomised trial. Lancet. 2001;357(9266):1385-90.

72. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348(14):1309-21.

73. Montalescot G, Pitt B, Lopez de Sa E, Hamm CW, Flather M, Verheugt F, et al. Early eplerenone treatment in patients with acute st-elevation myocardial infarction without heart failure: The randomized double-blind reminder study. Eur Heart J. 2014;35(34):2295-302.

74. Scirica BM, Morrow DA, Cannon CP, Ray KK, Sabatine MS, Jarolim P, et al. Intensive statin therapy and the risk of hospitalization for heart failure after an acute coronary syndrome in the prove it-timi 22 study. J Am Coll Cardiol. 2006;47(11):2326-31.

75. Aggarwal M, Bozkurt B, Panjrath G, Aggarwal B, Ostfeld RJ, Barnard ND, et al. Lifestyle modifications for preventing and treating heart failure. Journal of the American College of Cardiology. 2018;72(19):2391-405.

76. Hellénius ML, de Faire U, Berglund B, Hamsten A, Krakau I. Diet and exercise are equally effective in reducing risk for cardiovascular disease. Results of a randomized controlled study in men with slightly to moderately raised cardiovascular risk factors. Atherosclerosis. 1993;103(1):81-91.

77. Piepoli MF, Coats AJS. The 'skeletal muscle hypothesis in heart failure' revised. European Heart Journal. 2013;34(7):486-8.

78. Adamopoulos S, Coats AJ, Brunotte F, Arnolda L, Meyer T, Thompson CH, et al. Physical training improves skeletal muscle metabolism in patients with chronic heart failure. J Am Coll Cardiol. 1993;21(5):1101-6.

79. Pandey A, Garg S, Khunger M, Darden D, Ayers C, Kumbhani DJ, et al. Dose response relationship between physical activity and risk of heart failure: A meta-analysis. Circulation. 2015.

80. Kenchaiah S, Evans JC, Levy D, Wilson PWF, Benjamin EJ, Larson MG, et al. Obesity and the risk of heart failure. New England Journal of Medicine. 2002;347(5):305-13.

81. Goncalves A, Claggett B, Jhund PS, Rosamond W, Deswal A, Aguilar D, et al. Alcohol consumption and risk of heart failure: The atherosclerosis risk in communities study. Eur Heart J. 2015;36(15):939-45.

82. Wannamethee SG, Whincup PH, Lennon L, Papacosta O, Shaper AG. Alcohol consumption and risk of incident heart failure in older men: A prospective cohort study. Open Heart. 2015;2(1).

83. Djoussé L, Gaziano JM. Alcohol consumption and heart failure: A systematic review. Current atherosclerosis reports. 2008;10(2):117-20.

84. Suskin N, Sheth T, Negassa A, Yusuf S. Relationship of current and past smoking to mortality and morbidity in patients with left ventricular dysfunction. J Am Coll Cardiol. 2001;37(6):1677-82.

85. Levitan EB, Wolk A, Mittleman MA. Consistency with the dash diet and incidence of heart failure. Archives of internal medicine. 2009;169(9):851-7.

86. Nguyen HT, Bertoni AG, Nettleton JA, Bluemke DA, Levitan EB, Burke GL. Dash eating pattern is associated with favorable left ventricular function in the multi-

ethnic study of atherosclerosis. Journal of the American College of Nutrition. 2012;31(6):401-7.

87. Piazza G, Seddighzadeh A, Goldhaber S. Heart failure in patients with deep vein thrombosis. The American journal of cardiology. 2008;101:1056-9.

88. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, 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):2281-329.

89. Kirk JA, Kass DA. Electromechanical dyssynchrony and resynchronization of the failing heart. Circulation research. 2013;113(6):10.1161/CIRCRESAHA.113.300270.

90. Burkhoff D, Sagawa K. Ventricular efficiency predicted by an analytical model. Am J Physiol. 1986;250(6 Pt 2):R1021-7.

91. Schoeller R, Andresen D, Büttner P, Oezcelik K, Vey G, Schröder R. First- or second-degree atrioventricular block as a risk factor in idiopathic dilated cardiomyopathy. The American Journal of Cardiology. 1993;71(8):720-6.

92. Baldasseroni S, Opasich C, Gorini M, Lucci D, Marchionni N, Marini M, et al. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: A report from the italian network on congestive heart failure. Am Heart J. 2002;143(3):398-405.

93. Chakir K, Daya SK, Aiba T, Tunin RS, Dimaano VL, Abraham TP, et al. Mechanisms of enhanced beta-adrenergic reserve from cardiac resynchronization therapy. Circulation. 2009;119(9):1231-40.

94. Rosen BD, Fernandes VRS, Nasir K, Helle-Valle T, Jerosch-Herold M, Bluemke DA, et al. Age, increased left ventricular mass, and lower regional myocardial perfusion are related to greater extent of myocardial dyssynchrony in asymptomatic individuals. The multi-ethnic study of atherosclerosis. Circulation. 2009;120(10):859-66.

95. Nelson GS, Berger RD, Fetics BJ, Talbot M, Spinelli JC, Hare JM, et al. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. Circulation. 2000;102(25):3053-9.

96. Bader H, Garrigue S, Lafitte S, Reuter S, Jais P, Haissaguerre M, et al. Intra-left ventricular electromechanical asynchrony. A new independent predictor of severe cardiac events in heart failure patients. J Am Coll Cardiol. 2004;43(2):248-56.

97. Russell K, Smiseth OA, Gjesdal O, Qvigstad E, Norseng PA, Sjaastad I, et al. Mechanism of prolonged electromechanical delay in late activated myocardium during left bundle branch block. Am J Physiol Heart Circ Physiol. 2011;301(6):H2334-43.

98. Byrne MJ, Helm RH, Daya S, Osman NF, Halperin HR, Berger RD, et al. Diminished left ventricular dyssynchrony and impact of resynchronization in failing hearts with right versus left bundle branch block. J Am Coll Cardiol. 2007;50(15):1484-90.

99. Leyva F, Zegard A, Taylor RJ, Foley PWX, Umar F, Patel K, et al. Long-term outcomes of cardiac resynchronization therapy using apical versus nonapical left ventricular pacing. Journal of the American Heart Association. 2018;7(16):e008508-e.

100. Sundell J, Engblom E, Koistinen J, Ylitalo A, Naum A, Stolen KQ, et al. The effects of cardiac resynchronization therapy on left ventricular function, myocardial energetics, and metabolic reserve in patients with dilated cardiomyopathy and heart failure. J Am Coll Cardiol. 2004;43(6):1027-33.

101. Kyriacou A, Pabari PA, Mayet J, Peters NS, Davies DW, Lim PB, et al. Cardiac resynchronization therapy and av optimization increase myocardial oxygen consumption, but increase cardiac function more than proportionally. Int J Cardiol. 2014;171(2):144-52.

102. Cleland JGF, Daubert J-C, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. New England Journal of Medicine. 2005;352(15):1539-49.

103. Auricchio A, Kloss M, Trautmann SI, Rodner S, Klein H. Exercise performance following cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. Am J Cardiol. 2002;89(2):198-203.

104. Cundrle I, Jr., Johnson BD, Somers VK, Scott CG, Rea RF, Olson LJ. Effect of cardiac resynchronization therapy on pulmonary function in patients with heart failure. The American journal of cardiology. 2013;112(6):838-42.

105. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, et al. Cardiac-resynchronization therapy in heart failure with a narrow qrs complex. New England Journal of Medicine. 2013;369(15):1395-405.

106. Albatat M, Bergsland J, Arevalo H, Odland H, Bose P, Halvorsen P, et al. Technological and clinical challenges in lead placement for cardiac rhythm management devices. Annals of Biomedical Engineering. 2019;48.

107. Stanton T, Hawkins NM, Hogg KJ, Goodfield NER, Petrie MC, McMurray JJV. How should we optimize cardiac resynchronization therapy? European Heart Journal. 2008;29(20):2458-72.

108. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. New England Journal of Medicine. 2002;346(24):1845-53.

109. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. New England Journal of Medicine. 2001;344(12):873-80.

110. Auger D, Hoke U, Bax JJ, Boersma E, Delgado V. Effect of atrioventricular and ventriculoventricular delay optimization on clinical and echocardiographic outcomes of patients treated with cardiac resynchronization therapy: A meta-analysis. Am Heart J. 2013;166(1):20-9.

111. Abraham WT, Gras D, Yu CM, Guzzo L, Gupta MS. Rationale and design of a randomized clinical trial to assess the safety and efficacy of frequent optimization of cardiac resynchronization therapy: The frequent optimization study using the quickopt method (freedom) trial. Am Heart J. 2010;159(6):944-8.e1.

112. Ellenbogen KA, Gold MR, Meyer TE, Fernndez Lozano I, Mittal S, Waggoner AD, et al. Primary results from the smartdelay determined av optimization: A comparison to other av delay methods used in cardiac resynchronization therapy (smart-av) trial: A randomized trial comparing empirical, echocardiography-guided, and algorithmic atrioventricular delay programming in cardiac resynchronization therapy. Circulation. 2010;122(25):2660-8.

113. Daubert C, Behar N, Martins RP, Mabo P, Leclercq C. Avoiding non-responders to cardiac resynchronization therapy: A practical guide. European Heart Journal. 2017;38(19):1463-72.

114. Fornwalt BK, Sprague WW, BeDell P, Suever JD, Gerritse B, Merlino JD, et al. Agreement is poor among current criteria used to define response to cardiac resynchronization therapy. Circulation. 2010;121(18):1985-91.

115. Dickstein K, Bogale N, Priori S, Auricchio A, Cleland JG, Gitt A, et al. The european cardiac resynchronization therapy survey. European Heart Journal. 2009;30(20):2450-60.

116. Healey JS, Hohnloser SH, Exner DV, Birnie DH, Parkash R, Connolly SJ, et al. Cardiac resynchronization therapy in patients with permanent atrial fibrillation: Results from the resynchronization for ambulatory heart failure trial (raft). Circ Heart Fail. 2012;5(5):566-70.

117. Curtis AB, Worley SJ, Chung ES, Li P, Christman SA, St. John Sutton M. Improvement in clinical outcomes with biventricular versus right ventricular pacing: The block hf study. Journal of the American College of Cardiology. 2016;67(18):2148-57.

118. Poole-Wilson PA, Uretsky BF, Thygesen K, Cleland JGF, Massie BM, Rydén L, et al. Mode of death in heart failure: Findings from the atlas trial. Heart. 2003;89(1):42-8.

119. Estep JD, Starling RC, Horstmanshof DA, Milano CA, Selzman CH, Shah KB, et al. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: Results from the roadmap study. Journal of the American College of Cardiology. 2015;66(16):1747-61.

120. Nhs blood & transplant: Annual report on ventricular assist devices. NHS England. 2015.

121. Willey JZ, Gavalas MV, Trinh PN, Yuzefpolskaya M, Reshad Garan A, Levin AP, et al. Outcomes after stroke complicating left ventricular assist device. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2016;35(8):1003-9.

122. Kirklin JK, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, et al. Eighth annual intermacs report: Special focus on framing the impact of adverse events. The Journal of Heart and Lung Transplantation. 2017;36(10):1080-6.

123. Teuteberg JJ, Stewart GC, Jessup M, Kormos RL, Sun B, Frazier O, et al. Implant strategies change over time and impact outcomes: Insights from the intermacs (interagency registry for mechanically assisted circulatory support). JACC: Heart Failure. 2013;1(5):369-78.

124. Pya Y, Maly J, Bekbossynova M, Salov R, Schueler S, Meyns B, et al. First human use of a wireless coplanar energy transfer coupled with a continuous-flow left ventricular assist device. The Journal of Heart and Lung Transplantation. 2019;38(4):339-43.

125. Cheung A, Chorpenning K, Tamez D, Shambaugh C, Jr., Dierlam AE, Taskin ME, et al. Design concepts and preclinical results of a miniaturized heartware platform: The mvad system. Innovations (Phila). 2015;10(3):151-6.

126. Damadian R. Tumor detection by nuclear magnetic resonance. Science. 1971;171(3976):1151-3.

127. Behind the mri: Dr raymond damadian: DR. SHEM DHARAMPAUL; 2015. Available from: https://www.mrimovie.ca/history.html.

128. Magnetic resonance imaging (mri) equipment, operations and planning in the nhs: Report from the clinical imaging board. CIB, 2017.

129. Edelman RR. The history of mr imaging as seen through the pages of radiology. Radiology. 2014;273(2S):S181-S200.

130. Sadeghi-Tarakameh A, DelaBarre L, Lagore RL, Torrado-Carvajal A, Wu X, Grant A, et al. In vivo human head mri at 10.5t: A radiofrequency safety study and preliminary imaging results. Magn Reson Med. 2020;84(1):484-96.

131. Westbrook C, Roth C, Talbot J. Mri in practice. 4th ed: Wiley-Blackwell; 2011.

132. Ladd ME, Bachert P, Meyerspeer M, Moser E, Nagel AM, Norris DG, et al. Pros and cons of ultra-high-field mri/mrs for human application. Progress in Nuclear Magnetic Resonance Spectroscopy. 2018;109:1-50.

133. Westbrook C, Roth CK, Talbot J. Mri in practice. 4th ed: Wiley-Blackwell; 2011. p. 4-11.

134. Prothmann M, von Knobelsdorff-Brenkenhoff F, Töpper A, Dieringer MA, Shahid E, Graessl A, et al. High spatial resolution cardiovascular magnetic resonance at 7.0 tesla in patients with hypertrophic cardiomyopathy – first experiences: Lesson learned from 7.0 tesla. PLoS ONE. 2016;11(2):e0148066.

135. Foley JRJ, Swoboda PP, Fent GJ, Garg P, McDiarmid AK, Ripley DP, et al. Quantitative deformation analysis differentiates ischaemic and non-ischaemic cardiomyopathy: Sub-group analysis of the vindicate trial. European Heart Journal - Cardiovascular Imaging. 2017:jex235-jex.

136. Chavhan GB, Babyn PS, Jankharia BG, Cheng HL, Shroff MM. Steady-state mr imaging sequences: Physics, classification, and clinical applications. Radiographics. 2008;28(4):1147-60.

137. Raphael CE, Vassiliou V, Alpendurada F, Prasad SK, Pennell DJ, Mohiaddin RH. Clinical value of cardiovascular magnetic resonance in patients with mr-conditional pacemakers. Eur Heart J Cardiovasc Imaging. 2016;17(10):1178-85.

138. Walton C, Gergely S, Economides AP. Platinum pacemaker electrodes: Origins and effects of the electrode-tissue interface impedance. Pacing Clin Electrophysiol. 1987;10(1 Pt 1):87-99.

139. Schaefer DJ. Safety aspects of radiofrequency power deposition in magnetic resonance. Magn Reson Imaging Clin N Am. 1998;6(4):775-89.

140. Luechinger R, Zeijlemaker VA, Pedersen EM, Mortensen P, Falk E, Duru F, et al. In vivo heating of pacemaker leads during magnetic resonance imaging. Eur Heart J. 2005;26(4):376-83; discussion 25-7.

141. Langman DA, Goldberg IB, Finn JP, Ennis DB. Pacemaker lead tip heating in abandoned and pacemaker-attached leads at 1.5 tesla mri. J Magn Reson Imaging. 2011;33(2):426-31.

142. Salerno M, Sharif B, Arheden H, Kumar A, Axel L, Li D, et al. Recent advances in cardiovascular magnetic resonance: Techniques and applications. Circ Cardiovasc Imaging. 2017;10(6).

143. Radiology TBIo. Mr safety: Sar and b1+rms. 2016.

144. Lowe MD, Plummer CJ, Manisty CH, Linker NJ. Safe use of mri in people with cardiac implantable electronic devices. Heart. 2015;101(24):1950-3.

145. Roguin A, Schwitter J, Vahlhaus C, Lombardi M, Brugada J, Vardas P, et al. Magnetic resonance imaging in individuals with cardiovascular implantable electronic devices. Europace. 2008;10(3):336-46.

146. Koshy AO, Swoboda PPP, Gierula J, Witte KK. Cardiac magnetic resonance in patients with cardiac resynchronization therapy: Is it time to scan with resynchronization on? Europace. 2019;21(4):554-62.

147. van der Wall EE. Cardiac magnetic resonance: A safe procedure? Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation. 2009;17(10):363-.

148. Mansouri M, Aran S, Harvey HB, Shaqdan KW, Abujudeh HH. Rates of safety incident reporting in mri in a large academic medical center. J Magn Reson Imaging. 2016;43(4):998-1007.

149. Hudson D, Jones AP. A 3-year review of mri safety incidents within a uk independent sector provider of diagnostic services. BJR|Open. 2018;1(1):bjro.20180006.

150. Lupo P, Cappato R, Di Leo G, Secchi F, Papini GDE, Foresti S, 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):2406-16.

151. Nazarian S, Hansford R, Rahsepar AA, Weltin V, McVeigh D, Gucuk Ipek E, et al. Safety of magnetic resonance imaging in patients with cardiac devices. New England Journal of Medicine. 2017;377(26):2555-64.

152. Ching CK, Chakraborty RN, Kler TS, Pumprueg S, Ngarmukos T, Chan JYS, et al. Clinical safety and performance of a mri conditional pacing system in patients undergoing cardiac mri. Pacing Clin Electrophysiol. 2017;40(12):1389-95.

153. Mason S, Osborn JS, Dhar R, Tonkin A, Ethington JD, Le V, et al. Real world mri experience with nonconditional and conditional cardiac rhythm devices after magnasafe. J Cardiovasc Electrophysiol. 2017;28(12):1468-74.

154. Russo RJ, Costa HS, Silva PD, Anderson JL, Arshad A, Biederman RWW, et al. Assessing the risks associated with mri in patients with a pacemaker or defibrillator. New England Journal of Medicine. 2017;376(8):755-64.

155. Schwitter J, Gold MR, Al Fagih A, Lee S, Peterson M, Ciuffo 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).

156. Higgins JV, Watson RE, Jr., Jaffe AS, Dalzell C, Acker N, Felmlee JP, et al. Cardiac troponin t in patients with cardiac implantable electronic devices undergoing magnetic resonance imaging. J Interv Card Electrophysiol. 2016;45(1):91-7.

157. Bailey WM, Mazur A, McCotter C, Woodard PK, Rosenthal L, Johnson W, 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):464-71.

158. Awad K, Griffin J, Crawford TC, Lane Cox S, Ferrick K, Mazur A, 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):2155-61.

159. Shenthar J, Milasinovic G, Al Fagih A, Gotte M, Engel G, Wolff S, et al. Mri scanning in patients with new and existing capsurefix novus 5076 pacemaker leads: Randomized trial results. Heart Rhythm. 2015;12(4):759-65.

160. Friedman HL, Acker N, Dalzell C, Shen WK, Asirvatham SJ, Cha YM, et al. Magnetic resonance imaging in patients with recently implanted pacemakers. Pacing Clin Electrophysiol. 2013;36(9):1090-5.

161. Schwitter J, Kanal E, Schmitt M, Anselme F, Albert T, Hayes DL, 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):864-72.

162. Gimbel JR, Bello D, Schmitt M, Merkely B, Schwitter J, Hayes DL, et al. Randomized trial of pacemaker and lead system for safe scanning at 1.5 tesla. Heart Rhythm. 2013;10(5):685-91.

163. Nazarian S, Hansford R, Roguin A, Goldsher D, Zviman MM, Lardo AC, et al. A prospective evaluation of a protocol for magnetic resonance imaging of patients with implanted cardiac devices. Ann Intern Med. 2011;155(7):415-24.

164. Wilkoff BL, Bello D, Taborsky M, Vymazal J, Kanal E, Heuer H, et al. Magnetic resonance imaging in patients with a pacemaker system designed for the magnetic resonance environment. Heart Rhythm. 2011;8(1):65-73.

165. Strach K, Naehle CP, Muhlsteffen A, Hinz M, Bernstein A, Thomas D, et al. Low-field magnetic resonance imaging: Increased safety for pacemaker patients? Europace. 2010;12(7):952-60.

166. Mollerus M, Albin G, Lipinski M, Lucca J. Magnetic resonance imaging of pacemakers and implantable cardioverter-defibrillators without specific absorption rate restrictions. Europace. 2010;12(7):947-51.

167. Sasaki T, Hansford R, Zviman MM, Kolandaivelu A, Bluemke DA, Berger RD, 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):662-70.

168. Tops LF, Schalij MJ, Bax JJ. The effects of right ventricular apical pacing on ventricular function and dyssynchrony implications for therapy. J Am Coll Cardiol. 2009;54(9):764-76.

169. Verma A, Kumar I, Verma N, Aggarwal P, Ojha R. Magnetic resonance spectroscopy — revisiting the biochemical and molecular milieu of brain tumors. BBA Clinical. 2016;5:170-8.

170. Wade L, Simek J. Organic chemistry. Ninth ed: Pearson; 2016.

171. Harwood L, Moody C, Percy J. Experimental organic chemistry. UK: Blackwell Science Limited; 2003.

172. Tognarelli JM, Dawood M, Shariff MIF, Grover VPB, Crossey MME, Cox IJ, et al. Magnetic resonance spectroscopy: Principles and techniques: Lessons for clinicians. Journal of clinical and experimental hepatology. 2015;5(4):320-8.

173. Ulmer S, Backens M, Ahlhelm FJ. Basic principles and clinical applications of magnetic resonance spectroscopy in neuroradiology. J Comput Assist Tomogr. 2016;40(1):1-13.

174. Cohn M, Hughes TR, Jr. Phosphorus magnetic resonance spectra of adenosine di- and triphosphate. I. Effect of ph. J Biol Chem. 1960;235:3250-3.

175. Ackerman JJ, Grove TH, Wong GG, Gadian DG, Radda GK. Mapping of metabolites in whole animals by 31p nmr using surface coils. Nature. 1980;283(5743):167-70.

176. Öz G, Alger JR, Barker PB, Bartha R, Bizzi A, Boesch C, et al. Clinical proton mr spectroscopy in central nervous system disorders. Radiology. 2014;270(3):658-79.

177. Faller KME, Lygate CA, Neubauer S, Schneider JE. (1)h-mr spectroscopy for analysis of cardiac lipid and creatine metabolism. Heart failure reviews. 2013;18(5):657-68.

178. Ellis J, Valkovič L, Purvis LAB, Clarke WT, Rodgers CT. Reproducibility of human cardiac phosphorus mrs ((31) p-mrs) at 7 t. NMR in biomedicine. 2019;32(6):e4095-e.

179. Harris RK, Wasylishen R. The encyclopedia of magnetic resonance: Wiley; 2012.

180. Wallimann T, Wyss M, Brdiczka D, Nicolay K, Eppenberger HM. Intracellular compartmentation, structure and function of creatine kinase isoenzymes in tissues with high and fluctuating energy demands: The 'phosphocreatine circuit' for cellular energy homeostasis. The Biochemical journal. 1992;281 ( Pt 1)(Pt 1):21-40.

181. Gudbjarnason S, Mathes P, Ravens KG. Functional compartmentation of atp and creatine phosphate in heart muscle. J Mol Cell Cardiol. 1970;1(3):325-39.

182. Doorey A, Barry W. The effects of inhibition of oxidative phosphorylation and glycolysis in cultured chick heart cells. Circ Res. 1983;53:192-201.

183. Ingwall JS. Atp and the heart: Springer Science & Business Media; 2002.

184. Suga H. Ventricular energetics. Physiological reviews. 1990;70(2):247-77.

185. Chacko VP, Aresta F, Chacko SM, Weiss RG. Mri/mrs assessment of in vivo murine cardiac metabolism, morphology, and function at physiological heart rates. Am J Physiol Heart Circ Physiol. 2000;279(5):H2218-24.

186. Menon RS, Hendrich K, Hu X, Uğurbil K. 31p nmr spectroscopy of the human heart at 4 t: Detection of substantially uncontaminated cardiac spectra and differentiation of subepicardium and subendocardium. Magn Reson Med. 1992;26(2):368-76.

187. Neubauer S, Krahe T, Schindler R, Horn M, Hillenbrand H, Entzeroth C, et al. 31p magnetic resonance spectroscopy in dilated cardiomyopathy and coronary artery disease. Altered cardiac high-energy phosphate metabolism in heart failure. Circulation. 1992;86(6):1810-8.

188. Neubauer S, Horn M, Pabst T, Gödde M, Lübke D, Jilling B, et al. Contributions of 31p-magnetic resonance spectroscopy to the understanding of dilated heart muscle disease. European Heart Journal. 1995;16(suppl_O):115-8.

189. Hardy CJ, Weiss RG, Bottomley PA, Gerstenblith G. Altered myocardial high-energy phosphate metabolites in patients with dilated cardiomyopathy. Am Heart J. 1991;122(3 Pt 1):795-801.

190. Ingwall JS. Adaptive and maladaptive processes: Is cardiac failure a consequence of decreased energy reserve? Circulation. 1993;87(6S):58-62.

191. Zweier JL, Jacobus WE. Bioenergetic consequences of cardiac phosphocreatine depletion induced by creatine analogue feedin. The Journal of Biological Chemistry. 1991;266(30):20296-304.

192. Neubauer S, Horn M, Cramer M, Harre K, Newell John B, Peters W, et al. Myocardial phosphocreatine-to-atp ratio is a predictor of mortality in patients with dilated cardiomyopathy. Circulation. 1997;96(7):2190-6.

193. Hudsmith LE, Neubauer S. Magnetic resonance spectroscopy in myocardial disease. JACC Cardiovasc Imaging. 2009;2(1):87-96.

194. Haddadin IS, McIntosh A, Meisamy S, Corum C, Styczynski Snyder AL, Powell NJ, et al. Metabolite quantification and high-field mrs in breast cancer. NMR Biomed. 2009;22(1):65-76.

195. Kreis R. Issues of spectral quality in clinical 1h-magnetic resonance spectroscopy and a gallery of artifacts. NMR Biomed. 2004;17(6):361-81.

196. Maudsley AA, Hilal SK, Perman WH, Simon HE. Spatially resolved high resolution spectroscopy by “four-dimensional” nmr. Journal of Magnetic Resonance (1969). 1983;51(1):147-52.

197. Ordidge RJ, Connelly A, Lohman JA. Image-selected in vivo spectroscopy (isis). A new technique for spatially selective nmr spectroscopy. Journal of Magnetic Resonance (1969). 1986;66(2):283-94.

198. Pohmann R, von Kienlin M. Accurate phosphorus metabolite images of the human heart by 3d acquisition-weighted csi. Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine. 2001;45(5):817-26.

199. Liu Y, Gu Y, Yu X. Assessing tissue metabolism by phosphorous-31 magnetic resonance spectroscopy and imaging: A methodology review. Quantitative imaging in medicine and surgery. 2017;7(6):707-26.

200. McGavock JM, Lingvay I, Zib I, Tillery T, Salas N, Unger R, et al. Cardiac steatosis in diabetes mellitus: A 1h-magnetic resonance spectroscopy study. Circulation. 2007;116(10):1170-5.

201. Wilson J, Fink L, Maris J, Ferraro N, Power-Vanwart J, Eleff S, et al. Evaluation of energy metabolism in skeletal muscle of patients with heart failure with gated 31 -phosphorus nuclear magnetic resonance. Circulation. 1985;71(57).

202. Wiener DH, Fink LI, Maris J, Jones RA, Chance B, Wilson JR. Abnormal skeletal muscle bioenergetics during exercise in patients with heart failure: Role of reduced muscle blood flow. Circulation. 1986;73(6):1127-36.

203. Mancini DM, Coyle E, Coggan A, Beltz J, Ferraro N, Montain S, et al. Contribution of intrinsic skeletal muscle changes to 31p nmr skeletal muscle metabolic abnormalities in patients with chronic heart failure. Circulation. 1989;80(5):1338-46.

204. Mancini DM, Walter G, Reichek N, Lenkinski R, McCully KK, Mullen JL, et al. Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. Circulation. 1992;85(4):1364-73.

205. Coats AJ. The "muscle hypothesis" of chronic heart failure. J Mol Cell Cardiol. 1996;28(11):2255-62.

206. Weiss RG, Gerstenblith G, Bottomley PA. Atp flux through creatine kinase in the normal, stressed, and failing human heart. Proc Natl Acad Sci U S A. 2005;102(3):808-13.

207. Starling RC, Hammer DF, Altschuld RA. Human myocardial atp content and in vivo contractile function. Molecular and Cellular Biochemistry. 1998;180(1):171-7.

208. Nascimben L, Ingwall JS, Pauletto P, Friedrich J, Gwathmey JK, Saks V, et al. Creatine kinase system in failing and nonfailing human myocardium. Circulation. 1996;94(8):1894-901.

209. Ingwall JS. Adaptive and maladaptive processes: Is cardiac failure a consequence of decreased energy reserve? Circulation. 1993;87(6S).

210. Minotti JR, Johnson EC, Hudson TL, Zuroske G, Murata G, Fukushima E, et al. Skeletal muscle response to exercise training in congestive heart failure. J Clin Invest. 1990;86(3):751-8.

211. Layec G, Haseler LJ, Richardson RS. The effect of higher atp cost of contraction on the metabolic response to graded exercise in patients with chronic obstructive pulmonary disease. Journal of applied physiology (Bethesda, Md : 1985). 2012;112(6):1041-8.

212. Cohen-Solal A, Laperche T, Morvan D, Geneves M, Caviezel B, Gourgon R. Prolonged kinetics of recovery of oxygen consumption after maximal graded exercise in patients with chronic heart failure. Circulation. 1995;91(12):2924-32.

213. Chati Z, Zannad F, Jeandel C, Lherbier B, Escanye J-M, Robert J, et al. Physical deconditioning may be a mechanism for the skeletal muscle energy

phosphate metabolism abnormalities in chronic heart failure. American Heart Journal. 1996;131(3):560-6.

214. Melenovsky V, Hlavata K, Sedivy P, Dezortova M, Borlaug BA, Petrak J, et al. Skeletal muscle abnormalities and iron deficiency in chronic heart failure. Circulation: Heart Failure. 2018;11(9):e004800.

215. van der Ent M, Jeneson JA, Remme WJ, Berger R, Ciampricotti R, Visser F. A non-invasive selective assessment of type i fibre mitochondrial function using 31p nmr spectroscopy. Evidence for impaired oxidative phosphorylation rate in skeletal muscle in patients with chronic heart failure. Eur Heart J. 1998;19(1):124-31.

216. Nanbu T, Nakakoshi T, Yonezawa K, Kitabatake A. Myocardial high-energy phosphate metabolism in patients with stable chronic dilated cardiomyopathy under a dobutamine-induced prolonged mild workload. Am Heart J. 1999;138(4 Pt 1):641-5.

217. Ross J, Miura T, Kambayashi M, Eising GP, Ryu K-H. Adrenergic control of the force-frequency relation. Circulation. 1995;92(8):2327-32.

218. Bowditch H. Uber die eigentümlichkeiten der reizbarkeit, welche die muskelfasern des herzens zeigen. Berichte Ober die Verhandlungen der k6nighch s~ chsischen Gesellschaft der Wissenschaften zu Leipzig Mathemat-Phys Classe. 1871;23:652-589.

219. Frank KF, Bölck B, Erdmann E, Schwinger RHG. Sarcoplasmic reticulum ca2+-atpase modulates cardiac contraction and relaxation. Cardiovascular Research. 2003;57(1):20-7.

220. Puglisi JL, Negroni JA, Chen-Izu Y, Bers DM. The force-frequency relationship: Insights from mathematical modeling. Adv Physiol Educ. 2013;37(1):28-34.

221. MacLennan DH, Kranias EG. Phospholamban: A crucial regulator of cardiac contractility. Nature Reviews Molecular Cell Biology. 2003;4(7):566-77.

222. Puglisi JL, Negroni JA, Chen-Izu Y, Bers DM. The force-frequency relationship: Insights from mathematical modeling. Advances in physiology education. 2013;37(1):28-34.

223. Chapman JB, Gibbs CL, Gibson WR. Effects of calcium and sodium on cardiac contractility and heat production in rabbit papillary muscle. Circulation Research. 1970;27(4):601-10.

224. Mulieri LA, Leavitt BJ, Wright RK, Alpert NR. Role of camp in modulating relaxation kinetics and the force-frequency relation in mitral regurgitation heart failure. Basic Res Cardiol. 1997;92 Suppl 1:95-103.

225. Li GR, Yang B, Feng J, Bosch RF, Carrier M, Nattel S. Transmembrane ica contributes to rate-dependent changes of action potentials in human ventricular myocytes. Am J Physiol. 1999;276(1):H98-h106.

226. Sipido KR, Stankovicova T, Flameng W, Vanhaecke J, Verdonck F. Frequency dependence of ca2+ release from the sarcoplasmic reticulum in human ventricular myocytes from end-stage heart failure. Cardiovascular Research. 1998;37(2):478-88.

227. Matsubara I, Yagi N, Endoh M. Behaviour of myosin projections during the staircase phenomenon of heart muscle. Nature. 1978;273(5657):67.

228. Levy RL, White PD, Stroud WD, Hillman CC. Transient tachycardia: Prognostic significance alone and in association with transient hypertension. Journal of the American Medical Association. 1945;129(9):585-8.

229. Zhang D, Shen X, Qi X. Resting heart rate and all-cause and cardiovascular mortality in the general population: A meta-analysis. Canadian Medical Association Journal. 2016;188(3):E53-E63.

230. Seccareccia F, Pannozzo F, Dima F, Minoprio A, Menditto A, Lo Noce C, et al. Heart rate as a predictor of mortality: The matiss project. American journal of public health. 2001;91(8):1258-63.

231. Vazir A, Claggett B, Jhund P, Castagno D, Skali H, Yusuf S, et al. Prognostic importance of temporal changes in resting heart rate in heart failure patients: An analysis of the charm program. European Heart Journal. 2014;36(11):669-75.

232. Benschop RJ, Nieuwenhuis E, Tromp E, Godaert G, Ballieux RE, Van Doornen L. Effects of beta-adrenergic blockade on immunologic and cardiovascular changes induced by mental stress. Circulation. 1994;89(2):762-9.

233. Shigetoh Y, Adachi H, Yamagishi S-i, Enomoto M, Fukami A, Otsuka M, et al. Higher heart rate may predispose to obesity and diabetes mellitus: 20-year prospective study in a general population. American journal of hypertension. 2009;22(2):151-5.

234. Carnethon MR, Yan L, Greenland P, Garside DB, Dyer AR, Metzger B, et al. Resting heart rate in middle age and diabetes development in older age. Diabetes care. 2008;31(2):335-9.

235. Kemp CD, Conte JV. The pathophysiology of heart failure. Cardiovascular Pathology. 2012;21(5):365-71.

236. Balcazar D, Regge V, Santalla M, Meyer H, Paululat A, Mattiazzi A, et al. Serca is critical to control the bowditch effect in the heart. Scientific reports. 2018;8(1):12447-.

237. Hasenfuss G, Reinecke H, Studer R, Meyer M, Pieske B, Holtz J, et al. Relation between myocardial function and expression of sarcoplasmic reticulum ca(2+)-atpase in failing and nonfailing human myocardium. Circ Res. 1994;75(3):434-42.

238. Alpert NR, Leavitt BJ, Ittleman FP, Hasenfuss G, Pieske B, Mulieri LA. A mechanistic analysis of the force-frequency relation in non-failing and progressively failing human myocardium. Basic Research in Cardiology. 1998;93(1):s023-s32.

239. Santulli G, Lewis DR, Marks AR. Physiology and pathophysiology of excitation-contraction coupling: The functional role of ryanodine receptor. Journal of muscle research and cell motility. 2017;38(1):37-45.

240. Arai M, Alpert NR, MacLennan DH, Barton P, Periasamy M. Alterations in sarcoplasmic reticulum gene expression in human heart failure. A possible mechanism for alterations in systolic and diastolic properties of the failing myocardium. Circ Res. 1993;72(2):463-9.

241. Tadic M, Cuspidi C. Sympathetic overdrive in heart failure: What we can do? Int J Cardiol. 2020;321:126-7.

242. Fisher SA, Buttrick PM, Sukovich D, Periasamy M. Characterization of promoter elements of the rabbit cardiac sarcoplasmic reticulum ca(2+)-atpase gene required for expression in cardiac muscle cells. Circulation Research. 1993;73(4):622-8.

243. Reiken S, Wehrens XH, Vest JA, Barbone A, Klotz S, Mancini D, et al. B-blockers restore calcium release channel function and improve cardiac muscle performance in human heart failure. Circulation. 2003;107(19):2459-66.

244. Bristow MR, Minobe W, Rasmussen R, Larrabee P, Skerl L, Klein JW, et al. Beta-adrenergic neuroeffector abnormalities in the failing human heart are produced by local rather than systemic mechanisms. J Clin Invest. 1992;89(3):803-15.

245. Bouras G, Giannopoulos G, Hatzis G, Alexopoulos D, Leventopoulos G, Deftereos S. Inflammation and chronic heart failure: From biomarkers to novel anti-inflammatory therapeutic strategies. Medicinal chemistry. 2014;10(7):682-99.

246. Luo W, Wolska BM, Grupp IL, Harrer JM, Haghighi K, Ferguson DG, et al. Phospholamban gene dosage effects in the mammalian heart. Circ Res. 1996;78(5):839-47.

247. Movsesian MA, Karimi M, Green K, Jones LR. Ca(2+)-transporting atpase, phospholamban, and calsequestrin levels in nonfailing and failing human myocardium. Circulation. 1994;90(2):653-7.

248. Solaro RJ, Rarick HM. Troponin and tropomyosin: Proteins that switch on and tune in the activity of cardiac myofilaments. Circulation research. 1998;83(5):471-80.

249. Holroyde M, Howe E, Solaro R. Modification of calcium requirement for activation of cardiac myofibrillar atpase by cyclic amp dependent phosphorylation. Biochimica et Biophysica Acta (BBA)-General Subjects. 1979;586(1):63-9.

250. Takimoto E, Soergel DG, Janssen PML, Stull LB, Kass DA, Murphy AM. Frequency- and afterload-dependent cardiac modulation in vivo by troponin i with constitutively active protein kinase a phosphorylation sites. Circulation Research. 2004;94(4):496-504.

251. Strang KT, Sweitzer NK, Greaser ML, Moss RL. Beta-adrenergic receptor stimulation increases unloaded shortening velocity of skinned single ventricular myocytes from rats. Circulation research. 1994;74(3):542-9.

252. Zhang R, Zhao J, Mandveno A, Potter JD. Cardiac troponin i phosphorylation increases the rate of cardiac muscle relaxation. Circulation research. 1995;76(6):1028-35.

253. Zakhary DR, Moravec CS, Stewart RW, Bond M. Protein kinase a (pka)-dependent troponin-i phosphorylation and pka regulatory subunits are decreased in human dilated cardiomyopathy. Circulation. 1999;99(4):505-10.

254. Bodor GS, Oakeley AE, Allen PD, Crimmins DL, Ladenson JH, Anderson PA. Troponin i phosphorylation in the normal and failing adult human heart. Circulation. 1997;96(5):1495-500.

255. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the

european society of intensive care medicine. Intensive Care Med. 2014;40(12):1795-815.

256. Little WC, Cheng CP. Effect of exercise on left ventricular-arterial coupling assessed in the pressure-volume plane. American Journal of Physiology-Heart and Circulatory Physiology. 1993;264(5):H1629-H33.

257. Suga H, Sagawa K. Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. Circulation Research. 1974;35(1):117-26.

258. Robotham JL, Takata M, Berman M, Harasawa Y. Ejection fraction revisited. Anesthesiology. 1991;74(1):172-83.

259. Boissier F, Razazi K, Seemann A, Bedet A, Thille AW, de Prost N, et al. Left ventricular systolic dysfunction during septic shock: The role of loading conditions. Intensive Care Med. 2017;43(5):633-42.

260. Nutter D. Measuring and recording systemic blood pressure. In: Hurst J, Logue R, Schlant R, Wenger N, editors. The heart. 4th ed. New York: McGraw-Hill; 1978. p. 220-2.

261. Colonna P, Montisci R, Galiuto L, Meloni L, Iliceto S. Effects of acute myocardial ischemia on intramyocardial contraction heterogeneity. Circulation. 1999;100(17):1770-6.

262. Higginbotham MB, Morris KG, Williams RS, McHale PA, Coleman RE, Cobb FR. Regulation of stroke volume during submaximal and maximal upright exercise in normal man. Circ Res. 1986;58(2):281-91.

263. Kambayashi M, Miura T, Oh BH, Rockman HA, Murata K, Ross J. Enhancement of the force-frequency effect on myocardial contractility by adrenergic stimulation in conscious dogs. Circulation. 1992;86(2):572-80.

264. Rang HP, Dale MM, Flower RJ, Henderson G. Rang and dale's pharmacology. 8th ed. UK: Elsevier Churchill Livingstone; 2016.

265. Miura T, Miyazaki S, Guth BD, Kambayashi M, Ross J. Influence of the force-frequency relation on left ventricular function during exercise in conscious dogs. Circulation. 1992;86(2):563-71.

266. Indolfi C, Guth BD, Miura T, Miyazaki S, Schulz R, Ross Jr J. Mechanisms of improved ischemic regional dysfunction by bradycardia. Studies on ul-fs 49 in swine. Circulation. 1989;80(4):983-93.

267. Wang Z, Lam CF, Mukherjee R, Hebbar L, Wang Y, Spinale FG. Relationship between external load and isolated myocyte contractile function with chf in pigs. Am J Physiol. 1997;273(1 Pt 2):H183-91.

268. Ginzton LE, Laks MM, Brizendine M, Conant R, Mena I. Noninvasive measurement of the rest and exercise peak systolic pressure/end-systolic volume ratio: A sensitive two-dimensional echocardiographic indicator of left ventricular function. Journal of the American College of Cardiology. 1984;4(3):509-16.

269. Bombardini T, Correia MJ, Cicerone C, Agricola E, Ripoli A, Picano E. Force-frequency relationship in the echocardiography laboratory: A noninvasive assessment of bowditch treppe? Journal of the American Society of Echocardiography. 2003;16(6):646-55.

270. Bombardini T, Agrusta M, Natsvlishvili N, Solimene F, Pap R, Coltorti F, et al. Noninvasive assessment of left ventricular contractility by pacemaker stress echocardiography. Eur J Heart Fail. 2005;7(2):173-81.

271. Esfandiari S, Fuchs F, Wainstein RV, Chelvanathan A, Mitoff P, Sasson Z, et al. Heart rate-dependent left ventricular diastolic function in patients with and without heart failure. J Card Fail. 2015;21(1):68-75.

272. Gierula J, Paton MF, Lowry JE, Jamil HA, Byrom R, Drozd M, et al. Rate-response programming tailored to the force-frequency relationship improves exercise tolerance in chronic heart failure. JACC: Heart Failure. 2018;6(2):105-13.

273. Lund LH, Svennblad B, Dahlström U, Ståhlberg M. Effect of expanding evidence and evolving clinical guidelines on the prevalence of indication for cardiac resynchronization therapy in patients with heart failure. European Journal of Heart Failure. 2018;20(4):769-77.

274. Fontaine JM, Mohamed FB, Gottlieb C, Callans DJ, Marchlinski FE. Rapid ventricular pacing in a pacemaker patient undergoing magnetic resonance imaging. Pacing and Clinical Electrophysiology. 1998;21(6):1336-9.

275. Muthalaly RG, Nerlekar N, Ge Y, Kwong RY, Nasis A. Mri in patients with cardiac implantable electronic devices. Radiology. 2018;289(2):281-92.

276. Shurrab M, Kaoutskaia A, Baranchuk A, Lau C, Singarajah T, Lashevsky I, et al. Are there increased periprocedural complications with the mri-conditional medtronic revo surescan pacing system? : A meta-analysis. Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation. 2018;26(5):233-9.

277. Indik JH, Gimbel JR, Abe H, Alkmim-Teixeira R, Birgersdotter-Green U, Clarke GD, 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):e97-e153.

278. Medtronic. Attain performa mri surescan lead 2015. Available from: http://www.medtronic.me/content/dam/medtronic-com/01_crhf/hf/spec-sheets/uc201602593en-attain-performa-4598-spec-sheet.pdf.

279. Nelesen R, Dar Y, Thomas K, Dimsdale JE. The relationship between fatigue and cardiac functioning. Archives of internal medicine. 2008;168(9):943-9.

280. Cross R, Olivieri L, O'Brien K, Kellman P, Xue H, Hansen M. Improved workflow for quantification of left ventricular volumes and mass using free-breathing motion corrected cine imaging. Journal of Cardiovascular Magnetic Resonance. 2016;18(1):10.

281. Kellman P, Chefd'hotel C, Lorenz CH, Mancini C, Arai AE, McVeigh ER. High spatial and temporal resolution cardiac cine mri from retrospective reconstruction of data acquired in real time using motion correction and resorting. Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine. 2009;62(6):1557-64.

282. Shah AD, Morris MA, Hirsh DS, Warnock M, Huang Y, Mollerus M, et al. Magnetic resonance imaging safety in nonconditional pacemaker and defibrillator recipients: A meta-analysis and systematic review. Heart Rhythm. 2018;15(7):1001-8.

283. Seewöster T, Löbe S, Hilbert S, Bollmann A, Sommer P, Lindemann F, et al. Cardiovascular magnetic resonance imaging in patients with cardiac implantable electronic devices: Best practice and real-world experience. Europace. 2019;21(8):1220-8.

284. Yap JC, Moore DM, Cleland JG, Pride NB. Effect of supine posture on respiratory mechanics in chronic left ventricular failure. Am J Respir Crit Care Med. 2000;162(4 Pt 1):1285-91.

285. Ceridon ML, Morris NR, Olson TP, Lalande S, Johnson BD. Effect of supine posture on airway blood flow and pulmonary function in stable heart failure. Respiratory physiology & neurobiology. 2011;178(2):269-74.

286. Antoniou C-K, Manolakou P, Magkas N, Konstantinou K, Chrysohoou C, Dilaveris P, et al. Cardiac resynchronisation therapy and cellular bioenergetics: Effects beyond chamber mechanics. European cardiology. 2019;14(1):33-44.

287. Board TBCSatCI. Mri for patients with pacemakers and implantable cardioverter-defibrillators—mri-conditional and legacy devices. 2018.

288. Jo Y, Kim J, Park CH, Lee JW, Hur JH, Yang DH, et al. Guideline for cardiovascular magnetic resonance imaging from the korean society of cardiovascular imaging-part 1: Standardized protocol. Korean journal of radiology. 2019;20(9):1313-33.

289. Zange L, Muehlberg F, Blaszczyk E, Schwenke S, Traber J, Funk S, et al. Quantification in cardiovascular magnetic resonance: Agreement of software from three different vendors on assessment of left ventricular function, 2d flow and parametric mapping. Journal of Cardiovascular Magnetic Resonance. 2019;21(1):12.

290. McDiarmid AK, Swoboda PP, Erhayiem B, Lancaster RE, Lyall GK, Broadbent DA, et al. Athletic cardiac adaptation in males is a consequence of elevated myocyte mass. Circulation Cardiovascular imaging. 2016;9(4):e003579-e.

291. NICOR. National heart failure audit (nhfa) - summary report. 2020.

292. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, et al. Temporal trends and patterns in heart failure incidence: A population-based study of 4 million individuals. The Lancet. 2018;391(10120):572-80.

293. Ricci DR, Orlick AE, Alderman EL, Ingels NB, Daughters GT, Stinson EB. Influence of heart rate on left ventricular ejection fraction in human beings. The American Journal of Cardiology. 1979;44(3):447-51.

294. Claessen G, Schnell F, Bogaert J, Claeys M, Pattyn N, De Buck F, et al. Exercise cardiac magnetic resonance to differentiate athlete's heart from structural heart disease. Eur Heart J Cardiovasc Imaging. 2018;19(9):1062-70.

295. Occhetta E, Bortnik M, Marino P, Corbucci G, Pedrigi C, Droste HT, et al. Do electrical parameters of the cardiac cycle reflect the corresponding mechanical intervals as the heart rate changes? EP Europace. 2010;12(6):830-4.

296. Gohl K, Perl S, Wortmann A, Bachmann K. Ventricular performance in relation to heart rate and av delay at rest. Eur Heart J. 1992;13 Suppl E:91-8.

297. McLaughlin PR, Kleiman JH, Martin RP, Doherty PW, Reitz B, Stinson EB, et al. The effect of exercise and atrial pacing on left ventricular volume and contractility

in patients with innervated and denervated hearts. Circulation. 1978;58(3 Pt 1):476-83.

298. Erbel R, Schweizer P, Krebs W, Langen HJ, Meyer J, Effert S. Effects of heart rate changes on left ventricular volume and ejection fraction: A 2-dimensional echocardiographic study. Am J Cardiol. 1984;53(4):590-7.

299. Piérard LA, Serruys PW, Roelandt J, Meltzer RS. Left ventricular function at similar heart rates during tachycardia induced by exercise and atrial pacing: An echocardiographic study. British heart journal. 1987;57(2):154-60.

300. Klabunde RE. Cardiovascular physiology concepts. Second ed. Baltimore: Lippincott Williams & Wilkins; 2012.

301. Kjellberg SR, Rudhe U, Sjostrand T. The amount of hemoglobin (blood volume) in relation to the pulse rate and heart volume during work. Acta Physiologica Scandinavica. 1949;19(2-3):152-69.

302. Harrison DC, Goldblatt A, Braunwald E, Glick G, Mason DT. Studies on cardiac dimensions in intact, unanesthetized man. Circulation Research. 1963;13(5):448-67.

303. Sonnenblick EH, Braunwald E, Williams JF, Jr., Glick G. Effects of exercise on myocardial force-velocity relations in intact unanesthetized man: Relative roles of changes in heart rate, sympathetic activity, and ventricular dimensions. The Journal of clinical investigation. 1965;44(12):2051-62.

304. Brauwald E. An analysis of cardiac response to exercise. Circ Res. 1967;20:45-58.

305. Vatner SF, Franklin D, Higgins CB, Patrick T, Braunwald E. Left ventricular response to severe exertion in untethered dogs. The Journal of clinical investigation. 1972;51(12):3052-60.

306. Hai OY, Mentz RJ, Zannad F, Gasparini M, De Ferrari GM, Daubert J-C, et al. Cardiac resynchronization therapy in heart failure patients with less severe left ventricular dysfunction. European Journal of Heart Failure. 2015;17(2):135-43.

307. Abraham WT, Hayes DL. Cardiac resynchronization therapy for heart failure. Circulation. 2003;108(21):2596-603.

308. Miyai N, Arita M, Miyashita K, Morioka I, Shiraishi T, Nishio I. Blood pressure response to heart rate during exercise test and risk of future hypertension. Hypertension. 2002;39(3):761-6.

309. Kenny J, Plappert T, Doubilet P, Salzman D, Sutton MG. Effects of heart rate on ventricular size, stroke volume, and output in the normal human fetus: A prospective doppler echocardiographic study. Circulation. 1987;76(1):52-8.

310. McArdle W, Katch F, Katch V. Exercise physiology: Energy, nutrition and human performance. Linppincott. Williams & Wilkins; 2003.

311. Rodeheffer RJ, Gerstenblith G, Becker LC, Fleg JL, Weisfeldt ML, Lakatta EG. Exercise cardiac output is maintained with advancing age in healthy human subjects: Cardiac dilatation and increased stroke volume compensate for a diminished heart rate. Circulation. 1984;69(2):203-13.

312. Mertens HM, Mannebach H, Trieb G, Gleichmann U. Influence of heart rate on systolic time intervals: Effects of atrial pacing versus dynamic exercise. Clinical Cardiology. 1981;4(1):22-7.

313. Hamdan MH, Barbera S, Kowal RC, Page RL, Ramaswamy K, Joglar JA, et al. Effects of resynchronization therapy on sympathetic activity in patients with depressed ejection fraction and intraventricular conduction delay due to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 2002;89(9):1047-51.

314. DeVecchi F, Facchini E, Degiovanni A, Sartori C, Cavallino C, Santagostino M, et al. Acute contractile recovery extent during biventricular pacing is not associated with follow-up in patients undergoing resynchronization. International journal of cardiology Heart & vasculature. 2016;11:66-73.

315. Vollmann D, Lüthje L, Schott P, Hasenfuss G, Unterberg-Buchwald C. Biventricular pacing improves the blunted force–frequency relation present during univentricular pacing in patients with heart failure and conduction delay. Circulation. 2006;113(7):953-9.

316. Hay I, Melenovsky V, Fetics BJ, Judge DP, Kramer A, Spinelli J, et al. Short-term effects of right-left heart sequential cardiac resynchronization in patients with heart failure, chronic atrial fibrillation, and atrioventricular nodal block. Circulation. 2004;110(22):3404-10.

317. Bordachar P, Lafitte S, Reuter S, Garrigue S, Sanders P, Roudaut R, et al. Biventricular pacing and left ventricular pacing in heart failure: Similar hemodynamic improvement despite marked electromechanical differences. Journal of cardiovascular electrophysiology. 2004;15(12):1342-7.

318. Leclercq C, Faris O, Tunin R, Johnson J, Kato R, Evans F, et al. Systolic improvement and mechanical resynchronization does not require electrical synchrony in the dilated failing heart with left bundle-branch block. Circulation. 2002;106(14):1760-3.

319. Saffitz JE, Kléber AG. Effects of mechanical forces and mediators of hypertrophy on remodeling of gap junctions in the heart. Circulation Research. 2004;94(5):585-91.

320. Akar FG, Spragg DD, Tunin RS, Kass DA, Tomaselli GF. Mechanisms underlying conduction slowing and arrhythmogenesis in nonischemic dilated cardiomyopathy. Circulation Research. 2004;95(7):717-25.

321. Ukkonen H, Beanlands RSB, Burwash IG, Kemp RAd, Nahmias C, Fallen E, et al. Effect of cardiac resynchronization on myocardial efficiency and regional oxidative metabolism. Circulation. 2003;107(1):28-31.

322. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, et al. Effect of oral milrinone on mortality in severe chronic heart failure. New England Journal of Medicine. 1991;325(21):1468-75.

323. O'Connor CM, Gattis WA, Uretsky BF, Adams Jr KF, McNulty SE, Grossman SH, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: Insights from the flolan international randomized survival trial (first). American heart journal. 1999;138(1):78-86.

324. Sawyer DB, Colucci WS. Mitochondrial oxidative stress in heart failure: “Oxygen wastage” revisited. Am Heart Assoc; 2000.

325. Cikes M, Solomon SD. Beyond ejection fraction: An integrative approach for assessment of cardiac structure and function in heart failure. Eur Heart J. 2016;37(21):1642-50.

326. Steendijk P, Tulner SA, Bax JJ, Oemrawsingh PV, Bleeker GB, van Erven L, et al. Hemodynamic effects of long-term cardiac resynchronization therapy: Analysis by pressure-volume loops. Circulation. 2006;113(10):1295-304.

327. Linde C, Leclercq C, Rex S, Garrigue S, Lavergne T, Cazeau S, et al. Long-term benefits of biventricular pacing in congestive heart failure: Results from the multisite stimulation in cardiomyopathy (mustic) study. J Am Coll Cardiol. 2002;40(1):111-8.

328. Molhoek SG, Bax JJ, van Erven L, Bootsma M, Boersma E, Steendijk P, et al. Comparison of benefits from cardiac resynchronization therapy in patients with ischemic cardiomyopathy versus idiopathic dilated cardiomyopathy. Am J Cardiol. 2004;93(7):860-3.

329. Sutton MSJ, Keane MG. Reverse remodelling in heart failure with cardiac resynchronisation therapy. Heart (British Cardiac Society). 2007;93(2):167-71.

330. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. New England Journal of Medicine. 2002;346(24):1845-53.

331. Hamdan MH, Zagrodzky JD, Joglar JA, Sheehan CJ, Ramaswamy K, Erdner JF, et al. Biventricular pacing decreases sympathetic activity compared with right ventricular pacing in patients with depressed ejection fraction. Circulation. 2000;102(9):1027-32.

332. Adamson PB, Kleckner KJ, VanHout WL, Srinivasan S, Abraham WT. Cardiac resynchronization therapy improves heart rate variability in patients with symptomatic heart failure. Circulation. 2003;108(3):266-9.

333. Grassi G, Vincenti A, Brambilla R, Trevano FQ, Dell'Oro R, Cirò A, et al. Sustained sympathoinhibitory effects of cardiac resynchronization therapy in severe heart failure. Hypertension. 2004;44(5):727-31.

334. Najem B, Preumont N, Unger P, Jansens J-L, Houssière A, Ciarka A, et al. Sympathetic nerve activity after thoracoscopic cardiac resynchronization therapy in congestive heart failure. Journal of Cardiac Failure. 2005;11(7):529-33.

335. Cha Y-M, Chareonthaitawee P, Dong Y-X, Kemp BJ, Oh JK, Miyazaki C, et al. Cardiac sympathetic reserve and response to cardiac resynchronization therapy. Circulation: Heart Failure. 2011;4(3):339-44.

336. Ståhlberg M, Sander M, Mortensen L, Linde C, Braunschweig F. Increase in paced heart rate reduces muscle sympathetic nerve activity in heart failure patients treated with cardiac resynchronization therapy. Europace. 2015;17(3):439-46.

337. Donal E, Vignat N, De Place C, Leray E, Crocq C, Mabo P, et al. Acute effects of biventricular pacing on right ventricular function assessed by tissue doppler imaging. EP Europace. 2007;9(2):108-12.

338. Benchimol A, Liggett MS. Cardiac hemodynamics during stimulation of the right atrium, right ventricle, and left ventricle in normal and abnormal hearts. Circulation. 1966;33(6):933-44.

339. Colin P, Ghaleh B, Monnet X, Su J, Hittinger L, Giudicelli JF, et al. Contributions of heart rate and contractility to myocardial oxygen balance during exercise. Am J Physiol Heart Circ Physiol. 2003;284(2):H676-82.

340. Dual-chamber pacemakers for symptomatic bradycardia due to sick sinus syndrome and/or atrioventricular block NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE 2004.

341. Vignati C, Cattadori G. Measuring cardiac output during cardiopulmonary exercise testing. Ann Am Thorac Soc. 2017;14(Supplement_1):S48-s52.

342. Allman BL, Rice CL. An age-related shift in the force-frequency relationship affects quadriceps fatigability in old adults. J Appl Physiol (1985). 2004;96(3):1026-32.

343. Lee SCK, Russ DW, Binder-Macleod SA. Force-frequency relation of skeletal muscle. In: Binder MD, Hirokawa N, Windhorst U, editors. Encyclopedia of neuroscience. Berlin, Heidelberg: Springer Berlin Heidelberg; 2009. p. 1608-11.

344. Rumberger E, Timmermann J. Age-changes of the force-frequency-relationship and the duration of action potential of isolated papillary muscles of guinea pig. European Journal of Applied Physiology and Occupational Physiology. 1976;35(4):277-84.

345. Herraiz-Martínez A, Álvarez-García J, Llach A, Molina CE, Fernandes J, Ferrero-Gregori A, et al. Ageing is associated with deterioration of calcium homeostasis in isolated human right atrial myocytes. Cardiovascular Research. 2015;106(1):76-86.

346. Metra M, Dei Cas L, Massie BM. Treatment of heart failure in the elderly: Never say it's too late. European Heart Journal. 2009;30(4):391-3.

347. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. Esc guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: The task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the european society of cardiology. Developed in collaboration with the heart failure association of the esc (hfa) and endorsed by the european society of intensive care medicine (esicm). Eur Heart J. 2008;29(19):2388-442.

348. Gavazzi G, Krause KH. Ageing and infection. Lancet Infect Dis. 2002;2(11):659-66.

349. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. Clinical interventions in aging. 2006;1(3):253-60.

350. Brown J, Jenkins C, Marwick TH. Use of myocardial strain to assess global left ventricular function: A comparison with cardiac magnetic resonance and 3-dimensional echocardiography. American Heart Journal. 2009;157(1):102.e1-.e5.

351. Scatteia A, Baritussio A, Bucciarelli-Ducci C. Strain imaging using cardiac magnetic resonance. Heart failure reviews. 2017;22(4):465-76.

352. Muser D, Castro SA, Santangeli P, Nucifora G. Clinical applications of feature-tracking cardiac magnetic resonance imaging. World journal of cardiology. 2018;10(11):210-21.

353. Vo HQ, Marwick TH, Negishi K. Mri-derived myocardial strain measures in normal subjects. JACC Cardiovasc Imaging. 2018;11(2 Pt 1):196-205.

354. Amzulescu MS, De Craene M, Langet H, Pasquet A, Vancraeynest D, Pouleur AC, et al. Myocardial strain imaging: Review of general principles, validation, and sources of discrepancies. European Heart Journal - Cardiovascular Imaging. 2019;20(6):605-19.

355. Padiyath A, Gribben P, Abraham JR, Li L, Rangamani S, Schuster A, et al. Echocardiography and cardiac magnetic resonance-based feature tracking in the assessment of myocardial mechanics in tetralogy of fallot: An intermodality comparison. Echocardiography. 2013;30(2):203-10.

356. Schuster A, Stahnke V-C, Unterberg-Buchwald C, Kowallick J, Lamata P, Steinmetz M, et al. Cardiovascular magnetic resonance feature-tracking assessment of myocardial mechanics: Intervendor agreement and considerations regarding reproducibility. Clinical radiology. 2015;70(9):989-98.

357. Heermann P, Hedderich DM, Paul M, Schülke C, Kroeger JR, Baeßler B, et al. Biventricular myocardial strain analysis in patients with arrhythmogenic right ventricular cardiomyopathy (arvc) using cardiovascular magnetic resonance feature tracking. Journal of Cardiovascular Magnetic Resonance. 2014;16(1):75.

358. Cao JJ, Ngai N, Duncanson L, Cheng J, Gliganic K, Chen Q. A comparison of both dense and feature tracking techniques with tagging for the cardiovascular magnetic resonance assessment of myocardial strain. J Cardiovasc Magn Reson. 2018;20(1):26.

359. Maceira AM, Tuset-Sanchis L, López-Garrido M, San Andres M, López-Lereu MP, Monmeneu JV, et al. Feasibility and reproducibility of feature-tracking-based strain and strain rate measures of the left ventricle in different diseases and genders. J Magn Reson Imaging. 2018;47(5):1415-25.

360. Barreiro-Pérez M, Curione D, Symons R, Claus P, Voigt JU, Bogaert J. Left ventricular global myocardial strain assessment comparing the reproducibility of four commercially available cmr-feature tracking algorithms. Eur Radiol. 2018;28(12):5137-47.

361. Yip GW-K, Zhang Q, Xie J-M, Liang Y-J, Liu Y-M, Yan B, et al. Resting global and regional left ventricular contractility in patients with heart failure and normal ejection fraction: Insights from speckle-tracking echocardiography. Heart. 2011;97(4):287-94.

362. Zou H, Xi C, Zhao X, Koh AS, Gao F, Su Y, et al. Quantification of biventricular strains in heart failure with preserved ejection fraction patient using hyperelastic warping method. Frontiers in physiology. 2018;9:1295-.

363. Zhang Q, Fung JW-H, Yip GWK, Chan JY-S, Lee AP-W, Lam Y-Y, et al. Improvement of left ventricular myocardial short-axis, but not long-axis function or torsion after cardiac resynchronisation therapy: An assessment by two-dimensional speckle tracking. Heart. 2008;94(11):1464-71.

364. Burns KV, Gage RM, Curtin AE, Gorcsan J, 3rd, Bank AJ. Left ventricular-only pacing in heart failure patients with normal atrioventricular conduction improves global function and left ventricular regional mechanics compared with biventricular

pacing: An adaptive cardiac resynchronization therapy sub-study. Eur J Heart Fail. 2017;19(10):1335-43.

365. Weidemann F, Jamal F, Sutherland GR, Claus P, Kowalski M, Hatle L, et al. Myocardial function defined by strain rate and strain during alterations in inotropic states and heart rate. Am J Physiol Heart Circ Physiol. 2002;283(2):H792-9.

366. Suzuki R, Matsumoto H, Teshima T, Koyama H. Influence of heart rate on myocardial function using two-dimensional speckle-tracking echocardiography in healthy dogs. Journal of Veterinary Cardiology. 2013;15(2):139-46.

367. Hamabe L, Fukushima R, Kawamura K, Shinoda Y, Huai-Che H, Suzuki S, et al. Evaluation of changes in left ventricular myocardial function observed in canine myocardial dysfunction model using a two-dimensional tissue tracking technique. J Vet Sci. 2013;14(3):355-62.

368. Dohi K, Pinsky MR, Kanzaki H, Severyn D, Gorcsan J. Effects of radial left ventricular dyssynchrony on cardiac performance using quantitative tissue doppler radial strain imaging. Journal of the American Society of Echocardiography. 2006;19(5):475-82.

369. Xu L, Pagano JJ, Haykowksy MJ, Ezekowitz JA, Oudit GY, Mikami Y, et al. Layer-specific strain in patients with heart failure using cardiovascular magnetic resonance: Not all layers are the same. Journal of Cardiovascular Magnetic Resonance. 2020;22(1):81.

370. Hung CL, Verma A, Uno H, Shin SH, Bourgoun M, Hassanein AH, et al. Longitudinal and circumferential strain rate, left ventricular remodeling, and prognosis after myocardial infarction. J Am Coll Cardiol. 2010;56(22):1812-22.

371. Khan FZ, Virdee MS, Palmer CR, Pugh PJ, O'Halloran D, Elsik M, et al. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: The target study: A randomized, controlled trial. Journal of the American College of Cardiology. 2012;59(17):1509-18.

372. Nagata Y, Wu VC-C, Otsuji Y, Takeuchi M. Normal range of myocardial layer-specific strain using two-dimensional speckle tracking echocardiography. PLOS ONE. 2017;12(6):e0180584.

373. Voelkel NF, Quaife RA, Leinwand LA, Barst RJ, McGoon MD, Meldrum DR, et al. Right ventricular function and failure: Report of a national heart, lung, and blood institute working group on cellular and molecular mechanisms of right heart failure. Circulation. 2006;114(17):1883-91.

374. Zornoff LA, Skali H, Pfeffer MA, St John Sutton M, Rouleau JL, Lamas GA, et al. Right ventricular dysfunction and risk of heart failure and mortality after myocardial infarction. J Am Coll Cardiol. 2002;39(9):1450-5.

375. Meyer P, Filippatos GS, Ahmed MI, Iskandrian AE, Bittner V, Perry GJ, et al. Effects of right ventricular ejection fraction on outcomes in chronic systolic heart failure. Circulation. 2010;121(2):252-8.

376. Chua S, Levine RA, Yosefy C, Handschumacher MD, Chu J, Qureshi A, et al. Assessment of right ventricular function by real-time three-dimensional echocardiography improves accuracy and decreases interobserver variability compared with conventional two-dimensional views. European Journal of Echocardiography. 2009;10(5):619-24.

377. Rominger MB, Bachmann GF, Pabst W, Rau WS. Right ventricular volumes and ejection fraction with fast cine mr imaging in breath-hold technique: Applicability, normal values from 52 volunteers, and evaluation of 325 adult cardiac patients. Journal of Magnetic Resonance Imaging: An Official Journal of the International Society for Magnetic Resonance in Medicine. 1999;10(6):908-18.

378. Pattynama PM, Lamb HJ, Van der Velde EA, Van der Geest RJ, Van der Wall EE, De Roos A. Reproducibility of mri-derived measurements of right ventricular volumes and myocardial mass. Magnetic resonance imaging. 1995;13(1):53-63.

379. Foppa M, Arora G, Gona P, Ashrafi A, Salton CJ, Yeon SB, et al. Right ventricular volumes and systolic function by cardiac magnetic resonance and the impact of sex, age, and obesity in a longitudinally followed cohort free of pulmonary and cardiovascular disease: The framingham heart study. Circ Cardiovasc Imaging. 2016;9(3):e003810.

380. Movahed MR, Milne N. Presence of biventricular dysfunction in patients with type ii diabetes mellitus. Congestive Heart Failure. 2007;13(2):78-80.

381. Winter MM, Bernink FJP, Groenink M, Bouma BJ, van Dijk APJ, Helbing WA, et al. Evaluating the systemic right ventricle by cmr: The importance of consistent and reproducible delineation of the cavity. Journal of Cardiovascular Magnetic Resonance. 2008;10(1):40.

382. Johnston WE, Robertie PG, Dudas LM, Kon ND, Vinten-Johansen J. Heart rate-right ventricular stroke volume relation with myocardial revascularization. Ann Thorac Surg. 1991;52(4):797-804.

383. Meris A, Faletra F, Conca C, Klersy C, Regoli F, Klimusina J, et al. Timing and magnitude of regional right ventricular function: A speckle tracking-derived strain study of normal subjects and patients with right ventricular dysfunction. J Am Soc Echocardiogr. 2010;23(8):823-31.

384. Aschauer S, Kammerlander AA, Zotter-Tufaro C, Ristl R, Pfaffenberger S, Bachmann A, et al. The right heart in heart failure with preserved ejection fraction: Insights from cardiac magnetic resonance imaging and invasive haemodynamics. European journal of heart failure. 2016;18(1):71-80.

385. Erley J, Tanacli R, Genovese D, Tapaskar N, Rashedi N, Bucius P, et al. Myocardial strain analysis of the right ventricle: Comparison of different cardiovascular magnetic resonance and echocardiographic techniques. Journal of Cardiovascular Magnetic Resonance. 2020;22(1):51.

386. Rajagopalan N, Suffoletto MS, Tanabe M, Miske G, Thomas NC, Simon MA, et al. Right ventricular function following cardiac resynchronization therapy. American Journal of Cardiology. 2007;100(9):1434-6.

387. D'Andrea A, Salerno G, Scarafile R, Riegler L, Gravino R, Castaldo F, et al. Right ventricular myocardial function in patients with either idiopathic or ischemic dilated cardiomyopathy without clinical sign of right heart failure: Effects of cardiac resynchronization therapy. Pacing Clin Electrophysiol. 2009;32(8):1017-29.

388. Burri H, Domenichini G, Sunthorn H, Fleury E, Stettler C, Foulkes I, et al. Right ventricular systolic function and cardiac resynchronization therapy. Europace. 2010;12(3):389-94.

389. Bleeker GB, Schalij MJ, Nihoyannopoulos P, Steendijk P, Molhoek SG, van Erven L, et al. Left ventricular dyssynchrony predicts right ventricular remodeling after cardiac resynchronization therapy. Journal of the American College of Cardiology. 2005;46(12):2264-9.

390. Kanzaki H, Bazaz R, Schwartzman D, Dohi K, Sade LE, Gorcsan J. A mechanism for immediate reduction in mitral regurgitation after cardiac resynchronization therapy: Insights from mechanical activation strain mapping. Journal of the American College of Cardiology. 2004;44(8):1619-25.

391. Tourneau TL, Deswarte G, Lamblin N, Foucher-Hossein C, Fayad G, Richardson M, et al. Right ventricular systolic function in organic mitral regurgitation. Circulation. 2013;127(15):1597-608.

392. Setaro JF, Cleman MW, Remetz MS. The right ventricle in disorders causing pulmonary venous hypertension. Cardiology clinics. 1992;10(1):165-83.

393. Klima U, Guerrero J, Vlahakes G. Myocardial perfusion and right ventricular function. Annals of thoracic and cardiovascular surgery: official journal of the Association of Thoracic and Cardiovascular Surgeons of Asia. 1999;5(2):74-80.

394. Kia DS, Shen Y, Bachman TN, Goncharova EA, Kim K, Simon MA. Effects of healthy aging on right ventricular structure and biomechanical properties. bioRxiv. 2020:2020.09.08.288332.

395. Innelli P, Esposito R, Olibet M, Nistri S, Galderisi M. The impact of ageing on right ventricular longitudinal function in healthy subjects: A pulsed tissue doppler study. Eur J Echocardiogr. 2009;10(4):491-8.

396. Trensz F, Lucien F, Couture V, Söllrald T, Drouin G, Rouleau A-J, et al. Increased microenvironment stiffness in damaged myofibers promotes myogenic progenitor cell proliferation. Skeletal Muscle. 2015;5(1):5.

397. Lacraz G, Rouleau A-J, Couture V, Söllrald T, Drouin G, Veillette N, et al. Increased stiffness in aged skeletal muscle impairs muscle progenitor cell proliferative activity. PloS one. 2015;10(8):e0136217-e.

398. Wang G-Y, McCloskey DT, Turcato S, Swigart PM, Simpson PC, Baker AJ. Contrasting inotropic responses to α1-adrenergic receptor stimulation in left versus right ventricular myocardium. American Journal of Physiology-Heart and Circulatory Physiology. 2006;291(4):H2013-H7.

399. Blalock SE, Banka P, Geva T, Powell AJ, Zhou J, Prakash A. Interstudy variability in cardiac magnetic resonance imaging measurements of ventricular volume, mass, and ejection fraction in repaired tetralogy of fallot: A prospective observational study. Journal of Magnetic Resonance Imaging. 2013;38(4):829-35.

400. Liu B, Dardeer AM, Moody WE, Edwards NC, Hudsmith LE, Steeds RP. Reference ranges and reproducibility studies for right heart myocardial deformation by feature tracking cardiovascular magnetic resonance imaging. Data in Brief. 2018;16:244-9.

401. Bouzas-Cruz N, Koshy A, Gonzalez-Fernandez O, Ferrera C, Green T, Okwose NC, et al. Markers of right ventricular dysfunction predict maximal exercise capacity after left ventricular assist device implantation. Asaio j. 2021;67(3):284-9.

402. Craven TP, Tsao CW, La Gerche A, Simonetti OP, Greenwood JP. Exercise cardiovascular magnetic resonance: Development, current utility and future applications. Journal of Cardiovascular Magnetic Resonance. 2020;22(1):65.

403. Schulman PM, Stecker EC, Rozner MA. R-on-t and cardiac arrest from dual-chamber pacing without an atrial lead. Heart Rhythm Journal. 2012;9(6):970-3.

404. Chemello D, Subramanian A, Kumaraswamy N. Cardiac arrest caused by undersensing of a temporary epicardial pacemaker. The Canadian journal of cardiology. 2010;26(1):e13-e4.

405. Gladwell VF, Coote JH. Heart rate at the onset of muscle contraction and during passive muscle stretch in humans: A role for mechanoreceptors. The Journal of physiology. 2002;540(Pt 3):1095-102.

406. O'Driscoll JM, Taylor KA, Wiles JD, Coleman DA, Sharma R. Acute cardiac functional and mechanical responses to isometric exercise in prehypertensive males. Physiol Rep. 2017;5(7).

407. Meyer K, Hajric R, Westbrook S, Haag-Wildi S, Holtkamp R, Leyk D, et al. Hemodynamic responses during leg press exercise in patients with chronic congestive heart failure. Am J Cardiol. 1999;83(11):1537-43.

408. Koshy A, Green T, Toms A, Cassidy S, Schueler S, Jakovljevic D, et al. The role of exercise hemodynamics in assessing patients with chronic heart failure and left ventricular assist devices. Expert Review of Medical Devices. 2019;16(10):891-8.

409. Coulden R, Sonnex E. Inter-observer variation in lv analysis in a dedicated cmr unit: The impact of audit and consensus guideline on reproducibility. Journal of Cardiovascular Magnetic Resonance. 2014;16(1):P372.

410. Kovács A, Lakatos B, Tokodi M, Merkely B. Right ventricular mechanical pattern in health and disease: Beyond longitudinal shortening. Heart failure reviews. 2019;24(4):511-20.

411. Luijnenburg SE, Robbers-Visser D, Moelker A, Vliegen HW, Mulder BJM, Helbing WA. Intra-observer and interobserver variability of biventricular function, volumes and mass in patients with congenital heart disease measured by cmr imaging. The international journal of cardiovascular imaging. 2010;26(1):57-64.

412. Andre F, Steen H, Matheis P, Westkott M, Breuninger K, Sander Y, et al. Age- and gender-related normal left ventricular deformation assessed by cardiovascular magnetic resonance feature tracking. Journal of Cardiovascular Magnetic Resonance. 2015;17(1):25.

413. Schuster A, Morton G, Hussain ST, Jogiya R, Kutty S, Asrress KN, et al. The intra-observer reproducibility of cardiovascular magnetic resonance myocardial feature tracking strain assessment is independent of field strength. European journal of radiology. 2013;82(2):296-301.

414. Feisst A, Kuetting DLR, Dabir D, Luetkens J, Homsi R, Schild HH, et al. Influence of observer experience on cardiac magnetic resonance strain measurements using feature tracking and conventional tagging. IJC Heart & Vasculature. 2018;18:46-51.

415. Hu B-y, Wang J, Yang Z-g, Ren Y, Jiang L, Xie L-j, et al. Cardiac magnetic resonance feature tracking for quantifying right ventricular deformation in type 2 diabetes mellitus patients. Scientific Reports. 2019;9(1):11148.

416. Barreiro-Pérez M, Curione D, Symons R, Claus P, Voigt J-U, Bogaert J. Left ventricular global myocardial strain assessment comparing the reproducibility of four commercially available cmr-feature tracking algorithms. European Radiology. 2018;28(12):5137-47.

417. Backhaus SJ, Metschies G, Billing M, Kowallick JT, Gertz RJ, Lapinskas T, et al. Cardiovascular magnetic resonance imaging feature tracking: Impact of training on observer performance and reproducibility. PloS one. 2019;14(1):e0210127-e.

418. Agger P, Lass T, Smerup M, Frandsen J, Pedersen M. Optimal preservation of porcine cardiac tissue prior to diffusion tensor magnetic resonance imaging. Journal of anatomy. 2015;227(5):695-701.

419. Camacho P, Fan H, Liu Z, He J-Q. Large mammalian animal models of heart disease. Journal of cardiovascular development and disease. 2016;3(4):30.

420. Milani-Nejad N, Janssen PM. Small and large animal models in cardiac contraction research: Advantages and disadvantages. Pharmacol Ther. 2014;141(3):235-49.

421. Lelovas PP, Kostomitsopoulos NG, Xanthos TT. A comparative anatomic and physiologic overview of the porcine heart. Journal of the American Association for Laboratory Animal Science : JAALAS. 2014;53(5):432-8.

422. Loomis C, Alu M. Detailed discussion of tissue prep and formalin/formaldehyde fixation recommendations. Experimental Pathology Research Laboratory - Division of Advanced Research Technologies, 2016.

423. Purvis LA, Clarke WT, Biasiolli L, Robson MD, Rodgers CT, editors. Linewidth constraints in matlab amares using per-metabolite t2 and per-voxel δb0. Proc Intl Soc Mag Reson Med; 2014.

424. Do C, Barnes JL, Tan C, Wagner B. Type of mri contrast, tissue gadolinium, and fibrosis. American Journal of Physiology-Renal Physiology. 2014;307(7):F844-F55.

425. Xie L, Layton AT, Wang N, Larson PEZ, Zhang JL, Lee VS, et al. Dynamic contrast-enhanced quantitative susceptibility mapping with ultrashort echo time mri for evaluating renal function. American Journal of Physiology-Renal Physiology. 2016;310(2):F174-F82.

426. Buonocore MH, Maddock RJ. Magnetic resonance spectroscopy of the brain: A review of physical principles and technical methods. Reviews in the neurosciences. 2015;26(6).

427. Drangova M, Zhu Y, Pelc NJ. Effect of artifacts due to flowing blood on the reproducibility of phase-contrast measurements of myocardial motion. J Magn Reson Imaging. 1997;7(4):664-8.

428. Schuster A, Grünwald I, Chiribiri A, Southworth R, Ishida M, Hay G, et al. An isolated perfused pig heart model for the development, validation and translation of novel cardiovascular magnetic resonance techniques. Journal of Cardiovascular Magnetic Resonance. 2010;12(1):53.

429. Tse HF, Yu C, Wong KK, Tsang V, Leung YL, Ho WY, 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):1451-8.

430. Auricchio A, Stellbrink C, Block M, Sack S, Vogt J, Bakker P, et al. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The pacing therapies for congestive heart failure study group. The guidant congestive heart failure research group. Circulation. 1999;99(23):2993-3001.

431. St John Sutton MG, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation. 2003;107(15):1985-90.

432. Katz AM. Is the failing heart an energy-starved organ? Journal of Cardiac Failure. 1996;2(4):267-72.

433. Van Thielen G, Paelinck BP, Paul B, Vrints CJ, Conraads VMA. Rate response and cardiac resynchronisation therapy in chronic heart failure: Higher cardiac output does not acutely improve exercise performance: A pilot trial. European Journal of Cardiovascular Prevention & Rehabilitation. 2008;15(2):197-202.

434. Mulieri LA, Leavitt BJ, Martin BJ, Haeberle JR, Alpert NR. Myocardial force-frequency defect in mitral regurgitation heart failure is reversed by forskolin. Circulation. 1993;88(6):2700-4.

435. Schlepper M, Thormann J, Mitrovic V. Cardiovascular effects of forskolin and phosphodiesterase-iii inhibitors. Basic Research in Cardiology. 1989;84(1):197-212.

436. Alpendurada F, Guha K, Sharma R, Ismail TF, Clifford A, Banya W, et al. Right ventricular dysfunction is a predictor of non-response and clinical outcome following cardiac resynchronization therapy. Journal of Cardiovascular Magnetic Resonance. 2011;13(1):68.